



Jaguar Health

200 Pine Street, Suite 400, San Francisco, CA 94104
Tel: 415.371.8300 • Fax: 415.371.8311
<https://jaguar.health>

May 19, 2022

Dear Stockholder:

You are cordially invited to attend the 2022 Annual Meeting of Stockholders (the “Annual Meeting”) of Jaguar Health, Inc. (the “Company”) to be held at 200 Pine Street, Suite 400, San Francisco, CA 94104, on Friday, June 10, 2022, at 8:30 a.m., local time.

At the Annual Meeting you will be asked to (i) elect three (3) Class I directors to our Board of Directors (ii) ratify the appointment of RBSM LLP as the Company’s independent registered public accounting firm for the fiscal year ending December 31, 2022, (iii) approve, for purposes of Nasdaq Rule 5635(d), the issuance of shares of the Company’s voting common stock, par value \$0.0001 per share (the “Common Stock”) upon the exchange of certain royalty interests and a promissory note previously issued by the Company to certain accredited investors, and (iv) approve discretionary authority for the Company to adjourn the Annual Meeting, if necessary, to solicit additional proxies in the event that there are not sufficient votes at the time of the Annual Meeting to approve proposal (iii).

It is important that your shares be represented and voted whether or not you plan to attend the Annual Meeting in person. You may vote on the Internet, by telephone or by completing and mailing a proxy card or voting instruction form. Voting over the Internet, by telephone or by mail will ensure your shares are represented at the Annual Meeting. If you do attend the Annual Meeting, you may, of course, withdraw your proxy should you wish to vote in person. Please read the enclosed information carefully before voting.

Sincerely,

Lisa A. Conte
Chief Executive Officer & President

JAGUAR HEALTH, INC.
200 Pine Street
Suite 400
San Francisco, CA 94104

NOTICE OF 2022 ANNUAL MEETING OF STOCKHOLDERS
To Be Held June 10, 2022

NOTICE HEREBY IS GIVEN that the 2022 Annual Meeting of Stockholders (the “Annual Meeting”) of Jaguar Health, Inc. (the “Company”) will be held at 200 Pine Street, Suite 400, San Francisco, CA 94104, on Friday, June 10, 2022, at 8:30 a.m., local time, for the following purposes:

1. Electing three (3) Class I directors (Proposal 1);
2. Ratifying the appointment of RBSM LLP as the Company’s independent registered public accounting firm for the fiscal year ending December 31, 2022 (Proposal 2);
3. Approving, for purposes of Nasdaq Rule 5635(d), the issuance of shares of the Company’s voting common stock, par value \$0.0001 per share (the “Common Stock”) upon the exchange of certain royalty interests and a promissory note previously issued by the Company to certain accredited investors (Proposal 3);
4. Approving a proposal to grant discretionary authority to adjourn the Annual Meeting, if necessary, to solicit additional proxies in the event that there are not sufficient votes at the time of the Annual Meeting to approve Proposal 3 (Proposal 4); and
5. Such other business as properly may come before the Annual Meeting or any adjournment or postponement thereof.

The board of directors is not aware of any other business to be presented to a vote of the stockholders at the Annual Meeting. Information relating to the above matters is set forth in the attached Proxy Statement. Stockholders of record at the close of business on May 13, 2022 are entitled to receive notice of and to vote at the Annual Meeting and any adjournment or postponement thereof.

By Order of the Board of Directors.



Lisa A. Conte
Chief Executive Officer & President

San Francisco, California
May 19, 2022

Information relating to the above matters is set forth in the attached Proxy Statement. Stockholders of record at the close of business on May 13, 2022 are entitled to receive notice of and to vote at the Annual Meeting and any adjournment or postponement thereof. If you have questions concerning the proposals in the Proxy Statement, would like additional copies of the Proxy Statement or need help in voting your shares of Common Stock, please contact our proxy solicitor Georgeson LLC at 866-821-0284.

Important Notice Regarding the Availability of Proxy Materials for the Stockholder Meeting to be Held on June 10, 2022. The proxy materials are available at <https://jaguarhealth.gcs-web.com/financial-information/annual-reports>

PLEASE CAREFULLY READ THE PROXY STATEMENT. EVEN IF YOU EXPECT TO ATTEND THE ANNUAL MEETING, PLEASE PROMPTLY COMPLETE, EXECUTE, DATE AND RETURN THE ENCLOSED PROXY CARD OR VOTING INSTRUCTION FORM IN THE ACCOMPANYING POSTAGE-PAID ENVELOPE. NO POSTAGE IS NECESSARY IF MAILED IN THE UNITED STATES. YOU MAY ALSO VOTE ELECTRONICALLY VIA THE INTERNET OR BY TELEPHONE BY FOLLOWING THE INSTRUCTIONS ON THE ENCLOSED PROXY CARD OR VOTING INSTRUCTION FORM. IF YOU VOTE BY INTERNET OR TELEPHONE, THEN YOU NEED NOT RETURN A WRITTEN PROXY CARD OR VOTING INSTRUCTION FORM BY MAIL. STOCKHOLDERS WHO ATTEND THE ANNUAL MEETING MAY REVOKE THEIR PROXIES AND VOTE IN PERSON IF THEY SO DESIRE (AS DESCRIBED BELOW).

JAGUAR HEALTH, INC.

**200 Pine Street
Suite 400
San Francisco, CA 94104**

PROXY STATEMENT

**FOR THE 2022 ANNUAL MEETING OF STOCKHOLDERS
To Be Held June 10, 2022**

GENERAL INFORMATION ABOUT THE ANNUAL MEETING

We are furnishing this Proxy Statement to our stockholders in connection with the solicitation of proxies by our board of directors to be voted at the 2022 Annual Meeting of Stockholders (the “Annual Meeting”) and at any adjournment or postponement thereof. The Annual Meeting will be held at 200 Pine Street, Suite 400, San Francisco, CA 94104, on Friday, June 10, 2022, at 8:30 a.m., local time.

When used in this Proxy Statement, the terms the “Company,” “we,” “us,” “our” and “Jaguar” refer to Jaguar Health, Inc.

The Securities and Exchange Commission (“SEC”) rules require us to provide an annual report to stockholders who receive this Proxy Statement. Accordingly, we have enclosed our Annual Report on Form 10-K for the fiscal year ended December 31, 2021 (the “Annual Report”), which was filed on March 11, 2022, with this Proxy Statement, and we will also provide copies of such documents to brokers, dealers, banks, voting trustees and their nominees for the benefit of their beneficial owners of record. Pursuant to rules adopted by the SEC, the Company is also providing access to its proxy materials over the Internet. All stockholders will have the ability to access the proxy materials at <https://jaguarhealth.gcs-web.com/financial-information/annual-reports>.

The date on which the Notice of 2022 Annual Meeting of Stockholders, this Proxy Statement, the Annual Report and form of proxy card or voting instruction form are first being sent or given to stockholders is on or about May 19, 2022.

GENERAL INFORMATION ABOUT VOTING

Record Date

As of May 13, 2022, the record date for the Annual Meeting (the “Record Date”), we anticipate that there will be 77,863,506 shares of our common stock, par value \$0.0001 per share (the “Common Stock”), which are issued and outstanding. Only holders of record of our Common Stock as of the close of business on the Record Date are entitled to notice of, and to vote at, the Annual Meeting or at any adjournment or postponement thereof. A list of such holders will be open to the examination of any stockholder for any purpose germane to the meeting at Jaguar Health, Inc., 200 Pine Street, Suite 400, San Francisco, CA 94104 for a period of ten (10) days prior to the Annual Meeting. The list of stockholders will also be available for such examination at the Annual Meeting. In addition, as of May 13, 2022, there will be 673 shares of our non-voting common stock outstanding, but these shares will have no voting rights with respect to any of the proposals being considered at the Annual Meeting. Each share of non-voting common stock is convertible into one-three thousand fiftieth (1/3,150th) of a share of Common Stock at the election of the holder thereof.

The use of the capitalized term “Common Stock” in this Proxy Statement and related materials refers only to the Company’s common stock and does not include the Company’s convertible non-voting common stock.

Voting, Quorum and Revocability of Proxies

Each share of Common Stock entitles the holder of record thereof to one vote. No other securities are entitled to be voted at the Annual Meeting. Each stockholder holding Common Stock may vote in person or by proxy on all matters that properly come before the Annual Meeting and any adjournment or postponement thereof (except as otherwise described below).

Stockholders have no right to cumulative voting as to any matter, including the election of directors. The presence, in person or represented by proxy, of holders of one third (1/3) of the shares of capital stock of the Company outstanding on the Record Date and entitled to vote at the Annual Meeting will constitute a quorum for purposes of voting at the Annual Meeting. Properly executed proxies marked “ABSTAIN” or “WITHHOLD,” as well as broker non-votes, will be counted as “present” for purposes of determining the existence of a quorum. If a quorum should not be present, either the chairperson of the meeting or a majority in voting power of the stockholders entitled to vote on the adjournment may adjourn such meeting from time to time until a quorum is obtained.

Our board of directors is soliciting proxies for use in connection with the Annual Meeting and any postponement or adjournment thereof. If you vote your shares via the Internet or by telephone or execute and return the proxy card or voting instruction form accompanying this Proxy Statement, your shares will be voted as you direct on all matters properly coming before the Annual Meeting for a vote. For Proposal 1, you may vote “FOR” or “WITHHOLD” authority for one or more of the nominees. For Proposals 2, 3 and 4, you may vote “FOR,” “AGAINST” or “ABSTAIN.”

If your shares are registered directly in your name with our transfer agent, American Stock Transfer & Trust Company, LLC (the “Transfer Agent”), you are considered, with respect to those shares, the stockholder of record. As the stockholder of record, you have the right to grant your proxy directly to the Company or to vote your shares in person at the Annual Meeting. If you hold your shares in a stock brokerage account or through a bank or other financial intermediary, you are considered the beneficial owner of shares held in street name. Your bank, broker or other financial intermediary is considered, with respect to those shares, the stockholder of record. As the beneficial owner, you have the right to direct your bank, broker or other financial intermediary on how to vote your shares, but because you are not the stockholder of record, you may not vote these shares in person at the Annual Meeting unless you obtain a signed proxy from the record holder giving you the right to vote the shares. As a beneficial owner, you are, however, welcome to attend the Annual Meeting in person provided that you present a valid legal proxy from the record holder (i.e., bank, broker, trustee or other nominee) to you.

Even if you plan to attend the Annual Meeting, we recommend that you also submit your proxy as described in the proxy card or voting instruction form, so that your vote will be counted if you later decide not to attend the Annual Meeting. Submitting your proxy now will not prevent you from voting your shares in person by written ballot at the Annual Meeting if you desire to do so, as your proxy is revocable at your option.

You may revoke your proxy by (a) delivering to the Secretary of the Company at or before the Annual Meeting a written notice of revocation bearing a later date than the proxy, (b) duly executing a subsequent proxy and delivering it to the Secretary of the Company at or before the Annual Meeting or (c) attending the Annual Meeting and voting in person (although attendance at the Annual Meeting will not in and of itself constitute revocation of a proxy). Any written notice revoking a proxy should be delivered at or prior to the Annual Meeting to: Jaguar Health, Inc., 200 Pine Street, Suite 400, San Francisco, CA 94104, Attention: Jonathan S. Wolin. Beneficial owners of our Common Stock who are not holders of record and wish to revoke their proxy should contact their bank, brokerage firm or other custodian, nominee or fiduciary to inquire about how to revoke their proxy.

The shares represented by all valid proxies received will be voted in the manner specified. Where specific choices are not indicated on a validly executed and delivered proxy, the shares represented by such proxy will be voted: (i) “FOR” the nominees for director named in this Proxy Statement, (ii) “FOR” the

ratification of the appointment of RBSM LLP (“RBSM”) as the Company’s independent registered public accounting firm for the fiscal year ending December 31, 2022, (iii) “FOR” the approval of, for purposes of Nasdaq Rule 5635(d), the issuance of shares of the Company’s voting common stock, par value \$0.0001 per share (the “Common Stock”) upon the exchange of certain royalty interests and a promissory note previously issued by the Company to certain accredited investors; and (iv) “FOR” the approval of discretionary authority for the Company to adjourn the Annual Meeting, if necessary, to solicit additional proxies in the event that there are not sufficient votes at the time of the Annual Meeting to approve Proposal 3.

We will bear all expenses of this solicitation, including the cost of preparing and mailing this Proxy Statement. We have retained Georgeson LLC to solicit proxies for a base fee of \$6,500 plus reimbursement of reasonable out-of-pocket expenses. In addition to solicitation by use of the mail, proxies may be solicited by telephone, facsimile or personally by our directors, officers and employees, who will receive no extra compensation for their services. We will reimburse banks, brokerage firms and other custodians, nominees and fiduciaries for reasonable expenses incurred by them in sending proxy soliciting materials to beneficial owners of shares of Common Stock.

Broker Voting

Brokers holding shares of record in “street name” for a client have the discretionary authority to vote on some matters (routine matters) if they do not receive instructions from the client regarding how the client wants the shares voted at least 10 days before the date of the meeting; provided the proxy materials are transmitted to the client at least 15 days before the meeting. There are also some matters with respect to which brokers do not have discretionary authority to vote (non-routine matters) if they do not receive timely instructions from the client. When a broker does not have discretion to vote on a particular matter and the client has not given timely instructions on how the broker should vote, a broker non-vote results. Any broker non-vote will be counted as present at the Annual Meeting for purposes of determining a quorum, but will be treated as not entitled to vote with respect to non-routine matters.

The proposal to ratify the appointment of RBSM as our independent registered public accounting firm for the fiscal year ending December 31, 2022 (Proposal 2) is considered a routine matter and brokers will be permitted to vote in their discretion on this matter on behalf of clients who have not furnished voting instructions at least 10 days before the date of the Annual Meeting. In contrast, the proposal to elect directors (Proposal 1), the proposal to approve, for purposes of Nasdaq Rule 5635(d), the issuance of shares of the Company’s voting common stock, par value \$0.0001 per share (the “Common Stock”) upon the exchange of certain royalty interests and a promissory note previously issued by the Company to certain accredited investors (Proposal 3), and the proposal to approve discretionary authority for the Company to adjourn the Annual Meeting, if necessary, to solicit additional proxies in the event that there are not sufficient votes at the time of the Annual Meeting to approve Proposal 3 (Proposal 4) are not considered “routine” matters and brokers do not have discretionary authority to vote on behalf of clients on such matters.

Required Vote

Proposal 1 — Election of Class I Directors

With respect to the proposal to elect directors (Proposal 1), you may vote in favor of all nominees, withhold your vote as to all nominees or vote in favor of or withhold your vote as to specific nominees. The vote required to approve Proposal 1 is governed by Delaware law, the Company’s Third Amended and Restated Certificate of Incorporation, as amended (the “COI”), and our Amended and Restated Bylaws, as amended (the “Bylaws”) and is a plurality of the votes cast by the holders of shares represented and entitled to vote at the Annual Meeting, provided a quorum is present. As a result, in accordance with Delaware law, votes that are withheld will be counted in determining whether a quorum is present but will have no other effect on the election of directors. Stockholders have no right to cumulative voting as to any matter, including the election of directors.

Proposal 2 — Ratification of Independent Registered Public Accounting Firm

With respect to the proposal to ratify the Audit Committee’s appointment of RBSM as our independent registered public accounting firm for the fiscal year ending December 31, 2022 (Proposal 2), you may vote

in favor of the proposal, vote against the proposal or abstain from voting. The vote required to approve Proposal 2 is governed by Delaware law, the COI and the Bylaws and is the affirmative vote of the holders of a majority of votes cast on such proposal by the shares of Common Stock present in person or represented by proxy at the Annual Meeting and entitled to vote, provided a quorum is present. As a result, abstentions will be considered in determining whether a quorum is present but will have no effect on the vote for Proposal 2.

Proposal 3 — Issuance of Shares of Common Stock Upon Exchange of Royalty Interests and a Promissory Note for Purposes of Nasdaq Listing Rule 5635(d)

With respect to the proposal to approve, for purposes of Nasdaq Rule 5635(d), the issuance of shares of Common Stock upon the exchange, from time to time at Company's discretion, of all or any portion of certain royalty interests and a promissory note previously issued by the Company to certain accredited investors, you may vote in favor of the proposal, vote against the proposal or abstain from voting. The vote required to approve Proposal 3 is governed by Delaware law, the Nasdaq Listing Rules, the COI and the Bylaws and is the affirmative vote of the holders of a majority of the votes cast on such proposal by the shares of Common Stock present in person or represented by proxy at the Annual Meeting and entitled to vote, provided a quorum is present. As a result, abstentions will be considered in determining whether a quorum is present but will have no effect on the vote for Proposal 3.

Proposal 4 — Adjournment

With respect to the proposal to grant discretionary authority to adjourn the Annual Meeting, if necessary, to solicit additional proxies in the event that there are not sufficient votes at the time of the Annual Meeting to approve Proposal 3, you may vote in favor of the proposal, vote against the proposal or abstain from voting. The vote required to approve Proposal 4 is governed by Delaware law, the COI and the Bylaws and is the affirmative vote of the holders of a majority of votes cast affirmatively or negatively (excluding abstentions and broker non-votes), provided a quorum is present. As a result, abstentions will be considered in determining whether a quorum is present but will have no effect on the vote for Proposal 4.

NO DISSENTERS' RIGHTS

The corporate action described in this Proxy Statement will not afford to stockholders the opportunity to dissent from the actions described herein and receive an agreed or judicially appraised value for their shares of Common Stock.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

The statements in this Proxy Statement that are not historical statements, including statements regarding future capital-raising activities and expected use of proceeds therefrom, our estimates regarding expenses, future revenues, capital requirements, needs for additional financing, our ability to obtain additional financing, our success with regard to any business development initiatives, our ability to recruit or retain key scientific or management personnel or to retain our executive officers, our stock price and ability to meet the continued listing requirements of The Nasdaq Capital Market, and any other statements regarding our future expectations, beliefs, plans, objectives, financial conditions, assumptions or future events or performance that are not historical facts, are forward-looking statements within the meaning of the federal securities laws. These statements are subject to numerous risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from the results expressed or implied by the statements. We describe risks and uncertainties that could cause actual results and events to differ materially in the “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” section of our annual report on Form 10-K for the year ended December 31, 2021 (the “Annual Report”).

Any forward-looking statements should be considered in light of such important factors. We undertake no obligation to revise or update publicly any forward-looking statements for any reason. Readers are cautioned not to place undue reliance on any forward-looking statement, which speaks only as of the date on which such statement is made.

All subsequent written and oral forward-looking statements concerning the matters addressed in this Proxy Statement and attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this Proxy Statement.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table sets forth information regarding the beneficial ownership of shares of our Common Stock as of April 25, 2022 for:

- each person known to us to be the beneficial owner of more than 5% of our outstanding shares of Common Stock;
- each of our named executive officers;
- each of our directors; and
- all directors and named executive officers as a group.

Information with respect to beneficial ownership has been furnished by each director, executive officer or beneficial owner of more than 5% of our Common Stock. Beneficial ownership is determined in accordance with the rules of the SEC and generally includes voting and investment power with respect to the securities. Except as otherwise provided by footnote, and subject to applicable community property laws, the persons named in the table have sole voting and investment power with respect to all shares of Common Stock shown as beneficially owned by them. The number of shares of Common Stock used to calculate the percentage ownership of each listed person includes the shares of Common Stock underlying options or warrants or convertible securities held by such persons that are currently exercisable or convertible or exercisable or convertible within 60 days of April 25, 2022, but are not treated as outstanding for the purpose of computing the percentage ownership of any other person.

Percentage of beneficial ownership is based on 77,073,990 shares of Common Stock and 673 shares of non-voting common stock outstanding as of April 25, 2022.

Except as otherwise set forth below, the address of each beneficial owner listed in the table below is c/o Jaguar Health, Inc., 200 Pine Street, Suite 400, San Francisco, California 94104.

Name and address of beneficial owner	Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned
5% Stockholders:		
Josh Mailman ⁽¹⁾	8,614,138	11.06%
Oasis Capital, LLC ⁽²⁾	4,604,484	5.91%
Named executive officers and directors:		
Lisa A. Conte ⁽³⁾	578,222	*
Steven R. King, Ph.D. ⁽⁴⁾	180,415	*
Jonathan S. Wolin ⁽⁵⁾	137,038	*
Ian Wendt ⁽⁶⁾	78,471	*
James J. Bochnowski ⁽⁷⁾	375,796	*
Jonathan B. Siegel ⁽⁸⁾	136,016	*
John Micek III ⁽⁹⁾	84,456	*
Greg Divis ⁽¹⁰⁾	84,039	*
All current executive officers and directors as a group (8 persons) ⁽¹¹⁾	1,654,453	2.08%

* Less than 1%.

(1) Represents (i) 4,088,758 shares of Common Stock held by Joshua Mailman, (ii) 4,366,665 shares of Common Stock held by Joshua Mailman Foundation, and (iii) 158,715 shares of Common Stock held by EJM 2012 Trust. Mr. Mailman has voting and investment power over the shares held by the Joshua Mailman Foundation. Ms. Monica Winsor, Mr. Mailman's spouse, is the sole trustee of the EJM 2021 Trust and has voting and investment power over the shares held by the EJM 2021 Trust. The address of Mr. Mailman and Ms. Winsor are c/o Citrin Cooperman, 50 Rockefeller Plaza, New York, NY 10020.

- (2) As reported on Schedule 13G filed on January 11, 2022. The address for the reporting person is 208 Ponce de Leon Ave Ste 1600, San Juan, Puerto Rico 00918.
- (3) Represents (i) 7,978 shares of Common Stock (ii) 512,744 shares of Common Stock issuable to Ms. Conte under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022, (iii) 45,000 shares of RSUs that are exercisable, and (iv) Bridge Warrants exercisable in 12,500 shares of Common Stock. The weighted average exercise price of the 512,744 stock options is \$14.62.
- (4) Represents (i) 2 shares of Common Stock, (ii) 167,080 shares of Common Stock issuable to Dr. King under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022, and (iii) 13,133 shares of RSUs that are exercisable. The weighted average exercise price of the 167,080 stock options is \$15.13.
- (5) Represents (i) 130,372 shares of Common Stock issuable to Mr. Wolin under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022 and (ii) 6,666 shares of RSUs that are exercisable. The weighted average exercise price of the 130,372 stock options is \$5.02.
- (6) Represents (i) 71,805 shares of Common Stock issuable to Mr. Wendt under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022, and (ii) 6,666 shares of RSUs. The weighted average exercise price of the 71,805 stock options is \$3.48.
- (7) Represents (i) 60,632 shares of Common Stock, (ii) 108,678 shares of Common Stock issuable to Mr. Bochnowski under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022, (iii) 13,133 shares of RSUs that are exercisable, and (iii) Series 1, Series 2, and Bridge Warrants exercisable into 193,303 shares of Common Stock. The weighted average exercise price of the 108,678 stock options is \$19.33.
- (8) Represents (i) 4,425 shares of Common Stock, (ii) 105,589 shares of Common Stock issuable to Mr. Siegel under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022, (iii) 12,133 shares of RSUs that are exercisable, and (iii) Series 1, Series 2, and Bridge Warrants exercisable into 13,678 shares of Common Stock. The weighted average exercise price of the 10,589 stock options is \$7.12.
- (9) Represents (i) 72,323 shares of Common Stock issuable to Mr. Micek under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022 and (ii) 12,133 shares of RSUs that are exercisable. The weighted average exercise price of the 72,323 stock options is \$15.77.
- (10) Represents (i) 71,906 shares of Common Stock issuable to Mr. Divis under stock options that are exercisable or will become exercisable in the 60 days subsequent to April 25, 2022 and (ii) 12,133 shares of RSUs that are exercisable. The weighted average exercise price of the 70,323 stock options is \$6.28.
- (11) See footnotes (3 – 10).

PROPOSAL 1 — ELECTION OF DIRECTORS

Nominee

Our Board of Directors currently consists of five (5) members, James J. Bochnowski, Lisa A. Conte, Greg J. Divis, John Micek III and Jonathan B. Siegel, who are divided into three classes with staggered three-year terms. The Board has nominated James J. Bochnowski, Lisa A. Conte and Jonathan B. Siegel for re-election as Class I directors. If elected as a Class I director at the Annual Meeting, each of the nominees will serve and hold office for a three-year term expiring at the 2025 Annual Meeting of Stockholders and until his/her successor has been duly elected and qualified.

Each of the nominees has consented to continue his/her service as a director if elected. If any of the nominees should be unavailable to serve for any reason (which is not anticipated), the Board of Directors may designate a substitute nominee or nominees (in which event the persons named on the enclosed proxy card will vote the shares represented by all valid proxy cards for the election of such substitute nominee or nominees), allow the vacancy or vacancies to remain open until a suitable candidate or candidates are located, or by resolution provide for a lesser number of directors or fill the position(s). All of the nominees for director are, at present, directors of Jaguar and have been nominated by our Nominating and Corporate Governance Committee and ratified by our full Board.

Vote Required

The vote required to approve Proposal 1 is the plurality of the votes cast by the holders of shares of Common Stock represented and entitled to vote at the Annual Meeting, provided a quorum is present. As a result, in accordance with Delaware law, votes that are withheld will be counted in determining whether a quorum is present but will have no other effect on the election of directors. Stockholders have no right to cumulative voting as to any matter, including the election of directors.

The Board of Directors unanimously recommends that the stockholders vote “FOR” Proposal No. 1 to elect James J. Bochnowski, Lisa A. Conte and Jonathan B. Siegel as Class I directors.

Information Regarding the Board of Directors and Director Nominees

The following table lists our directors and proposed director nominee, their respective ages and positions as of April 11, 2022:

Name	Age	Position
James J. Bochnowski ⁽¹⁾⁽²⁾⁽³⁾	78	Chairman of the Board (Class I)
Lisa A. Conte	63	Chief Executive Officer, President and Director (Class I)
Greg J. Divis	55	Director (Class III)
John Micek III ⁽¹⁾⁽³⁾	69	Director (Class II)
Jonathan B. Siegel ⁽¹⁾⁽²⁾	48	Director (Class I)

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- (1) Member of the audit committee.
 - (2) Member of the compensation committee.
 - (3) Member of the nominating committee.

James J. Bochnowski. Mr. Bochnowski has served as a member of our board of directors since February 2014 and as Chairperson of our board since June 2014. He also serves as a member of the board of directors of our wholly-owned subsidiary, Napo Pharmaceuticals, Inc. (“Napo”), since February 2014. Since 1988, Mr. Bochnowski has served as the founder and Managing Member of Delphi Ventures, a venture capital firm. In 1980, Mr. Bochnowski co-founded Technology Venture Investors. Mr. Bochnowski holds an M.B.A. from Harvard University Graduate School of Business and a B.S. in Aeronautics and Astronautics from Massachusetts Institute of Technology.

We believe Mr. Bochnowski is qualified to serve on our board of directors due to his significant experience with venture capital backed healthcare companies and experience as both an executive officer and member of the board of directors of numerous companies.

Lisa A. Conte. Ms. Conte has served as our President, Chief Executive Officer and a member of our board of directors since she founded the Company in June 2013. Ms. Conte also serves as the Chief Executive Officer and a member of the board of Napo since she founded Napo in November 2001 and a member of the board of our majority owned subsidiary Napo Therapeutics, S.p.A. (f/k/a Napo EU S.p.A.) (“Napo Therapeutics”) since its inception in March 2021. In 1989, Ms. Conte founded Shaman Pharmaceuticals, Inc., a natural product pharmaceutical company. Ms. Conte is also currently a member of the board of directors of Healing Forest Conservatory, a California not-for-profit public benefit corporation, and serves on the Editorial Advisory Board of *Life Science Leader* magazine. Ms. Conte holds an M.S. in Physiology and Pharmacology from the University of California, San Diego, and an M.B.A. and A.B. in Biochemistry from Dartmouth College.

We believe Ms. Conte is qualified to serve on our board of directors due to her extensive knowledge of our Company and experience with our product and product candidates, as well as her experience managing and raising capital for public and private companies.

Greg J. Divis. Mr. Divis has served as a member of our board of directors and the board of directors of Napo since June 2018. Mr. Divis currently serves as the Chief Executive Officer of Avadel Pharmaceuticals plc (“Avadel”), an emerging bio-pharmaceutical company he joined in 2017. He served as a Chief Operating Officer at Avadel from January 2017 through December 2018. He served as a board member at Tolero Pharmaceuticals, Inc., a privately held oncology development company, from May 2015 until its sale to Dainippon Sumitomo in June 2017. Prior to Avadel he served as an Operating Partner for Linden Capital Partners, a healthcare-focused middle market private equity firm. Previous roles also include President and Chief Executive Officer of Lumara Health, Inc., a specialty-branded pharmaceutical company focused on women’s health, where Mr. Divis led the successful turnaround and transformation of the business resulting in a series of transactions culminating in the successful sale to AMAG Pharmaceuticals, Inc. Mr. Divis has also held such notable roles as Vice President, Business Development & Lifecycle Management at Sanofi-Aventis, and Vice-President and General Manager, UK and Ireland, for Schering-Plough Corporation. He currently serves on the board of directors of Avadel Pharmaceuticals and previously served on the board of directors of Tolero Pharmaceuticals. Mr. Divis is a graduate of the University of Iowa.

We believe Greg J. Divis is qualified to serve on our board of directors due to his extensive experience in the pharmaceutical industry and experience as both an executive officer and member of the board of directors of other companies.

John Micek III. Mr. Micek has served as a member of our board of directors and the board of directors of Napo since April 2016 and a member of the board of directors of Napo Therapeutics since March 2021. From 2000 to 2010, Mr. Micek was managing director of Silicon Prairie Partners, LP, a Palo Alto, California based family-owned venture fund. Since 2010, Mr. Micek has been managing partner of Verdant Ventures, a merchant bank dedicated to sourcing and funding university and corporate laboratory spinouts in areas including pharmaceuticals and cleantech. Mr. Micek serves on the board of directors of Armanino Foods of Distinction, Innovare Corporation and JAL/Universal Assurors. He is also a board member and the Chief Executive Officer and Chief Financial Officer of Enova Systems and from March 2014 to August 2015 he served as interim Chief Financial Officer for Smith Electric Vehicles, Inc. Mr. Micek is a cum laude graduate of Santa Clara University and the University of San Francisco School of Law, and is a practicing California attorney specializing in financial services.

We believe Mr. Micek is qualified to serve on our board of directors due to his many years of executive experience in management and on boards of director of other companies.

Jonathan B. Siegel. Mr. Siegel has served as a member of our board of directors since March 2018 and the board of directors of Napo since March 2018 and a member of the board of directors of Napo Therapeutics since March 2021. Mr. Siegel has served as the Chief Executive Officer of JBS Healthcare Ventures, which pursues investments in public and private healthcare entities, since he founded the company in 2017. In June 2021, he also assumed the role of CEO and Chairman of the board of OPY Acquisition

Corp. I, a public Nasdaq-listed company. From 2011 until 2017, he was a partner and healthcare sector head at Kingdon Capital Management. Prior to joining Kingdon, Mr. Siegel was a healthcare portfolio manager at SAC Capital Advisors from 2005 until 2011; an associate director of pharmaceutical and specialty pharmaceutical research at Bear, Stearns & Co.; a pharmaceuticals research associate at Dresdner Kleinwort Wasserstein; and a consultant in the Life Sciences Division of Computer Sciences Corporation. Mr. Siegel worked as a research associate at the Novartis Center for Immunobiology at Harvard Medical School and as a research assistant at Tufts University School of Medicine. He is also a director at Sol-Gel Technologies Ltd, a Nasdaq-listed company, and has served on the board of advisors of Vitalis LLC, a private pharmaceutical company, since March 2019. Previously he served on the Board of Directors of Lumara Health. Mr. Siegel received a BS in Psychology from Tufts University in 1995 and an MBA from Columbia Business School in 1999.

We believe Mr. Siegel is qualified to serve on our board of directors due to his extensive experience in the pharmaceutical investment sector.

There are no family relationships among any of our executive officers or among any of our executive officers and our directors. There is no arrangement or understanding between any director and any other person pursuant to which the director was selected except to the extent provided in our Certificate of Designation.

See “Corporate Governance” and “Compensation of Directors and Executive Officers” below for additional information regarding the Board of Directors.

PROPOSAL 2 — RATIFICATION OF APPOINTMENT OF THE INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Audit Committee has appointed RBSM LLP (“RBSM”) as our independent registered public accounting firm for the fiscal year ending December 31, 2022, and the Board of Directors is asking stockholders to ratify that selection. Representatives of RBSM are expected to attend the Annual Meeting in order to respond to questions from stockholders and will have the opportunity to make a statement. RBSM has served as our independent registered public accounting firm since November 22, 2021.

Independent Registered Public Accounting Firm Services and Fees

Current Principal Accountant Fees and Services

RBSM served as our independent registered public accounting firm for the fiscal year ended December 31, 2021. There were no fees paid by us to RBSM in 2021 for audit and other services rendered.

Former Principal Accountant Fees and Services

On November 17, 2021, Mayer Hoffman McCann P.C. (“MHM”) notified us of its decision to resign as the Company’s independent registered public accounting firm, which became effective on November 22, 2021 upon our appointment of RBSM as the Company’s new independent registered public accounting firm. The reports of MHM on our consolidated financial statements for the fiscal years ended December 31, 2020 and 2019 contained explanatory paragraphs regarding our ability to continue as a going concern and contained no adverse opinion or disclaimer of opinion and were not qualified or modified as to uncertainty, audit scope or accounting principles. During the fiscal years ended December 31, 2020 and 2019, and in the subsequent interim period through November 17, 2021, there were no disagreements with MHM on any matters of accounting principles or practices, financial statement disclosure or auditing scope and procedure. Substantially all of MHM’s personnel who work under the control of MHM shareholders are employees of wholly-owned subsidiaries of CBIZ, Inc., which provide personnel and various services to MHM in an alternative practice structure.

MHM served as our independent registered public accounting firm for the fiscal year ended December 31, 2020 and for the nine months ended September 30, 2021. The following table represents the aggregate fees billed to us by MHM in 2021 and 2020 for audit and other services rendered:

	Years ended December 31,	
	2021	2020
Audit Fees	\$943,122	\$641,178
Audit Related Fees	—	—
Tax Fees	—	—
All Other Fees	—	100,000
Total	<u>\$943,122</u>	<u>\$741,178</u>

Fees referenced in the table above include fees for our follow-on public offering, auditor transition fees, as well as services provided in connection with the issuance of consents for other SEC filings.

Policy on Audit Committee Preapproval of Audit and Permissible Non-Audit Services of the Independent Registered Public Accounting Firm

As specified in the Audit Committee charter, the Audit Committee pre-approves all audit and non-audit services provided by the independent registered public accounting firm prior to the receipt of such services. Thus, the Audit Committee approved 100% of the services set forth in the above table prior to the receipt of such services and no services were provided under the permitted de minimis threshold provisions.

The Audit Committee determined that the provision of such services was compatible with the maintenance of the independence of RBSM and MHM.

Vote Required

The vote required to approve Proposal 2 is the affirmative vote of the holders of a majority of votes cast by holders of shares of our Common Stock present in person or represented by proxy at the Annual Meeting, provided a quorum is present. As a result, abstentions will be considered in determining whether a quorum is present but will have no effect on the vote for Proposal 2.

The Board of Directors unanimously recommends that the stockholders vote “FOR” Proposal No. 2 to ratify the appointment of RBSM LLP as the Company’s independent registered public accounting firm for the fiscal year ending December 31, 2022.

PROPOSAL 3 — APPROVAL OF THE ISSUANCE OF SHARES OF COMMON STOCK UPON EXCHANGE OF CERTAIN ROYALTY INTERESTS AND SECURED PROMISSORY NOTE

At the Annual Meeting, stockholders will be asked to approve, for purposes of Nasdaq Rule 5635(d), the issuance of shares of Common Stock upon exchange, from time to time at Company’s discretion, of all or any portion of certain royalty interests and a promissory note previously issued by the Company to certain accredited investors. All per share dollar figures included in this Proposal 3 are subject to adjustment for stock splits, stock dividends, reclassifications and other similar recapitalization transactions.

Background

Royalty Financings

Between October 2020 and March 2021, the Company entered into royalty interest purchase agreements with certain accredited investors affiliated with one another (collectively, the “Royalty Investors”), pursuant to which the Company sold the royalty interests (collectively, the “Royalty Interests”) entitling the Royalty Investors to receive future royalties on sales of certain of the Company’s products and certain up-front license fees and milestone payments from licensees and/or distributors (the “Royalty Repayment Amounts” and the amount payable under any individual Royalty Interest, the “Royalty Repayment Amount”) in private placement transactions in reliance upon the exemption from securities registration under by Section 4(a)(2) of the Securities Act of 1933, as amended (the “Securities Act”). The Company used the proceeds to support advancement of research activities associated with its pipeline, including the Company’s lead product candidate, crofelemer, for cancer therapy-related diarrhea, and general corporate purposes. Interest accrues on the Royalty Repayment Amounts at a rate ranging between 5% and 10% per annum. The Company is obligated to make minimum royalty payments on a monthly basis beginning on a specified date (the “Minimum Royalty Payment Start Date”). The key terms of the Royalty Interests are summarized below:

	<u>October 2020 Royalty Interest</u>	<u>December 2020 Royalty Interest</u>	<u>March 2021 Royalty Interest</u>
Issuance Date	October 8, 2020	December 22, 2020	March 8, 2021
Royalty Repayment Amount as of March 31, 2022	\$13.4 million ⁽¹⁾	\$14.3 million	\$10.8 million
Interest Rate	10% per annum, compounding quarterly	10% per annum, compounding daily	5% per annum from March 8, 2021 until March 8, 2022 and 10% per annum thereafter, compounding quarterly
Minimum Royalty Payment Start Date	May 10, 2021	Earlier of (i) December 29, 2022 and (ii) 30 days following the full satisfaction of the October 2020 Royalty Interest, but in no event less than 18 months from December 23, 2020	Earlier of (i) March 8, 2024 and (ii) 30 days following the full satisfaction of both the October 2020 Royalty Interest and the December 2020 Royalty Interest, but in no event less than 18 months from March 8, 2021

	<u>October 2020 Royalty Interest</u>	<u>December 2020 Royalty Interest</u>	<u>March 2021 Royalty Interest</u>
Monthly Minimum Royalty Payment Amount	The greater of (i) \$250,000 (which increases to \$400,000 beginning on October 9, 2021, \$600,000 beginning on April 9, 2022, and \$750,000 beginning on October 9, 2022) and (ii) 10% of the Company’s net sales of Mytesi and 10% of worldwide revenues related to upfront licensing fees and milestone payments from licensees and/or distributors	The greater of (i) \$750,000 and (ii) 10% of the Company’s net sales of Mytesi and 10% of worldwide revenues related to upfront licensing fees and milestone payments from licensees and/or distributors	The greater of (A) \$250,000 (which increases to \$400,000 beginning September 8, 2021, \$600,000 beginning March 8, 2022, and \$750,000 beginning September 8, 2022) and (B) the royalty payments to which the Royalty Investor is entitled, consisting of (1) 10% of the Company’s net sales of crofelemer for the COVID-related indication (including any improvements, modifications and follow-on products, collectively, the “Included Products”), (2) 10% of worldwide revenues related to upfront licensing fees and milestone payments from licensees and/or distributors and (3) 50% of royalties collected from licenses of the Included Products to third parties.

(1) Pursuant to the terms of the October 2020 Royalty Interest, the Royalty Repayment Amount for the October 2020 Royalty Interest was automatically increased from \$12 million to \$18 million on May 1, 2021 as a result of the volume weighted average price of the Company’s common stock not equaling or exceeding \$0.9105 at least twice during each calendar month during the six-month period beginning on November 1, 2020.

Between February 11, 2022 and March 9, 2022, the Company entered into privately negotiated exchange agreements with the holder of the October 2020 Royalty Interest, pursuant to which the Company issued 8,650,000 shares of Common Stock in the aggregate at an effective price per share equal to the market price (defined as the Minimum Price under Nasdaq Listing Rule 5635(d)) as of the date of the applicable exchange agreement in exchange for a \$4,441,657.50 reduction in the outstanding balance of the October 2020 Royalty Interest. As a result of such exchange transactions, the Company is fully paid up on its monthly minimum royalty payments with respect to the Royalty Interests until mid-October 2022.

The foregoing descriptions of the Royalty Interests and royalty interests purchase agreement are not complete and are qualified in their entirety by reference to the Royalty Interests and royalty interest purchase agreements, respectively, which are filed as exhibits to our Current Reports on Form 8-K filed with the SEC on October 9, 2020, December 29, 2020 and March 11, 2021.

Note Financing

On January 19, 2021, the Company and Napo Pharmaceuticals, Inc., a wholly-owned subsidiary of Jaguar (“Napo” and, together with Jaguar, the “Borrower”), entered into a note purchase agreement (the “Note Purchase Agreement”) with an accredited investor (“Note Investor”), pursuant to which the Borrower

issued to Note Investor a secured promissory note (the “Note”) in the aggregate principal amount of \$6,220,812.50 (the “Note Offering”) in a private placement transaction in reliance upon the exemption from securities registration under by Section 4(a)(2) of the Securities Act. The Company used the proceeds to fund development of the Company’s NP-300 (lechlemer) drug product candidate for the indication of the symptomatic relief of diarrhea from cholera (the “Cholera Indication”) and general corporate purposes, including the Company’s product pipeline activities. The Note bears interest at 3.25% per annum and matures on January 20, 2025. Interest is prepaid each 12 months at the beginning of the period. The Note is secured by a first priority security interest in all existing and future lechlemer technology, and Napo has agreed, with certain exceptions, not to grant any lien on any of the collateral securing the Note and not to grant any license under any of the intellectual property relating to such collateral.

Under the Note Purchase Agreement, if a tropical disease priority review voucher (“TDPRV”) is granted to the Company by the U.S. Food & Drug Administration in connection with the Company’s development of lechlemer for the Cholera Indication and the Company sells the TDPRV, then Note Investor will be entitled to a specified percentage of the gross proceeds from such sale, ranging from 18% to 1%, depending on the percentage of the original balance of the Note that remains outstanding as of the date of the sale of the TDPRV, which percentage will decrease to 1% once the Note is paid in full.

In addition, beginning on the earlier of (i) July 19, 2021 and (ii) the initiation of human clinical trials with lechlemer, (the “Optional Prepayment Period”), the Company will have the right, from time to time at in its sole discretion, to prepay all or any portion of the Note (such amount, the “Principal Prepayment Amount”) at a price equal to 112.5% multiplied by the Principal Prepayment Amount (the “Optional Prepayment Amount”). Beginning on the date that the last patient is enrolled in a pivotal trial with lechlemer for the Cholera Indication, the Company must receive Note Investor approval before prepaying the Note.

The foregoing descriptions of the Note and Note Purchase Agreement are not complete and are qualified in their entirety by reference to the Note and Note Purchase Agreement, respectively, which are filed as exhibits to our Current Report on Form 8-K filed with the SEC on January 22, 2021.

Global Amendments

On April 14, 2022, the Company entered into amendments with the Royalty Investors (collectively, the “Royalty Interest Global Amendments”), pursuant to which the Company was granted the right to exchange from time to time at the Company’s sole discretion all or any portion of the Royalty Interests for shares of the Company’s common stock at a price per share equal to the Nasdaq Minimum Price (as defined in Nasdaq Listing Rule 5635(d)) as of the date of the applicable exchange (the “Exchange Price”).

On April 14, 2022, the Borrower entered into an amendment to the Note (the “Note Global Amendment”), pursuant to which the Borrower was granted the right to exchange from time to time at the Company’s sole discretion all or any portion of the Note for shares of the Company’s common stock at a price per share equal to the Exchange Price.

Under the applicable rules of The Nasdaq Stock Market LLC (“Nasdaq”), in no event may the Company issue any shares of Common Stock upon exchange of the Royalty Interests or Note or otherwise pursuant to the terms of the Royalty Interests or Note if the issuance of such shares of Common Stock would exceed the requirements of The Nasdaq Capital Market (including the rules related to the aggregate of offerings under Nasdaq Listing Rule 5635(d) if applicable) (the “Exchange Cap”), unless the Company obtains stockholder approval to issue shares of Common Stock in excess of the Exchange Cap.

The foregoing descriptions of the Royalty Interest Global Amendments and the Note Global Amendment are not complete and are qualified in their entirety by the copies of the Royalty Interest Global Amendments and the Note Global Amendment attached as [Appendix A](#) and [Appendix B](#), respectively, to this proxy statement, the Company’s Current Report on Form 8-K filed on April 15, 2022 and the transaction documents filed as exhibits to such report.

Stockholder Approval Requirements

Pursuant to Nasdaq Listing Rule 5635(d), stockholder approval is required prior to a 20% Issuance at a price that is less than the Minimum Price. For purposes of Nasdaq Listing Rule 5635(d), (A) “20% Issuance” means a transaction, other than a public offering, involving: (i) the sale, issuance or potential issuance by

us of Common Stock (or securities convertible into or exercisable for Common Stock), which alone or together with sales by our officers, directors or substantial stockholders equals 20% or more of Common Stock (which for purposes of this calculation, includes issued and outstanding shares of our voting Common Stock and non-voting common stock) or 20% or more of the voting power outstanding before the issuance and (B) “Minimum Price” means a price that is the lower of: (i) the closing price (as reflected on Nasdaq.com) immediately preceding the signing of the binding agreement; or (ii) the average closing price of Common Stock (as reflected on Nasdaq.com) for the five trading days immediately preceding the signing of the binding agreement. Stockholder approval of this proposal will constitute stockholder approval for purposes of Nasdaq Listing Rule 5635(d).

The issuance of shares of Common Stock to Note Investor upon the exchange of the Note, together with the issuance of shares of Common Stock to Investors upon the exchange of the Royalty Interests, could result in the issuance of shares of Common Stock to the Investors that represents more than 20% of our Common Stock or 20% of the voting power outstanding prior to the issuance of the Note and the Royalty Interests.

On April 14, 2022, there were 77,858,506 shares of our Common Stock issued and outstanding. Accordingly, our issuance of more than 15,563,915 shares under the Note and the Royalty Interests requires the approval of our stockholders under Nasdaq Listing Rules 5635(d), assuming that the Note and the Royalty Interests transactions are integrated for purposes of the Nasdaq rules.

As a result, in order to enhance the Company’s overall capitalization and retain maximum flexibility to repay the Royalty Interests and Note in shares of Common Stock, we are seeking stockholder approval pursuant to Nasdaq Listing Rule 5635(d) for the issuance to the Investors of shares of Common Stock, from time to time at the Company’s discretion upon exchange of the Note and the Royalty Interests at the Exchange Price. If this proposal is approved, we will not solicit further authorization from our stockholders prior to any exchange of the Note or Royalty Interests pursuant to the terms thereof.

Impact of Stockholder Approval

If stockholders do not approve this proposal, shares of our Common Stock may not be issued in exchange transactions with the Royalty Investors and the Note Investor with respect to the Royalty Interests and the Note, respectively, in excess of the Exchange Cap, unless and until stockholder approval of this proposal is obtained.

Dilution and Potential Adverse Impact of this Proposal

The exchange of all or any portion of the Royalty Interests and the Note for shares of our Common Stock will have a dilutive effect on our current stockholders in that the percentage ownership of the Company held by our current stockholders would decline as a result of the issuance of additional shares of our Common Stock upon exchange of the Royalty Interests and the Note. As a result, our current stockholders would own a smaller proportionate interest in the Company and therefore have less ability to influence corporate decisions requiring stockholder approval. The issuance of shares of our Common Stock upon exchange of the Royalty Interests and the Note could also have a dilutive effect on our book value per share and on any future earnings per share, and the sale or any resale of such shares could cause prevailing market prices for our Common Stock to decline.

Because of the effective share price for any future exchange would be the Exchange Price as of the time of such exchange, the exact magnitude of the dilutive effect of future exchange transactions cannot be conclusively determined but may be material to our current stockholders. By way of example, based on an assumed effective Exchange Price of \$0.71 per share (the closing price on March 31, 2022) (the “Assumed Exchange Price”), and assuming that the full \$38.5 million aggregate outstanding amount of the Royalty Interests as of March 31, 2022 and full \$6.6 million outstanding amount of the Note as of March 31, 2022 is exchanged for shares, up to a maximum of 63,498,126 shares of our Common Stock would be issuable upon exchange of the Royalty Interests and the Note (without giving effect to any interest accrued beyond March 31, 2022). Based on the shares of our common stock outstanding as of March 31, 2022, the shares issued upon exchange of the Royalty Interests and the Note in full would represent approximately 45.2% of our outstanding Common Stock (after giving effect to such exchanges). The exchange price in connection

with future exchanges could be materially lower than the Assumed Exchange Price, which could have a significant dilutive effect on our current stockholders.

For illustration purposes only, below is a table showing the number of shares of Common Stock that may potentially be issued upon exchange of the outstanding balance of the Royalty Interests and the Note based on three hypothetical exchange prices, assuming that all \$38.5 million outstanding amount of Royalty Interests and all \$6.6 million outstanding amount of the Note is exchanged into shares. The number of shares issuable will correspondingly increase or decrease depending on the actual exchange price for the Royalty Interests and the Note.

	Scenario A*	Scenario B	Scenario C
Hypothetical Exchange Price	\$ 0.62	\$ 0.71	\$ 0.85
Hypothetical Aggregate Outstanding Amount of Royalty Interests	\$38,515,788	\$38,515,788	\$38,515,788
Hypothetical Aggregate Outstanding Amount of Note	\$ 6,567,882	\$ 6,567,882	\$ 6,567,882
Total Hypothetical Aggregate Outstanding Amount of Royalty Interests and Note	<u>\$45,083,670</u>	<u>\$45,083,670</u>	<u>\$45,083,670</u>
Total Number of Shares Issued Upon Full Exchange of Royalty Interests and Note	<u>72,715,596</u>	<u>63,498,126</u>	<u>53,039,611</u>

* More authorized shares would be needed to fully repay all the royalty interests and note in shares under Scenario A at a hypothetical exchange price of \$0.62 per share.

In addition, the exchange of all or any portion of the Royalty Interests and the Note for shares of our Common Stock may result in our having insufficient authorized capital stock to issue common stock to all of the holders of outstanding stock options, RSUs and warrants and we will have to seek stockholder approval to authorize additional shares of common stock in connection with the exercise of such outstanding securities or any future equity financing transactions. Our COI authorizes us to issue up to 150,000,000 shares of Common Stock, of which 77,863,506 shares were issued and outstanding as of April 25, 2022 and 6,953,014 of which are reserved for issuance upon exercise of options, warrants, vesting of RSUs. If all of our outstanding stock options and warrants were exercised and RSUs were to vest, the total number of shares of our Common Stock that we issue in connection with the exchange of the Royalty Interests and the Note may, depending on the Exchange Price, exceed the number of our remaining authorized but unissued shares of Common Stock. We cannot assure you that our stockholders will authorize an increase in the number of shares of our Common Stock in the future to the extent required. Our failure to have a sufficient number of authorized shares of Common Stock for issuance upon future exchange of our Royalty Interests and the Note, upon future exercise of our stock options and warrants or upon future vesting of RSUs could result in a breach under such securities, which could adversely affect our business, financial condition, results of operations and prospects.

Required Vote of Stockholders

To approve the issuance of shares of common stock upon the exchange of all or a portion of the Royalty Interests and the Note from time to time at the Company’s sole discretion (this Proposal 3), the affirmative vote of the holders of a majority of shares of votes cast, in person or by remote communication, if applicable, or represented by proxy at the Annual Meeting, voting together as a single class and entitled to vote, is required. Although failure to submit a proxy or vote in person at the Annual Meeting, or a failure to provide your broker, nominee, fiduciary or other custodian, as applicable, with instructions on how to vote your shares will not affect the outcome of the vote on this proposal, the failure to submit a proxy or vote in person at the Annual Meeting will make it more difficult to meet the requirement under the Bylaws that the holders of 1/3 of our capital stock issued and outstanding and entitled to vote at the Annual Meeting be present in person or represented by proxy to constitute a quorum at the Annual Meeting.

The board of directors unanimously recommends that the stockholders vote “FOR” Proposal No. 3 to authorize the issue, pursuant to Nasdaq Listing Rule 5635(d), shares of common stock upon exchange of certain royalty interests and promissory note previously issued pursuant to the terms of such royalty interests and promissory note.

PROPOSAL 4 — GRANT OF DISCRETIONARY AUTHORITY TO ADJOURN THE ANNUAL MEETING IF NECESSARY TO SOLICIT ADDITIONAL PROXIES

Although it is not expected, the Annual Meeting may be adjourned for the purpose of soliciting additional proxies. Any such adjournment of the Annual Meeting may be made without notice, other than by the announcement made at the Annual Meeting, by approval of the holders of a majority of the outstanding shares of our Common Stock, present in person or represented by proxy and entitled to vote at the Annual Meeting. We are soliciting proxies to grant discretionary authority to the chairperson of the Annual Meeting to adjourn the Annual Meeting, if necessary, for the purpose of soliciting additional proxies in favor of Proposal 3. The chairperson will have the discretion to decide whether or not to use the authority granted to such person pursuant to this Proposal 3 to adjourn the Annual Meeting.

Required Vote of Stockholders

To approve the grant of discretionary authority to the chairperson of the Annual Meeting to adjourn the Annual Meeting, if necessary, for the purpose of soliciting additional proxies in favor of Proposal 3, the affirmative vote of the holders of a majority of votes cast by shares of our Common Stock present in person or represented by proxy at the Annual Meeting and entitled to vote is required. Although failure to submit a proxy or vote in person at the Annual Meeting, or a failure to provide your broker, nominee, fiduciary or other custodian, as applicable, with instructions on how to vote your shares will not affect the outcome of the vote on this proposal, the failure to submit a proxy or vote in person at the Annual Meeting will make it more difficult to meet the requirement under the Bylaws that the holders of 1/3 of our capital stock issued and outstanding and entitled to vote at the Annual Meeting be present in person or by proxy to constitute a quorum at the Annual Meeting.

The Board of Directors unanimously recommends that the stockholders vote “FOR” Proposal 4 to grant discretionary authority to adjourn the Annual Meeting, if necessary, to solicit additional proxies in favor of Proposal 3.

CORPORATE GOVERNANCE

Director Independence

Our Common Stock is listed on The Nasdaq Capital Market. Under Nasdaq rules, independent directors must comprise a majority of a listed company's board of directors. In addition, Nasdaq rules require that, subject to specified exceptions, each member of a listed company's Audit, Compensation and Nominating Committee must be independent. Audit Committee members must also satisfy the independence criteria set forth in Rule 10A-3 under the Exchange Act. Under Nasdaq rules, a director will only qualify as an "independent director" if, in the opinion of the company's board of directors, such person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director.

To be considered independent for purposes of Rule 10A-3, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, our board of directors, or any other board committee (1) accept, directly or indirectly, any consulting, advisory, or other compensatory fee from the listed company or any of its subsidiaries or (2) be an affiliated person of the listed company or any of its subsidiaries.

Our board of directors periodically undertakes a review of its composition, the composition of its committees and the independence of our directors and considered whether any director has a material relationship with us that could compromise his or her ability to exercise independent judgment in carrying out his or her responsibilities. Based upon information requested from and provided by each director concerning his or her background, employment and affiliations, including family relationships, our board of directors has determined that four of our five directors (i.e., Mr. Bochnowski, Mr. Micek, Mr. Siegel and Mr. Divis) do not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director and that each of these directors is "independent" as that term is defined under the Nasdaq rules. Our board of directors also determined that Mr. Micek (chairperson), Mr. Bochnowski and Mr. Siegel, who comprise our Audit Committee, Mr. Bochnowski (chairperson) and Mr. Siegel, who comprise our Compensation Committee, and Mr. Bochnowski and Mr. Micek, who comprised our Nominating Committee, satisfy the independence standards for those committees established by applicable SEC rules and the Nasdaq rules and listing standards.

In making this determination, our board of directors considered the relationships that each non-employee director has with us and all other facts and circumstances our board of directors deemed relevant in determining independence, including the beneficial ownership of our capital stock by each non-employee director.

MEETINGS AND COMMITTEES OF THE BOARD OF DIRECTORS

Audit Committee

The members of our Audit Committee are Mr. Micek, Mr. Bochnowski, and Mr. Siegel. Mr. Micek is the chairperson of the Audit Committee. Our Audit Committee's responsibilities include:

- appointing, approving the compensation of, and assessing the independence of our registered public accounting firm;
- overseeing the work of our independent registered public accounting firm, including through the receipt and consideration of reports from that firm;
- reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements and related disclosures;
- monitoring our internal control over financial reporting, disclosure controls and procedures and code of conduct;
- discussing our risk management policies;
- establishing policies regarding hiring employees from our independent registered public accounting firm and procedures for the receipt and retention of accounting related complaints and concerns;
- reviewing and approving or ratifying any related person transactions; and
- preparing the Audit Committee report required by SEC rules.

All audit and non-audit services, other than *de minimis* non-audit services, to be provided to us by our independent registered public accounting firm must be approved in advance by our Audit Committee.

Our board of directors has determined that each of Mr. Micek, Mr. Bochnowski, and Mr. Siegel is an independent director under Nasdaq rules and under Rule 10A-3. All members of our Audit Committee meet the requirements for financial literacy under the applicable rules and regulations of the SEC and Nasdaq. Our board of directors has determined that Mr. Micek is an "audit committee financial expert," as defined by applicable SEC rules, and has the requisite financial sophistication as defined under the applicable Nasdaq rules and regulations.

The Audit Committee held four meetings in 2021. The audit committee has adopted a written charter approved by our board of directors, which is available on our website at: <https://jaguarhealth.gcs-web.com/static-files/aeabd726-16c2-4219-a755-475e9c87b851>.

Compensation Committee

The members of our Compensation Committee are Mr. Bochnowski (chairperson) and Mr. Siegel. Mr. Bochnowski is the chairperson of the Compensation Committee. Our Compensation Committee's responsibilities include:

- determining, or making recommendations to our board of directors with respect to, the compensation of our Chief Executive Officer;
- determining, or making recommendations to our board of directors with respect to, the compensation of our other executive officers;
- overseeing and administering our cash and equity incentive plans;
- reviewing and making recommendations to our board of directors with respect to director compensation; and
- preparing the Compensation Committee report and necessary disclosure in our annual proxy statement in accordance with applicable SEC rules.

To determine compensation, the Compensation Committee, with input from the Chief Executive Officer (who does not participate in the deliberations regarding her own compensation), reviews, at least

annually, and makes recommendations to the board of directors about appropriate compensation levels for each executive officer of the Company. The Compensation Committee considers all factors it deems relevant in setting executive compensation.

Our board has determined that each of Mr. Bochnowski (chairperson) and Mr. Siegel is independent under the applicable Nasdaq rules and regulations, is a “non-employee director” as defined in Rule 16b-3 promulgated under the Exchange Act, and is an “outside director” as that term is defined in Section 162(m) of the Internal Revenue Code of 1986, as amended.

The Compensation Committee held 5 meetings in 2021. All compensation-related matters were approved at the board of directors’ level. The Compensation Committee has adopted a written charter approved by the board of directors, which is available on our website at: <https://jaguarhealth.gcs-web.com/static-files/653862da-1aa9-4819-b559-5c5654189e80>. Under its charter, the Compensation Committee has the authority, in its sole discretion, to select, retain and obtain the advice of a compensation consultant as necessary to assist with the execution of its duties and responsibilities as set forth in its charter but only after taking into consideration factors relevant to the compensation consultant’s independence from management specified in Nasdaq Listing Rule 5605(d)(3)(D). The Compensation Committee currently has not retained or sought advice from a compensation consultant.

Nominating Committee

The members of our Nominating Committee are Mr. Bochnowski and Mr. Micek. Our Nominating Committee’s responsibilities include:

- identifying individuals qualified to become members of our board of directors;
- evaluating qualifications of directors;
- recommending to our board of directors the persons to be nominated for election as directors and to each of the committees of our board of directors; and
- overseeing an annual evaluation of our board of directors.

The Nominating Committee did not hold any meetings in 2021. All nomination-related matters were approved at the board of directors’ level. The Nominating Committee has adopted a written charter approved by the board of directors, which is available on our website at: <https://jaguarhealth.gcs-web.com/static-files/02dfed04-9508-44cd-a96a-3215e565111c>.

Meetings and Attendance During 2021

The board of directors held 17 meetings in 2021. Each director who served as a director during 2021 participated in 75% or more of the meetings of the board of directors and of the committees on which he or she served, if any, during the year ended December 31, 2021 (during the period that such director served).

We do not have a written policy on director attendance at annual meetings of stockholders. We encourage, but do not require, our directors to attend the Annual Meeting. One director attended the 2021 Annual Meeting of Stockholders.

Code of Business Conduct and Ethics

We have adopted a Code of Business Conduct and Ethics that applies to our directors, officers and employees, including our President and Chief Executive Officer, our Chief Financial Officer and other employees who perform financial or accounting functions. The Code of Business Conduct and Ethics sets forth the basic principles that guide the business conduct of our employees. A current copy of the code is on our website at <https://jaguarhealth.gcs-web.com/corporate-governance>. We intend to disclose future amendments to certain provisions of our code of business conduct and ethics, or waivers of such provisions on our website to the extent required by applicable rules and exchange requirements. The inclusion of our website address in this proxy statement does not incorporate by reference the information on or accessible through our website into this proxy statement.

Policy Against Pledging and Hedging of the Company's Securities

Our Policy on Insider Trading and Tipping expressly prohibits directors, officers, employees and other persons determined by us to be "Insiders," including their immediate family members sharing the same household and entities over which they exercise control, from engaging in hedging transactions involving our securities (or any other financial transactions that are designed to hedge or offset any decrease in market value of our equity securities) without advance approval from the Compliance Officer. The policy similarly prohibits such individuals from holding our securities in a margin account and pledging our securities as collateral for loans without advance approval from the Compliance Officer. The policy applies to all of our securities held, excluding the exercise of options for cash under an equity plan of the Company, bona fide gifts of our securities and transactions in our securities made through an authorized Rule 10b5-1 trading plan. There were no exceptions approved by the Compliance Officer during the last fiscal year.

Compensation Committee Interlocks and Insider Participation

None of the members of our Compensation Committee has ever been an officer or employee of our Company. None of our executive officers currently serves, or in the past year has served, as a member of the board of directors or Compensation Committee or other board committee performing equivalent functions of any entity that has one or more of its executive officers serving on our board of directors or Compensation Committee.

Limitation of Liability and Indemnification

The COI and Bylaws contain provisions that limit the personal liability of our directors for monetary damages to the fullest extent permitted by Delaware law. Delaware law provides that directors of a corporation will not be personally liable to us or our stockholders for monetary damages for any breach of fiduciary duties as directors, except liability for:

- any breach of the director's duty of loyalty to us or our stockholders;
- any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the DGCL; or
- any transaction from which the director derived an improper personal benefit.

Such limitation of liability does not apply to liabilities arising under federal securities laws and does not affect the availability of equitable remedies, such as injunctive relief or rescission.

The COI provides that we indemnify our directors to the fullest extent permitted by Delaware law. In addition, the Bylaws provide that we indemnify our directors and officers to the fullest extent permitted by Delaware law. The Bylaws also provide that we shall advance expenses incurred by a director or officer in advance of the final disposition of any action or proceeding, and permit us to secure insurance on behalf of any officer, director, employee or other agent for any liability arising out of his or her actions in that capacity, regardless of whether we would otherwise be permitted to indemnify him or her under the provisions of Delaware law. We have entered and expect to continue to enter into agreements to indemnify our directors, executive officers and other employees as determined by our board of directors. With certain exceptions, these agreements provide for indemnification for related expenses including, among others, attorneys' fees, judgments, fines and settlement amounts incurred by any of these individuals in any action or proceeding. We believe that these bylaw provisions and indemnification agreements are necessary to attract and retain qualified persons as directors and officers. We also maintain directors' and officers' liability insurance.

The limitation of liability and indemnification provisions in the COI and Bylaws and our indemnification agreements, may discourage stockholders from bringing a lawsuit against our directors for breach of their fiduciary duty of care. They may also reduce the likelihood of derivative litigation against our directors and officers, even though an action, if successful, might benefit us and other stockholders. Furthermore, a stockholder's investment may be adversely affected to the extent that we pay the costs of settlement and

damage awards against directors and officers. There is no pending litigation or proceeding involving any of our directors, officers or employees for which indemnification is sought, and we are not aware of any threatened litigation that may result in claims for indemnification.

Board Leadership Structure

The Bylaws and corporate governance guidelines provide our board of directors with flexibility in its discretion to combine or separate the positions of Chairperson of the board of directors and chief executive officer. As a general policy, our board of directors believes that separation of the positions of Chairperson and chief executive officer reinforces the independence of the board of directors from management, creates an environment that encourages objective oversight of management's performance and enhances the effectiveness of the board of directors as a whole. We expect and intend the positions of Chairperson of the board and chief executive officer to be held by two individuals in the future.

Risk Oversight

Our board of directors monitors our exposure to a variety of risks through our Audit Committee. Our Audit Committee charter gives the Audit Committee responsibilities and duties that include discussing with management and the independent auditors our major financial risk exposures and the steps management has taken to monitor and control such exposures, including our risk assessment and risk management policies. Our Audit Committee is also responsible for monitoring and controlling exposures to cybersecurity risks and discussing such risks with management.

Nomination of Directors

There have been no material changes to the procedures by which stockholders may recommend nominees to our board of directors. Recommendations to the board of directors for election as directors of Jaguar at an annual meeting may be made only by the Nominating Committee or by the Company's stockholders (through the Nominating Committee) who comply with the timing, informational, and other requirements of the Bylaws. Stockholders have the right to recommend persons for nomination by submitting such recommendation, in written form, to the Nominating Committee, and such recommendation will be evaluated pursuant to the policies and procedures adopted by the board of directors. Such recommendation must be delivered to or mailed to and received by the Secretary of the Company at the principal executive offices not less than 90 days nor more than 120 calendar days prior to the first anniversary of the date the preceding year's annual meeting, except that if no annual meeting of stockholders was held in the preceding year or if the date of the annual meeting of stockholders has been changed by more than 30 calendar days from the date contemplated at the time of the preceding year's proxy statement, the notice shall be received by the Secretary at the Company's principal executive offices not less than 150 calendar days prior to the date of the contemplated annual meeting or the date that is 10 calendar days after the date of the first public announcement or other notification to stockholders of the date of the contemplated annual meeting, whichever first occurs. The deadline to submit recommendations for election as directors at the 2022 Annual Meeting has already passed.

The Nominating Committee, in accordance with the board of directors' governance principles, seeks to create a board that has the ability to contribute to the effective oversight and management of the Company, that is as a whole strong in its collective knowledge of and diversity of skills and experience with respect to accounting and finance, management and leadership, vision and strategy, business judgment, biotechnology industry knowledge, corporate governance and global markets. The Nominating Committee does not currently have a policy with regard to the consideration of diversity in identifying director nominees. When the Nominating Committee reviews a potential new candidate, the Nominating Committee looks specifically at the candidate's qualifications in light of the needs of the board of directors and the Company at that time given the then current mix of director attributes.

General criteria for the nomination and evaluation of director candidates include:

- loyalty and commitment to promoting the long-term interests of the Company's stockholders;
- the highest personal and professional ethical standards and integrity;

- an ability to provide wise, informed and thoughtful counsel to top management on a range of issues;
- a history of achievement that reflects superior standards for themselves and others;
- an ability to take tough positions in constructively challenging the Company's management while at the same time working as a team player; and
- individual backgrounds that provide a portfolio of personal and professional experience and knowledge commensurate with the needs of the Company.

The Nominating Committee must also ensure that the members of the board of directors as a group maintain the requisite qualifications under the applicable Nasdaq Stock Market listing standards for populating the Audit, Compensation and Nominating Committees.

Written recommendations from a stockholder for a director candidate must include the following information:

- the stockholder's name and address, as they appear on our corporate books;
- the class and number of shares that are beneficially owned by such stockholder;
- the dates upon which the stockholder acquired such shares; and
- documentary support for any claim of beneficial ownership.

Additionally, the recommendation needs to include, as to each person whom the stockholder proposes to recommend to the Nominating Committee for nomination to election or reelection as a director, all information relating to the person that is required pursuant to Regulation 14A under the Exchange Act, as amended, and evidence satisfactory to us that the nominee has no interests that would limit their ability to fulfill their duties of office.

Once the Nominating Committee receives a recommendation, it will deliver a questionnaire to the director candidate that requests additional information about his or her independence, qualifications and other information that would assist the Nominating Committee in evaluating the individual, as well as certain information that must be disclosed about the individual in the Company's proxy statement, if nominated. Individuals must complete and return the questionnaire within the time frame provided to be considered for nomination by the Nominating Committee.

The Nominating Committee will review the stockholder recommendations and make recommendations to the board of directors that the Committee feels are in the best interests of the Company and its stockholders.

The Nominating Committee has not received any recommendations from stockholders for the Annual Meeting.

Communications with the Board of Directors

Stockholders may contact an individual director or the board of directors as a group, or a specified board committee or group, including the non-employee directors as a group, by the following means:

Mail: Attn: Board of Directors
 Jaguar Health, Inc.
 200 Pine Street, Suite 400
 San Francisco, CA 94104

Email: AskBoard@jaguar.health

Each communication should specify the applicable addressee or addressees to be contacted as well as the general topic of the communication. We will initially receive and process communications before forwarding them to the addressee. We also may refer communications to other departments within the Company. We generally will not forward to the directors a communication that is primarily commercial in nature, relates to an improper or irrelevant topic, or requests the Company's general information.

Complaint and Investigation Procedures for Accounting, Internal Accounting Controls, Fraud or Auditing Matters

We have created procedures for confidential submission of complaints or concerns relating to accounting or auditing matters and contracted with Nasdaq to facilitate the gathering, monitoring and delivering reports on any submissions. As of the date of this report, there have been no submissions of complaints or concerns to Nasdaq. Complaints or concerns about our accounting, internal accounting controls or auditing matters may be submitted to the Audit Committee and our executive officers by contacting Nasdaq. Nasdaq provides phone, internet and e-mail access and is available 24 hours per day, seven days per week, 365 days per year. The hotline number is 1-844-417-8861 and the website is <https://www.openboard.info/jagx>. Any person may submit a written Accounting Complaint to jagx@openboard.info.

Our Audit Committee under the direction and oversight of the Audit Committee Chair will promptly review all submissions and determine the appropriate course of action. The Audit Committee Chair has the authority, in his discretion, to bring any submission immediately to the attention of other parties or persons, including the full board of directors, accountants and attorneys. The Audit Committee Chair shall determine the appropriate means of addressing the concerns or complaints and delegate that task to the appropriate member of senior management, or take such other action as it deems necessary or appropriate to address the complaint or concern, including obtaining outside counsel or other advisors to assist the Audit Committee.

EXECUTIVE OFFICERS

Our executive officers as of the date of this proxy statement are as follows:

Name	Age	Position
Lisa A. Conte	63	Chief Executive Officer, President and Director
Steven R. King, Ph.D.	64	Chief of Sustainable Supply, Ethnobotanical Research and Intellectual Property and Secretary
Carol R. Lizak	58	Chief Financial Officer
Jonathan S. Wolin	60	Chief of Staff, General Counsel and Chief Compliance Officer
Pravin Chaturvedi, Ph.D.	59	Chief Scientific Officer
Ian Wendt	54	Chief Commercial Officer

Set forth below is a summary of the business experience of our Chief of Sustainable Supply, Ethnobotanical Research and Intellectual Property and Secretary, Steven R. King, our Chief Financial Officer, Carol R. Lizak, and our Chief of Staff and General Counsel, Jonathan S. Wolin. Our Chief Executive Officer's biography has been provided above.

Steven R. King, Ph.D. Dr. King has served as our Executive Vice President of Sustainable Supply, Ethnobotanical Research and Intellectual Property since March 2014 and as our Secretary since September 2014. He was promoted to Chief of Sustainable Supply, Ethnobotanical Research and Intellectual Property in March 2020. From 2002 to 2014, Dr. King served as the Senior Vice President of Sustainable Supply, Ethnobotanical Research and Intellectual Property at our wholly-owned subsidiary, Napo Pharmaceuticals, Inc. Prior to that, Dr. King served as the Vice President of Ethnobotany and Conservation at Shaman Pharmaceuticals, Inc. Dr. King has been recognized by the International Natural Products and Conservation Community for the creation and dissemination of research on the long-term sustainable harvest and management of *Croton lechleri*, the widespread source of crofelemer. Dr. King is currently a member of the board of directors of Healing Forest Conservatory, a California not-for-profit public benefit corporation. Dr. King holds a Ph.D. in Biology from the Institute of Economic Botany of the New York Botanical Garden and an M.S. in Biology from the City University of New York.

Carol R. Lizak. Ms. Lizak has served as our Chief Financial Officer since April 2021. She joined the Company in May 2019 as Vice President of Finance and Corporate Controller and was promoted to Chief Accounting Officer in August 2019 and Senior Vice-President of Finance and Chief Accounting Officer in March 2020. Prior to joining us, Ms. Lizak served as Senior Director and Corporate Controller of Zosano Pharma Corporation from November 2017 to January 2019, as Controller of Quantum Secure, Inc. from July 2016 to August 2017, and as Executive Director, Corporate Controller of Alexza Pharmaceuticals, Inc. from September 2014 to July 2016. Prior thereto, she spent nine years as Corporate Controller of a subsidiary of HID Global Corporation. Ms. Lizak holds an M.B.A from Pepperdine University, Graziadio School of Business and Management and a B.S. in Business Administration from the University of Santo Tomas.

Jonathan S. Wolin. Mr. Wolin has served as our Chief of Staff and General Counsel since September 4, 2019. He joined the Company in November 2018 as Chief Compliance Officer and Corporate Counsel of the Company and continues to serve as Chief Compliance Officer. Prior to joining the Company, Mr. Wolin served as an independent consultant advising clients on corporate compliance from June 2017 to November 2018, as Chief Administrative Officer of Braden Partners (d/b/a Pacific Pulmonary Services) from September 2016 to May 2017, as Chief Compliance Officer of Natera, Inc. from June 2015 to August 2016, and as Chief Compliance Officer of Braden Partners from September 2013 to May 2015. Mr. Wolin holds a J.D. from The Catholic University of America, Columbus School of Law, an M.B.A. from The George Washington University School of Business and a B.S. in Accounting from the University of Maryland.

Pravin Chaturvedi, Ph.D. Dr. Chaturvedi has served as our Chief Scientific Officer in addition to continuing his responsibilities as the Chair of the company's Scientific Advisory Board (SAB) since March 1, 2022. He joined the Company in May 2017 as Chair of the SAB of Jaguar and Napo. Over his more-than-30-year career in the pharmaceutical industry, Dr. Chaturvedi has participated in the successful development

and commercialization of multiple drugs in the therapeutic areas of epilepsy, HIV, hepatitis C, memory and gastrointestinal disorders. Dr. Chaturvedi served as the President and Chief Scientific Officer of Napo from 2006 to 2013 and remained a scientific adviser of Napo from 2013 through 2017. Dr. Chaturvedi has co-founded and led multiple biotech enterprises. From 2001 through 2004, he served as the President, Chief Executive Officer and Director of Scion Pharmaceuticals, Inc. He is the founder of IndUS Pharmaceuticals, where he has served as Chairman and Director since 2017, and held the same roles from 2005 through 2007 and from 2010 through 2015. IndUS Pharmaceuticals merged with Pivot Pharmaceuticals in 2015 and Dr. Chaturvedi served as the President and CEO of Pivot Pharmaceuticals from 2015 to 2017, prior to assuming his role as the Chair of the SAB for Napo and Jaguar. Dr. Chaturvedi also co-founded Oceanix Pharmaceuticals, where he has served as Chief Executive Officer and Director since 2011, and he continues to serve on the boards of IndUS, Oceanix, Enlivity and Cellanyx. He has been an adjunct faculty member at Georgetown University since 2013. Earlier in his career, from 1994 through 2001, Dr. Chaturvedi served in various roles as the head of lead evaluation at Vertex Pharmaceuticals, and from 1993 through 1994 he was in the preclinical group at Alkermes Inc. He started his career in the product development group at Parke-Davis/Warner-Lambert Company (now Pfizer) in 1988, where he worked through 1993. Dr. Chaturvedi holds a Ph.D. in Pharmaceutical Sciences from West Virginia University and a Bachelor's in Pharmacy from the University of Bombay.

Ian Wendt. Mr. Wendt has served as our Chief Commercial Officer since December 2020. He joined the Company in November 2019 as Vice President of Commercial Strategy. Prior to joining the Company served in various positions at Gilead Sciences, including Executive Director — HIV Community Operations from December 2018 to October 2019, Senior Director — HIV Marketing and Field Operations from October 2017 to December 2018, Director — HCV Marketing from February 2017 to October 2017, Associate Director — HCV Marketing Field POA from March 2016 to February 2017 and Regional Director — HIV Field Operations from April 2011 to March 2016. Before Gilead, Mr. Wendt was at Boehringer Ingelheim, where he led HIV and oncology sales teams across the US, and led commercial operations at Roxane Laboratories, which included sales operations, analytics, incentive compensation, and training. He received a BSc from Acadia University and an MBA from Dalhousie University in Nova Scotia.

Officers serve at the discretion of the board of directors. There are no family relationships among any of our executive officers or among any of our executive officers and our directors. There is no arrangement or understanding between any executive officer and any other person pursuant to which the executive officer was selected.

COMPENSATION OF DIRECTORS AND EXECUTIVE OFFICERS

Summary Compensation Table (2021 and 2020)

The total compensation paid to the Company's Principal Executive Officer and its two highest compensated executive officers other than the Principal Executive Officer, respectively, for services rendered in 2021 and 2020, as applicable, is summarized as follows:

	Year	Salary (\$)	Bonus (\$)	Option awards (\$) ⁽¹⁾	All other compensation (\$) ⁽²⁾	Total (\$)
Lisa A. Conte	2021	526,775	185,000	1,168,682	10,770	1,891,227
President and Chief Executive Officer	2020	500,000	—	874,451	25,213	1,399,664
Steven R. King, Ph.D.	2021	308,925	117,000	369,674	26,685	822,284
Chief, Sustainable Supply, Ethnobotanical Research and Intellectual Property	2020	300,000	—	300,073	32,228	632,301
Jonathan Wolin	2021	335,850	117,792	251,454	25,075	730,171
Chief of Staff, General Counsel and Chief Compliance Officer	2020	306,750	—	172,334	29,762	508,846
Ian Wendt	2021	329,175	102,375	127,902	—	559,452
Chief Commercial Officer	2020	300,000	10,769	48,478	—	359,247

Footnotes to Summary Compensation Table

- (1) Represents the dollar amounts recognized for financial statement reporting purposes with respect to the fiscal year (for stock option awards) determined under FASB ASC Topic 718. On June 3, 2019, the Company filed the Certificate of Fifth Amendment to its Third Amended and Restated Certificate of Incorporation with the Secretary of State of the State of Delaware to effect a 1-for-70 reverse split of the Company's voting common stock, effective June 7, 2019 (the "2019 Reverse Stock Split"). On September 3, 2021, the Company filed the Certificate of Sixth Amendment to its Third Amended and Restated Certificate of Incorporation with the Secretary of State of the State of Delaware to effect a 1-for-3 reverse split of the Company's voting common stock, effective September 8, 2021 (the "2021 Reverse Stock Split"). The 2021 Reverse Stock Split and 2019 Reverse Stock Split have been retrospectively reflected in the following options held by each executive officer as of December 31, 2021:
- a. Ms. Conte — an aggregate of 831,653 shares were granted as follows: 50 shares granted April 1, 2014, 27 shares granted July 2, 2015 which became effective at the annual stockholders' meeting of June 14, 2016, 36 shares granted July 7, 2015 which became effective at the annual stockholders' meeting of June 14, 2016, 22 shares granted April 1, 2016 which became effective at the annual stockholders' meeting of June 14, 2016, 100 shares granted September 22, 2016, 5 shares granted December 19, 2016, 90 shares granted December 21, 2017, 1,031 shares granted on March 12, 2018, 2,133 shares granted on June 1, 2018, and 347,350 shares granted on July 24, 2019. On March 20, 2020, Ms. Conte was granted 75,809 shares at an exercise price of \$1.34. On April 5, 2021, Ms. Conte was granted 270,000 shares at an exercise price of \$5.97 and 135,000 restricted stock units. The weighted average exercise price of all of Ms. Conte's option grants is \$12.18.
 - b. Dr. King — an aggregate of 262,272 shares were granted as follows: 29 shares granted April 1, 2014, 15 shares granted July 2, 2015 which became effective at the annual stockholders' meeting of June 14, 2016, 9 shares granted April 1, 2016 which became effective at the annual stockholders' meeting of June 14, 2016, 6 shares granted September 22, 2016, 1 share granted December 21, 2016, 29 shares granted December 21, 2017, 421 shares granted on March 12, 2018, 710 shares granted on June 1, 2018, and 115,783 shares granted on July 24, 2019. On March 20, 2020, Dr. King was granted 25,269 shares at an exercise price of \$1.34. On April 5, 2021, Dr. King was granted

80,000 shares at an exercise price of \$5.97 and 40,000 restricted stock units. The weighted average exercise price of all of Dr. King's option grants is \$12.67.

- c. Mr. Wolin — an aggregate of 180,764 shares were granted as follows: 476 shares granted November 28, 2019, 86,837 shares granted on July 24, 2019, and 14,499 shares granted on September 5, 2019. On March 20, 2020, Mr. Wolin was granted 18,952 shares at an exercise price of \$1.34. On April 5, 2021, Mr. Wolin was granted 40,000 shares at an exercise price of \$5.97 and 20,000 restricted stock units. The weighted average exercise price of all of Mr. Wolin's options grants is \$5.04.
 - d. Mr. Wendt — an aggregate of 118,333 shares were granted as follows: 50,000 shares granted November 12, 2019; on March 20, 2020, Mr. Wendt was granted 8,333 shares at an exercise price of \$5.97. On April 5, 2021, Mr. Wendt was granted 40,000 shares at an exercise price of \$5.97 and 20,000 restricted stock units. The weighted average exercise price of all of Mr. Wendt's options grants is \$4.06.
 - e. All of the April 1, 2014 option grants vested 25% on January 1, 2015 (nine months from grant date), with the remainder vesting equally over the following 27 months such that the options are vested in full on April 1, 2017. All of the July 2, 2015 options were granted contingent upon approval of the Company's stockholders at the June 14, 2016 annual stockholders' meeting and vest 1/36th per month beginning one month after grant date, with the remainder vesting equally over the following 35 months such that the option is vested in full on July 2, 2018. Ms. Conte's July 7, 2015 option was likewise granted contingent upon approval of the Company's stockholders at the June 14, 2016 annual stockholders' meeting and vests 1/36th per month beginning one month after grant date, with the remainder vesting equally over the following 35 months such that the option is vested in full on July 7, 2018. All of the options granted on April 1, 2016 which became effective at the annual stockholders' meeting of June 14, 2016, September 22, 2016, December 19, 2016 vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on December 19, 2019. All of the December 21, 2017 options grants vested in full as of March 31, 2018 if the option holder was an employee on that date. All of the March 12, 2018 options grants vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on March 12, 2021. All of the June 1, 2018 options grants vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on June 1, 2021. All of the July 24, 2019 option grants vest 1/36th per month over thirty-six months with additional vesting credited to an employee at a rate of 1/36 for every year of service at time of grant. The options will vest in full on July 24, 2022. All of the March 20, 2020 option grants vest 1/36th per month over thirty-six months with additional vesting credited to an employee at a rate of 1/36 for every year of service at time of grant. The options will vest in full on March 19, 2023. The options that were granted on April 5, 2021 vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on April 5, 2024, subject to continued service with us through each relevant vesting date. All of the restricted stock units granted on April 5, 2021 will vest yearly for the next three years.
- (2) Amounts shown in this column reflect incremental health insurance premiums paid for such executive's family members.

Narrative to Summary Compensation Table

Base Salary

Effective May 1, 2018, the Compensation Committee increased Ms. Conte's annual base salary from \$440,000 to \$500,000 and Dr. King's annual base salary from \$280,500 to \$290,317, and on November 1, 2019, Dr. King's annual base salary was increased from \$290,317 to \$300,000. Effective April 1, 2021, the Compensation Committee increased Ms. Conte's annual base salary from \$500,000 to \$535,700 and Dr. King's annual base salary from \$300,000 to \$311,900. Effective April 1, 2022, the Compensation Committee increased Ms. Conte's annual base salary from \$535,700 to \$576,374 and Dr. King's annual base salary from \$311,900 to \$352,900. Mr. Wolin was hired on November 28, 2018 with an annual base salary of \$260,000.

On September 6, 2019, we entered into a promotion letter with Mr. Wolin, pursuant to which his base salary was increased to \$280,800, effective September 1, 2019. His annual base salary was increased to \$300,000 and \$309,000 effective November 1, 2019 and April 1, 2020, respectively. Effective April 1, 2021, the Compensation Committee increased Mr. Wolin's annual base salary from \$309,000 to \$344,800. Effective April 1, 2022, the Compensation Committee increased Mr. Wolin's annual base salary from \$344,800 to \$396,520. Mr. Ian Wendt was hired on November 12, 2019 with an annual base salary of \$300,000. On April 1, 2021, we entered into a promotion letter with Mr. Wendt, pursuant to which his base salary was increased to \$338,900, effective April 1, 2021. Effective April 1, 2022, the Compensation Committee increased Mr. Wendt's annual base salary from \$338,900 to \$350,100.

Equity Compensation

Ms. Conte and Dr. King received stock option grants at the time they were hired by privately-held Jaguar Animal Health, Inc. Such options generally vest over time, with 25% of the options vesting after nine months of employment and monthly vesting thereafter with full vesting after three years. Mr. Wolin received stock option grants with a similar vesting schedule at the time they were hired by us. The board of directors periodically grants additional options to the current named executive officers that typically vest ratably over a three-year period.

All stock options and RSUs issued to our current named executive officers vest and become exercisable upon a change in control.

Outstanding Equity Awards at 2021 Fiscal Year End

The following table provides information regarding outstanding equity awards held by our named executive officers as of December 31, 2021.

The following table provides information regarding outstanding equity awards held by our named executive officers as of December 31, 2021.

	Options Vesting Commencement Date	Number of Securities Underlying Unexercised Options		Option exercise price	Stock Option expiration date
		Exercisable	Unexercisable		
Lisa A Conte	4/1/2014	50	— ⁽¹⁾	\$ 7,985.25	4/1/2024
	7/2/2015	27	— ⁽²⁾	\$16,033.50	7/2/2025
	7/7/2015	36	— ⁽³⁾	\$15,246.00	7/7/2025
	4/1/2016	22	— ⁽⁴⁾	\$ 4,977.00	4/1/2026
	9/22/2016	100	— ⁽⁵⁾	\$ 3,937.50	9/22/2026
	12/19/2016	5	— ⁽⁶⁾	\$ 2,331.00	12/19/2026
	12/21/2017	90	— ⁽⁷⁾	\$ 388.71	12/21/2027
	3/12/2018	1,031	— ⁽⁸⁾	\$ 1,764.00	3/12/2028
	6/01/2018	2,133	— ⁽⁹⁾	\$ 572.59	6/1/2028
	7/24/2019	328,052	19,298 ⁽¹¹⁾	\$ 5.19	7/24/2029
3/20/2020	44,222	31,587 ⁽¹⁴⁾	\$ 1.34	3/20/2030	
4/05/2021	60,000	210,000 ⁽¹⁵⁾	\$ 5.97	4/5/2031	
Steven R. King, Ph.D	4/1/2014	29	— ⁽¹⁾	7,985.25	4/1/2024
	7/2/2015	15	— ⁽²⁾	\$14,559.30	6/14/2026
	4/1/2016	9	— ⁽⁴⁾	\$ 7,434.00	4/1/2026
	9/22/2016	6	— ⁽⁵⁾	\$ 3,937.50	9/22/2026
	12/19/2016	1	— ⁽⁶⁾	\$ 2,331.00	12/19/2026
	12/21/2017	29	— ⁽⁷⁾	\$ 388.71	12/21/2027
	3/12/2018	421	— ⁽⁸⁾	\$ 1,764.00	3/12/2028
	6/1/2018	710	— ⁽⁹⁾	\$ 572.59	6/1/2028
	7/24/2019	109,350	6,433 ⁽¹¹⁾	\$ 5.19	7/24/2029
	3/20/2020	14,740	10,529 ⁽¹⁴⁾	\$ 1.34	3/20/2030
4/05/2021	17,777	62,223 ⁽¹⁵⁾	\$ 5.97	4/05/2031	
Jonathan Wolin	11/28/2018	476	— ⁽¹⁰⁾	\$ 92.40	11/28/2028
	7/24/2019	72,364	14,473 ⁽¹¹⁾	\$ 5.19	7/24/2029
	9/5/2019	10,874	3,625 ⁽¹²⁾	\$ 3.60	9/5/2029
	3/20/2020	11,055	7,897 ⁽¹⁴⁾	\$ 1.34	3/20/2030
	4/5/2021	8,888	31,112 ⁽¹⁵⁾	\$ 5.97	4/05/2031
Ian Wendt	11/12/2019	41,666	8,334 ⁽¹³⁾	\$ 2.98	11/12/2020
	3/20/2020	4,861	3,472 ⁽¹⁴⁾	\$ 1.34	3/20/2030
	4/5/2021	8,888	31,112 ⁽¹⁵⁾	\$ 5.97	4/5/2031

- (1) On January 1, 2015, 25% of each of such named executive officer's shares vested and became exercisable. The remainder of the shares were vested in approximately equal monthly installments through April 1, 2017, subject to continued service with us through each relevant vesting date.

- (2) The shares were granted on July 2, 2015 contingent upon the approval of the stockholders at the June 14, 2016 annual stockholders' meeting and vest 1/36th per month beginning one month after grant date, with the remainder vested equally over the following 35 months such that the option was fully vested on July 2, 2018, subject to continued service with us through each relevant vesting date.
- (3) The shares were granted on July 7, 2015 contingent upon the approval of the stockholders at the June 14, 2016 annual stockholders' meeting and vested 1/36th per month beginning one month after grant date, with the remainder vested equally over the following 35 months such that the option was fully vested on July 7, 2018, subject to continued service with us through each relevant vesting date.
- (4) The options were granted on April 1, 2016, which became effective at the annual stockholders' meeting of June 14, 2016, and vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on April 1, 2019, subject to continued service with us through each relevant vesting date.
- (5) The options were granted on September 22, 2016 and vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on September 22, 2019, subject to continued service with us through each relevant vesting date.
- (6) The options were granted on December 19, 2016 and vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on December 19, 2019, subject to continued service with us through each relevant vesting date.
- (7) The options were granted on December 21, 2017 and vest 100% on March 31, 2018 if the officer is an employee as of such date.
- (8) The options were granted on March 12, 2018 and vest 1/36th per month over thirty-six months such that the option is vested in full on March 12, 2021, subject to continued service with us through each relevant vesting date.
- (9) The options were granted on June 1, 2018 and vest 1/36th per month over thirty-six months such that the option is vested in full on June 12, 2021, subject to continued service with us through each relevant vesting date.
- (10) The options were granted November 29, 2018, 9/36ths of which vested nine months from date of hire, then 1/36th per month over the remaining twenty-seven months. The option will vest in full on November 29, 2021.
- (11) The options that were granted on July 24, 2019 vest 1/36th per month over thirty-six months with additional vesting credited to an employee at a rate of 1/36 for every year of service at time of grant. The option will vest in full on July 24, 2022.
- (12) The options that were granted on September 5, 2019 vest 1/36th per month over thirty-six months with additional vesting credited to an employee at a rate of 1/36 for every year of service at time of grant. The option will vest in full on September 5, 2023.
- (13) The options were granted on November 12, 2019, 9/36ths of which vested nine months from the date of hire, then 1/36th per month over the remaining twenty-seven months. The option will vest in full on November 12, 2021.
- (14) The options that were granted on March 20, 2020 vest 1/36th per month over thirty-six months with additional vesting credited to an employee at a rate of 1/36 for every year of service at time of grant. The option will vest in full on March 20, 2023.
- (15) The options that were granted on April 5, 2021 vest 1/36th per month beginning one month after grant, with the remainder vesting equally over the following 35 months such that the option is vested in full on April 5, 2024, subject to continued service with us through each relevant vesting date.

Executive Employment Agreements

Lisa A. Conte

In March 2014, we entered into an offer letter with Ms. Conte to serve as our Chief Executive Officer, effective March 1, 2014, in an at-will capacity. Under this offer letter, Ms. Conte's annual base salary is \$400,000, she is eligible for an annual target bonus of 30% of her base salary. Effective June 15, 2015, our

board of directors has reviewed the terms of Ms. Conte's employment arrangement in connection with its annual compensation review, and has adjusted Ms. Conte's base salary to \$440,000. Ms. Conte is entitled to participate in all employee benefit plans, including group health care plans and all fringe benefit plans. Effective May 1, 2018, the Compensation Committee adjusted Ms. Conte's base salary to \$500,000. Effective May 14, 2018, Ms. Conte was eligible for annual target bonus of 40% of her base salary. Effective April 1, 2021, the Compensation Committee adjusted Ms. Conte's base salary to \$535,700. Effective April 1, 2022, the Compensation Committee increased Ms. Conte's annual base salary from \$535,700 to \$576,374.

Steven R. King, Ph.D.

In February 2014, we entered into an offer letter with Dr. King to serve as our Executive Vice President, Sustainable Supply, Ethnobotanical Research and Intellectual Property, effective March 1, 2014, in an at-will capacity. Under the offer letter, Dr. King's annual base salary is \$255,000, he is eligible for an annual target bonus of 30% of his base salary, and he is eligible to participate in the employee benefit plans we offer to our other employees. Effective June 15, 2015, our board of directors has reviewed the terms of Dr. King's employment arrangement in connection with its annual compensation review, and has adjusted Dr. King's base salary to \$280,500. Dr. King is entitled to participate in all employee benefit plans, including group health care plans and all fringe benefit plans. Effective May 14, 2018, Dr. King was eligible for annual target bonus of 40% of his base salary. His annual base salary was increased to \$290,317, \$300,000 and \$311,900 effective May 1, 2018, November 1, 2019 and April 1, 2021, respectively. Effective April 1, 2022, the Compensation Committee increased Dr. King's annual base salary from \$311,900 to \$352,900.

Jonathan S. Wolin

In November 2018, we entered into an offer letter with Mr. Wolin to serve as our Chief Compliance Officer, effective November 28, 2018, in an at will capacity. Under the offer letter Mr. Wolin's annual base salary is \$260,000, he is eligible to receive an annual target bonus of 40% of his base salary, and he is eligible to participate in the employee benefit plans we offer to our other employees. On September 6, 2019, we entered into a promotion letter with Mr. Wolin, pursuant to which his base salary was increased to \$280,800, effective September 1, 2019. His annual base salary was increased to \$300,000, \$309,000 and \$344,800 effective November 1, 2019, April 1, 2020 and April 1, 2021, respectively. Effective April 1, 2022, the Compensation Committee increased Mr. Wolin's annual base salary from \$344,800 to \$396,520.

Ian Wendt

Mr. Ian Wendt was hired on November 12, 2019 with an annual base salary of \$300,000. On April 1, 2021, we entered into a promotion letter with Mr. Wendt, pursuant to which his base salary was increased to \$338,900, effective April 1, 2021. Effective April 1, 2022, the Compensation Committee increased Mr. Wendt's annual base salary from \$338,900 to \$350,100.

Severance Arrangements with our Executive Officers

In June 2020, the Company entered into certain agreements relating to the payment of severance and other benefits to certain executive officers of the Company (the "Severance Agreements"), including Ms. Conte, Dr. King, Ms. Lizak and Mr. Wolin. In May 2021, the Company entered into a severance agreement with Mr. Ian Wendt on terms that were substantially identical to the Severance Agreement. In March 2022, the Company entered into a severance agreement with Dr. Chaturvedi on terms that were substantially identical to the Severance Agreement. The Severance Agreements provide for compensation and benefits if the executive officer is subject to (a) a termination of employment by the Company without Cause (as defined in the Severance Agreements) (other than death or disability) or (b) a Good Reason Termination (as defined in the Severance Agreements), within three months following a change in control. The compensation and benefits payable to the executive officer pursuant to the Severance Agreements are as follows:

- Severance payment in an amount equal to twelve months of the executive officer's base salary, which amount will be payable, in the Company's discretion, as a lump sum or in equal installments over twelve months (the "Severance Period"), consistent with the Company's normal payroll practices.

- Payment of premiums for any Consolidated Omnibus Budget Reconciliation Act continuation coverage under the Company's group health plan for twelve months following the termination of employment.
- All unvested stock options and restricted stock units will accelerate and become fully vested as of the date of termination of employment and the executive officer will be entitled to exercise any of his or her vested stock options until the one-year anniversary of the termination of employment.

Each of the executive officer's rights to receive benefits under the Severance Agreements is contingent upon the executive officer's execution of a release agreement.

Compensation of Directors

The following table summarizes the total compensation earned in 2020 and 2021 for the Company's non-management directors. Ms. Conte receives no additional compensation for her service as a director.

	Year	Fees Earned or Paid in Cash (\$)	Option awards (\$) ⁽¹⁾	Total (\$)
James J. Bochnowski	2021	33,333	228,774	262,107
	2020	—	259,210	259,210
John Micek III	2021	21,667	161,457	183,124
	2020	—	149,635	149,635
Greg J. Divis	2021	15,000	163,172	178,172
	2021	—	104,041	104,041
Jonathan B. Siegel	2021	22,501	204,865	227,366
	2020	—	159,525	159,525

(1) Represents the dollar amounts recognized for financial statement reporting purposes with respect to the fiscal year (for stock option awards) determined under FASB ASC Topic 718. The aggregate number of options held by each non-management director officer as of December 31, 2021 was as follows: Mr. Bochnowski holds an aggregate of 112,468 options (12 options granted in fiscal year 2014, 6 options granted in fiscal year 2015, 31 options granted in fiscal year 2016, 1,539 options granted in fiscal year 2018 and 69,469 options granted in fiscal year 2019). Mr. Bochnowski was granted 15,161 options in March 2020. He was granted 26,250 options and 13,133 restricted stock units in May 2021; Mr. Micek III holds an aggregate of 74,534 options (33 options granted fiscal year 2016, 883 options granted fiscal year 2018 and 40,524 options granted in fiscal year 2019). Mr. Micek was granted 8,844 options in March 2020; He was granted 24,250 options and 12,133 restricted stock units in May 2021. Mr. Divis holds an aggregate of 74,117 options (499 options granted fiscal year 2018 and 40,524 options granted in fiscal year 2019). Mr. Divis was granted 8,844 options in March 2020. He was granted 24,250 options and 12,133 restricted stock units, and Mr. Siegel holds an aggregate of 109,380 options (499 options granted fiscal year 2018 and 69,469 options granted in fiscal year 2019). Mr. Siegel was granted 15,162 options in March 2020. He was granted 24,250 options and 12,133 restricted stock units in May 2021.

CERTAIN RELATIONSHIPS AND RELATED PERSON TRANSACTIONS

The following includes a summary of transactions since January 1, 2020, to which we have been a party in which the amount involved exceeded or will exceed the lesser of (i) \$120,000 and (ii) one percent (1%) of the average of our total assets at year-end for the prior two fiscal years, and in which any of our directors, executive officers or beneficial owners of more than 5% of our capital stock or any member of the immediate family of any of the foregoing persons had or will have a direct or indirect material interest. Compensation arrangements for our directors and executive officers are described in our annual proxy statement on Schedule 14A.

Transactions with Napo Therapeutics, S.p.A.

On June 1, 2021, the Company entered into a subscription agreement with Dragon SPAC S.p.A. (“Dragon SPAC”) and its sponsor, pursuant to which Dragon SPAC agreed to issue and sell, in a private placement by Dragon SPAC directly to the Company, units of Dragon SPAC, with each unit consisting of one ordinary share of Dragon SPAC and a warrant to purchase a share, for gross proceeds of approximately €8.8 million (corresponding, as at June 1, 2021, to \$10.8 million). Dragon SPAC was an Italy special purpose acquisition company formed for the purpose of entering into a business combination with Napo Therapeutics, S.p.A. (f/k/a Napo EU, S.p.A.), with the aim of developing the pharmaceutical activities of Dragon SPAC/Napo Therapeutics combined entity in Europe. Each warrant entitles the holder thereof to purchase one share at an exercise price of €10 per share at any time prior to the earlier of (i) the 10-year anniversary of the consummation of the business combination and (ii) the five-year anniversary of the listing of the combined entity on a public exchange.

On August 18, 2021, Napo Pharmaceuticals, Inc. (“Napo”), the wholly-owned subsidiary of the Company, entered into a license agreement (as amended, the “License Agreement”) with Napo Therapeutics, S.p.A. (“Napo Thera”), an Italy joint stock company and majority-owned subsidiary of Napo, pursuant to which Napo granted Napo Thera (i) an exclusive license to develop, commercialize and manufacture pharmaceutical products utilizing crofelemer or lechlemer as its active drug substance (collectively, “Products”) in Europe for short bowel syndrome with intestinal failure, HIV-related diarrhea, and symptomatic relief and treatment in patients with congenital diarrheal disorders and (ii) options to licenses to develop, commercialize and manufacture Products in Europe for additional indications. Pursuant to the License Agreement, Napo received an upfront cash payment of \$10 million, 33% of which was payable no later than the earlier of sixty days following the consummation of the Merger (defined below) or December 15, 2021 and the remaining balance of which is payable no later than the earlier of the twelve-month anniversary of the consummation of the Merger or within sixty days of when Napo Thera receives more than \$20 million from the Merger or private placement proceeds directly into the Combined Company (as defined below). Napo is also eligible to receive development and regulatory milestone payments of up to \$12.5 million, tiered royalties ranging from 12% to 18% and additional one-time license fees of up to \$40 million in the event that Napo Thera elects to acquire the license to exploit the Products in Europe for additional indications. Napo Thera’s ability to acquire the license for additional indications is subject to the availability of additional funds through financing or otherwise.

On November 3, 2021, Napo Thera and Dragon SPAC consummated a business combination (“Merger”). Following such business combination, Jaguar and the sponsor of the Dragon SPAC owned approximately 97% and 3%, respectively, of the combined company (the “Combined Company”) without taking into effect any ordinary shares of the Combined Company issuable upon conversion of any special shares of the Combined Company or the exercise of any warrants of the Combined Company.

Transactions with Executive Officers

On September 13, 2021 the Company entered into a securities purchase agreement (the “PIPE Purchase Agreement”) with certain investors named therein (collectively, “PIPE Investors”), pursuant to which the Company agreed to issue and sell to the Investors in a private placement an aggregate of 309,242 unregistered shares (the “PIPE Shares”) of Common Stock for an aggregate purchase price of approximately \$776,197 (the “Private Placement”) or \$2.51 per share, a \$0.01 premium to market price (defined as the Minimum Price under Nasdaq Listing Rule 5635(d)). PIPE Investors in the Private Placement include

Lisa Conte, Chief Executive Officer of the Company, and Carol Lizak, Chief Financial Officer of the Company, who each invested approximately \$20,000 in the Private Placement.

Transactions with Sagard

On September 1, 2020, the Company entered into the Stock Plan Agreement for Payment of Consulting Services with Sagard Capital Partners Management Corp. (“SCPM”) and Sagard Capital Partners, L.P. (“Sagard”), pursuant to which the Company agreed to issue Sagard 763,158 shares of Common Stock in full satisfaction of all amounts owed by the Company to SCPM for services rendered by SCPM to the Company under the Management Services Agreement, dated March 23, 2018, by and between the Company and SCPM.

At the time of the above-referenced transactions, Sagard held in excess of 5% of our outstanding shares of Common Stock on an as-converted basis.

Transactions with CVP and Its Affiliates

On March 4, 2020, the Company sold to Iliad Research and Trading, L.P. (“Iliad”), a Utah limited partnership affiliated with Chicago Venture Partners L.P. (“CVP”), a royalty interest entitling Iliad to \$500,000 of future royalties on sales of Mytesi (crofelemer) and certain up-front license fees and milestone payments from licensees and/or distributors for an aggregate purchase price of \$350,000.

On April 15, 2020, Napo entered into a patent purchase agreement with Atlas Sciences, LLC (“Atlas”), an affiliate of CVP, pursuant to which Atlas agreed to purchase certain patents and patent applications (the “Patent Rights”) relating to Napo’s NP-500 drug product candidate (the “Sale”) for an upfront cash payment of \$1.5 million. Concurrently with the Sale, the Company entered into a license agreement with Atlas (as amended on July 30, 2020, the “License Agreement”), pursuant to which Atlas granted the Company an exclusive 10-year license to use the Patent Rights and improvements thereon to develop and commercialize NP-500 in all territories worldwide except greater China, inclusive of the right to sublicense NP-500 development and commercialization rights. As consideration for such license, the Company is obligated to initiate a proof-of-concept Phase 2 study of NP-500 under an investigational new drug (“IND”) application with the U.S. Food and Drug Administration or an IND-equivalent dossier under appropriate regulatory authorities (the “Phase 2 study”) within six months of April 15, 2020. If the Company fails to initiate the Phase 2 study by this date for any reason, including the timely receipt of adequate funding to initiate the Phase 2 study, the Company will incur a trial delay fee equal to \$2,515,000 (the “Trial Delay Fee”), which amount is payable monthly over a period of approximately ten months. On October 7, 2020, the Company entered into a fee settlement agreement Atlas, pursuant to which the Company issued to Atlas 666,666 shares of Common Stock (the “Settlement Shares”) and (ii) pre-funded warrants to purchase 2,072,984 shares of Common Stock (the “Settlement Warrants” and, together with the Settlement Shares and the shares of Common Stock underlying the Settlement Warrants, the “Settlement Securities”) as complete settlement and satisfaction of the Trial Delay Fee for an effective offering price of \$0.918 per share, which equals the Minimum Price as defined under Nasdaq Listing Rule 5635(d).

On September 1, 2020, the Company entered into an exchange agreement with Iliad, the holder of 5,524,926 shares (the “Original Shares”) of the Company’s Series A Convertible Participating Preferred Stock, par value \$0.0001 per share (the “Series A Preferred Stock”), pursuant to which the Company and Iliad agreed to exchange the Original Shares for (i) 842,500 shares (the “Series C Preferred Shares”) of the Company’s Series C Perpetual Preferred Stock, par value \$0.0001 per share (the “Series C Preferred Stock”) and (ii) 842,500 shares (the “Series D Preferred Shares” and, together with the Series C Preferred Shares, the “Exchange Shares”) of the Company’s Series D Perpetual Preferred Stock, par value \$0.0001 per share (the “Series D Preferred Stock”).

Between October 8, 2020 and December 28, 2020, the Company entered into privately negotiated exchange agreements with Iliad, pursuant to which the Company issued 8,114,583 shares of Common Stock and pre-funded warrants to purchase 2,352,564 shares of Common Stock in the aggregate at an effective price per share equal to the market price (defined as the Minimum Price under Nasdaq Listing Rule 5635(d)) in exchange for 572,719 Exchange Shares (collectively, the “Preferred Exchange Transactions”).

As a result of the Preferred Exchange Transactions, no Series C Preferred Shares or Series D Preferred Shares remain outstanding.

Between September 23, 2020 and January 4, 2021, the Company entered into privately negotiated exchange agreements with CVP, pursuant to which we issued 7,628,443 shares of Common Stock in the aggregate at an effective price per share equal to the market price (defined as the Minimum Price under Nasdaq Listing Rule 5635(d)) in exchange for a \$7,791,619 reduction in the outstanding balance of the Exchange Notes (collectively, the “Note Exchange Transactions”). As a result of the Note Exchange Transactions, as of January 4, 2021, the Exchange Notes have been repaid in full and are no longer outstanding.

On October 8, 2020, the Company sold to Iliad a royalty interest (the “October 2020 Royalty Interest”) entitling Iliad to \$18 million of future royalties on sales of Mytesi (crofelemer) and certain up-front license fees and milestone payments from licensees and/or distributors for an aggregate purchase price of \$6 million.

On December 22, 2020, the Company sold to Uptown Capital, LLC (f/k/a Irving Park Capital, LLC), an affiliate of CVP (“IPC”), a royalty interest entitling IPC to \$12 million of future royalties on sales of Mytesi (crofelemer) and certain up-front license fees and milestone payments from licensees and/or distributors for an aggregate purchase price of \$6 million.

On January 19, 2021, the Company and Napo issued a secured promissory note in the aggregate principal amount of \$6,220,813 to Streeterville Capital, LLC, an affiliate of CVP (“Streeterville”), which note bears interest at 3.25% per annum and matures on January 20, 2025.

On March 8, 2021, the Company sold to Streeterville a royalty interest entitling Streeterville to \$10 million of future royalties on sales of Mytesi (crofelemer) for the prophylaxis and/or symptomatic relief of inflammatory diarrhea and certain up-front license fees and milestone payments from licensees and/or distributors for an aggregate purchase price of \$5 million.

Between February 11, 2022 and March 9, 2022, the Company entered into privately negotiated exchange agreements with Iliad, pursuant to which the Company issued 8,650,000 shares of Common Stock in the aggregate at an effective price per share equal to the market price (defined as the Minimum Price under Nasdaq Listing Rule 5635(d)) as of the date of the applicable exchange agreement in exchange for a \$4,441,657.50 reduction in the outstanding balance of the October 2020 Royalty Interest. At the time of certain of the above-referenced transactions, CVP and its affiliates held in excess of 5% of our outstanding shares of Common Stock.

Transactions with Oasis Capital

On March 24, 2020, the Company entered into an equity purchase agreement (the “ELOC Purchase Agreement”) with Oasis Capital, LLC (“Oasis Capital”) which provides that, upon the terms and subject to the conditions and limitations set forth therein, Oasis Capital is committed to purchase up to an aggregate of \$2.0 million of shares of Common Stock over the 36-month term of the ELOC Purchase Agreement.

On May 12, 2020, the Company and Napo, entered into an accounts receivable purchase agreement (as amended, the “A/R Purchase Agreement”) with Oasis Capital, pursuant to which Oasis Capital may from time to time in its discretion purchase accounts receivable of the Company or Napo on a recourse basis at a purchase price equal to 37.5% of the face amount of each of the purchased accounts (“A/R Purchase Price”). With respect to a purchased account, in the event Purchaser receives more than an amount equal to the sum of (i) the face amount of such purchased account multiplied by 0.0545 and (ii) the A/R Purchase Price from collection on such purchased account, then Oasis Capital will return any such excess overage amount to Company or Napo, as applicable, within five days after Purchaser’s receipt thereof. Between May 12, 2020 and December 3, 2021, Oasis Capital has purchased accounts receivable with an aggregate face amount of \$8.0 million for an aggregate purchase price of \$7.2 million, which purchases were effectuated pursuant to assignment agreements entered into between Napo and Oasis Capital from time to time.

On April 7, 2021, the Company entered into an amendment (the “ELOC Amendment”) to the ELOC Purchase Agreement with Oasis Capital, pursuant to which the parties agreed to increase (i) the purchase price per share of Common Stock issuable under the ELOC Purchase Agreement from \$1.308 to \$9.00 and

the threshold trading price of the Common Stock for conducting sales under the ELOC Purchase Agreement from \$1.5042 to \$10.35 per share. In consideration for Oasis Capital's entry into the ELOC Amendment, the Company issued Oasis Capital a common stock purchase warrant exercisable for 33,333 shares of Common Stock (the "ELOC Warrant") with an exercise price per share equal to \$5.61, the Minimum Price (as defined under Nasdaq Listing Rules) on the date of the ELOC Amendment.

On October 6, 2020, the Company entered into an exchange agreement with Oasis Capital, pursuant to which the Company and Oasis Capital agreed to exchange 790 out of the 10,165 Series B-2 Preferred Shares held by Oasis Capital for 166,728 shares of Common Stock. Oasis Capital exercised its right to convert the remaining Series B-2 Preferred Shares into shares of Common Stock in accordance with the terms of such Series B-2 Preferred Shares on January 17, 2020 and December 23, 2020, such that no Series B-2 remain outstanding.

At the time of certain of the above-referenced transactions, Oasis Capital held in excess of 5% of our outstanding shares of Common Stock.

Transactions with Ionic Ventures, LLC

On March 24, 2020, the Company entered into a warrant exercise and preferred stock amendment agreement (the "Amendment Agreement") with Ionic Ventures, LLC ("Ionic"), pursuant to which Ionic agreed to exercise in cash its Series 2 warrants to purchase 416,666 shares of Common Stock ("Series 2 Warrants") at a reduced exercise price of \$1.5681 per share for gross proceeds to the Company of approximately \$653,400. As further inducement to enter into the Amendment Agreement, the Company agreed to reduce the conversion price of the Company's Series B Preferred Stock (of which Ionic remains the sole holder) from \$6.00 to \$1.3368.

At the time of certain of the above-referenced transactions, Ionic and its affiliates held in excess of 5% of our outstanding shares of Common Stock.

Transactions with Charles C. Conte

Charles C. Conte is the brother of Lisa A. Conte, who has served as our President, Chief Executive Officer and a member of our board of directors since she founded the company in June 2013.

On March 24, 2020, the Company entered into a Landlord Letter of Credit Agreement with Charles Conte (the "LC Facilitator"), pursuant to which the Company will pay the LC Facilitator an amount equal to \$10,000 per month as consideration for delivering to the landlord (the "Landlord") of the Company's office space located at 201 Mission Street, Suite 2375, San Francisco, California (the "Premises"), a standby, unconditional, irrevocable, transferable letter of credit (the "Letter of Credit"), naming the Landlord as beneficiary, as collateral for the full performance by the Company of all of its obligations under the office lease agreement relating to the Premises. The Company also agreed to reimburse LC Facilitator up to \$7,500 for reasonable out-of-pocket expenses incurred in establishing the Letter of Credit. The parties terminated the Letter of Credit in October 2020.

Indemnification Agreements

We have entered into indemnification agreements with each of our directors and officers. These agreements, among other things, require us or will require us to indemnify each director to the fullest extent permitted by Delaware law, including indemnification of expenses such as expenses, judgments, penalties, fines and amounts paid in settlement to the extent legally permitted incurred by the director or officer in any action or proceeding, including any action or proceeding by or in right of us, arising out of the person's services as a director or officer.

DELINQUENT SECTION 16(A) REPORTS

Section 16(a) of the Exchange Act, and regulations of the SEC thereunder require our directors, officers and persons who own more than 10% of our Common Stock, as well as certain affiliates of such persons, to file initial reports of their ownership of our Common Stock and subsequent reports of changes in such ownership with the SEC. Directors, officers and persons owning more than 10% of our Common Stock are required by SEC regulations to furnish us with copies of all Section 16(a) reports they file. Based solely on our review of the copies of such reports and amendments thereto received by us and written representations from these persons that no other reports were required, we believe that during the fiscal year ended December 31, 2021, our directors, officers and owners of more than 10% of our Common Stock complied with all applicable filing requirements except that each of Lisa Conte and Carol Lizak filed a Form 4 on March 30, 2022 reporting the purchase of shares of Common Stock that should have been filed on September 15, 2021 pursuant to Section 16(a) of the Exchange Act.

AUDIT COMMITTEE REPORT

Management has primary responsibility for our financial statements and the overall reporting process, including maintaining effective internal control over financial reporting and assessing the effectiveness of our system of internal controls. The independent registered public accounting firm audits the annual financial statements prepared by management, expresses an opinion as to whether those financial statements fairly present our financial position, results of operations and cash flows in conformity with U.S. generally accepted accounting principles, and discusses with the Audit Committee any issues it believes should be raised with the Audit Committee. These discussions include a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements. The Audit Committee monitors our processes, relying, without independent verification, on the information provided to it and on the representations made by management and the independent registered public accounting firm.

RBSM LLP (“RBSM”), our Company’s independent auditor for the year ended December 31, 2021, is responsible for expressing an opinion on the fairness of the presentation of the Company’s financial statements in conformity with accounting principles generally accepted in the United States of America, in all material respects.

In this context, the Audit Committee has reviewed and discussed with management and RBSM the audited financial statements for the year ended December 31, 2021. The Audit Committee has discussed with RBSM the matters that are required to be discussed under the Public Accounting Oversight Board Auditing Standard No. 1301 “*Communications with Audit Committees*”. RBSM has provided to the Audit Committee the written disclosures and the letter required by applicable requirements of the Public Company Accounting Oversight Board’s Ethics and Independence rule 3526 “*Communications with Audit Committees Concerning Independence*”, and the Audit Committee has discussed with RBSM that firm’s independence.

The Audit Committee has concluded that RBSM’s provision of audit and non-audit services to the Company are compatible with RBSM’s independence.

Based on the considerations and discussions referred to above, the Audit Committee recommended to our Board of Directors that the audited financial statements for the year ended December 31, 2021 be included in our Annual Report on Form 10-K. This report is provided by the following independent directors, who comprise the Audit Committee:

Audit Committee:

John Micek III, Chairperson
James J. Bochnowski
Jonathan B. Siegel

March 11, 2022

STOCKHOLDER PROPOSALS FOR 2023 ANNUAL MEETING

In accordance with SEC Rule 14a-8, in order for stockholder proposals intended to be presented at the 2023 Annual Meeting of Stockholders to be eligible for inclusion in our proxy statement for such meeting, they must be received by us at our executive offices in San Francisco, California, before January 19, 2023. The board of directors has not determined the date of the 2023 Annual Meeting of the Company's Stockholders, but does not currently anticipate that the date will be changed by more than 30 calendar days from the date of the 2022 Annual Meeting of Stockholders.

Stockholder proposals (including recommendations of nominees for election to the board of directors) intended to be presented at the 2023 Annual Meeting of Stockholders, other than a stockholder proposal submitted pursuant to SEC Rule 14a-8, must be received in writing at our principal executive office no earlier than February 10, 2023 and no later March 12, 2023, in accordance with our bylaws. If the date of the 2023 Annual Meeting of Stockholders is scheduled for a date more than 30 days before or more than 60 days after June 10, 2023, then such proposals must be received not later than the close of business on the later of the 90th day prior to the scheduled date of the 2023 Annual Meeting or the 10th day following the day on which public disclosure of the date of the 2023 Annual Meeting of Stockholders is first made, as set forth in our bylaws.

AVAILABILITY OF ANNUAL REPORT TO STOCKHOLDERS AND REPORT ON FORM 10-K

A copy of our Annual Report, which includes certain financial information about the Company, is being provided with this Proxy Statement. Copies of our Annual Report (exclusive of exhibits and documents incorporated by reference) may also be obtained for free by directing written requests to: Jaguar Health, Inc., Attention: Jonathan S. Wolin, 200 Pine Street, Suite 400, San Francisco, CA 94104 (415.371.8300 phone). Copies of exhibits and basic documents filed with the Annual Report or referenced therein will be furnished to stockholders upon written request and payment of a nominal fee in connection with the furnishing of such documents. You may also obtain the Annual Report over the Internet at the SEC's website, www.sec.gov, or at <https://jaguarhealth.gcs-web.com/financial-information/annual-reports>.

LIST OF THE COMPANY'S STOCKHOLDERS

A list of our stockholders as of May 13, 2022, the Record Date, will be available for inspection at our corporate headquarters during normal business hours during the 10-day period prior to the Annual Meeting. The list of stockholders will also be available for such examination at the Annual Meeting.

DELIVERY OF PROXY MATERIALS TO HOUSEHOLDS

Unless contrary instructions are received, we may send a single copy of the Annual Report, Proxy Statement and Notice of Annual Meeting to any household at which two or more stockholders reside if we believe the stockholders are members of the same family. Each stockholder in the household will continue to receive a separate proxy card. This process is known as "householding" and helps reduce the volume of duplicate information received at a single household, which reduces costs and expenses borne by us.

If you would like to receive a separate set of our annual disclosure documents this year or in future years, follow the instructions described below and we will deliver promptly a separate set. Similarly, if you share an address with another stockholder and the two of you would like to receive only a single set of our annual disclosure documents, follow the instructions below:

1. If your shares are registered in your own name, please contact our transfer agent by writing to them at American Stock Transfer & Trust Company, LLC, 6201 15th Ave., Brooklyn, NY 11219 (Attn: Jaguar Health, Inc. Representative), calling 1-800-937-5449, or emailing help@astfinancial.com.
2. If a bank, broker or other nominee holds your shares, please contact your bank, broker or other nominee directly.

OTHER MATTERS THAT MAY COME BEFORE THE ANNUAL MEETING

Our board of directors knows of no matters other than those referred to in the accompanying Notice of Annual Meeting of Stockholders which may properly come before the Annual Meeting. However, if any other matter should be properly presented for consideration and voting at the Annual Meeting or any adjournments or postponements thereof, it is the intention of the persons named as proxies on the enclosed form of proxy card to vote the shares represented by all valid proxy cards in accordance with their judgment of what is in the best interest of the Company.

By Order of the Board of Directors.

A handwritten signature in black ink that reads "Lisa A. Conte". The signature is written in a cursive, flowing style.

Lisa A. Conte
Chief Executive Officer & President

San Francisco, California
May 19, 2022

Appendix A
Global Amendment — Note

GLOBAL AMENDMENT

This Global Amendment (this “**Amendment**”) is entered into as of April 14, 2022 by and among Streeterville Capital, LLC, a Utah limited liability company (“**Lender**”), Jaguar Health, Inc. a Delaware corporation (“**Jaguar**”), and Napo Pharmaceuticals, Inc., a Delaware corporation (“**Napo**,” and together with Jaguar, “**Borrower**”). Capitalized terms used in this Amendment without definition shall have the meanings given to them in the Note (as defined below).

A. Borrower previously sold and issued to Lender that certain Secured Promissory Note dated January 19, 2021 in the original principal amount of \$6,220,812.50 (the “**Note**”).

B. Lender and Borrower have agreed, subject to the terms, amendments, conditions and understandings expressed in this Amendment, to amend the Note as set forth herein.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties agree as follows:

1. **Recitals.** Each of the parties hereto acknowledges and agrees that the recitals set forth above in this Amendment are true and accurate and are hereby incorporated into and made a part of this Amendment.

2. **Definitions.** For purposes of this Amendment, the following terms will have the following meanings:

(a) “**Exchange Amount**” means the amount of the Note that Borrower desires to exchange for Exchange Shares.

(b) “**Exchange Cap**” means the maximum number of Exchange Shares that could be issued to Lender without violating The Nasdaq Capital Market rules related to the aggregation of offerings under Nasdaq Listing Rule 5635(d), if applicable.

(c) “**Exchange Conditions**” means: (a) with respect to the applicable Exchange Date all of the Exchange Shares would be (i) registered for trading under applicable federal and state securities laws, (ii) freely tradable under Rule 144, or (iii) otherwise freely tradable without the need for registration under any applicable federal or state securities laws; (b) the applicable Exchange Shares would be eligible for immediate resale by Lender; (c) no Event of Default shall have occurred under the Note; (d) if Jaguar’s Common Stock is trading on OTCQB or OTCQX, the Exchange Amount is less than or equal to twenty-five percent (25%) of the median daily dollar trading volume of Jaguar’s Common Stock during the ten (10) Trading Days preceding the Exchange Date; and (e) the Common Stock is trading on Nasdaq, NYSE, OTCQB or OTCQX.

(d) “**Exchange Date**” means the date that an Exchange Notice is submitted by Borrower to Lender.

(e) “**Exchange Notice**” means a notice delivered by Borrower to Lender specifying the Exchange Amount to be exchanged and the number of Exchange Shares to be issued.

(f) “**Exchange Shares**” the number of shares of Jaguar’s Common Stock to be issued pursuant to an applicable Exchange Notice.

(g) “**Nasdaq Minimum Price**” means such term as defined in Nasdaq Listing Rule 5635(d).

3. **Borrower Exchange Right.** The Note is hereby amended to grant Borrower the right to exchange from time to time at Borrower’s sole discretion any Exchange Amount for Exchange Shares at a price per share equal to the Nasdaq Minimum Price as of each applicable Exchange Date. Notwithstanding the foregoing, Borrower will not have the right to exchange any Exchange Amount and issue any Exchange Shares to Lender if: (a) the issuance of such Exchange Shares would cause Lender’s beneficial ownership to exceed 4.99% of Jaguar’s issued and outstanding Common Stock as of such date; (b) any of the Exchange Conditions has not been satisfied as of the applicable Exchange Date; and (c) the total cumulative number of Exchange Shares to be issued to Lender would exceed the Exchange Cap unless (i) stockholder approval is obtained to issue more than the Exchange Cap or (ii) the Common Stock is not listed for quotation on Nasdaq or NYSE American. The Exchange Cap shall be appropriately adjusted for any reorganization,

recapitalization, non-cash dividend, stock split, reverse stock split or other similar transaction. Following delivery of an Exchange Notice, Borrower may not deliver another Exchange Notice to Lender for at least three (3) Trading Days.

4. Representations and Warranties. In order to induce Lender to enter into this Amendment, Borrower, for itself, and for its affiliates, successors and assigns, hereby acknowledges, represents, warrants and agrees as follows:

(a) Borrower has full power and authority to enter into this Amendment and to incur and perform all obligations and covenants contained herein, all of which have been duly authorized by all proper and necessary action. No consent, approval, filing or registration with or notice to any governmental authority is required as a condition to the validity of this Amendment or the performance of any of the obligations of Borrower hereunder.

(b) There is no fact known to Borrower or which should be known to Borrower which Borrower has not disclosed to Lender on or prior to the date of this Amendment which would or could materially and adversely affect the understanding of Lender expressed in this Amendment or any representation, warranty, or recital contained in this Amendment.

(c) Except as expressly set forth in this Amendment, Borrower acknowledges and agrees that neither the execution and delivery of this Amendment nor any of the terms, provisions, covenants, or agreements contained in this Amendment shall in any manner release, impair, lessen, modify, waive, or otherwise affect the liability and obligations of Borrower under the terms of the Note.

(d) Borrower has no defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action of any kind or nature whatsoever against Lender, directly or indirectly, arising out of, based upon, or in any manner connected with, the transactions contemplated hereby, whether known or unknown, which occurred, existed, was taken, permitted, or begun prior to the execution of this Amendment and occurred, existed, was taken, permitted or begun in accordance with, pursuant to, or by virtue of any of the terms or conditions of the Note. To the extent any such defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action exist or existed, such defenses, rights, claims, counterclaims, actions and causes of action are hereby waived, discharged and released. Borrower hereby acknowledges and agrees that the execution of this Amendment by Lender shall not constitute an acknowledgment of or admission by Lender of the existence of any claims or of liability for any matter or precedent upon which any claim or liability may be asserted.

(e) Borrower represents and warrants that as of the date hereof no Events of Default or other material breaches exist under the Note, or have occurred prior to the date hereof.

5. Other Terms Unchanged. The Note, as amended by this Amendment, remains and continues in full force and effect, constitutes legal, valid, and binding obligations of each of the parties, and is in all respects agreed to, ratified, and confirmed. Any reference to the Note after the date of this Amendment is deemed to be a reference to the Note as amended by this Amendment. If there is a conflict between the terms of this Amendment and the Note, the terms of this Amendment shall control. No forbearance or waiver may be implied by this Amendment. Borrower acknowledges that it is unconditionally obligated to pay the remaining balance of the Note and represents that such obligation is not subject to any deductions, defenses, rights of offset, or counterclaims of any kind. Except as expressly set forth herein, the execution, delivery, and performance of this Amendment shall not operate as a waiver of, or as an amendment to, any right, power, or remedy of Lender under the Note, as in effect prior to the date hereof.

6. No Reliance. Borrower acknowledges and agrees that neither Lender nor any of its officers, directors, members, managers, equity holders, representatives or agents has made any representations or warranties to Borrower or any of its agents, representatives, officers, directors, or employees except as expressly set forth in this Amendment and the Note and, in making its decision to enter into the transactions contemplated by this Amendment, Borrower is not relying on any representation, warranty, covenant or promise of Lender or its officers, directors, members, managers, equity holders, agents or representatives other than as set forth in this Amendment.

7. Counterparts. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, but all of which together shall constitute one instrument. The parties hereto confirm that any electronic copy of another party's executed counterpart of this Amendment (or such party's signature page thereof) will be deemed to be an executed original thereof.

8. Further Assurances. Each party shall do and perform or cause to be done and performed, all such further acts and things, and shall execute and deliver all such other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Amendment and the consummation of the transactions contemplated hereby.

[Remainder of page intentionally left blank]

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the date set forth above.

BORROWER:

JAGUAR HEALTH, INC.

By: /s/ Lisa Conte

Lisa Conte, President and CEO

NAPO PHARMACEUTICALS, INC.

By: /s/ Lisa Conte

Lisa Conte, President and CEO

LENDER:

STEETERVILLE CAPITAL, LLC

By: /s/ John M. Fife

John M. Fife, President

Appendix B
Global Amendment — Royalty Interests

Appendix B-1

Amendment to October 2020 Royalty Interest

GLOBAL AMENDMENT

This Global Amendment (this “**Amendment**”) is entered into as of April 14, 2022 by and between Iliad Research and Trading, L.P., a Utah limited partnership (“**Investor**”), and Jaguar Health, Inc. a Delaware corporation (“**Company**”). Capitalized terms used in this Amendment without definition shall have the meanings given to them in the Royalty Interest (as defined below).

A. Company previously sold and issued to Investor that certain Royalty Interest dated October 8, 2020 in the original principal amount of \$12,000,000 (the “**Royalty Interest**”).

B. Investor and Company have agreed, subject to the terms, amendments, conditions and understandings expressed in this Amendment, to amend the Royalty Interest as set forth herein.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties agree as follows:

1. Recitals. Each of the parties hereto acknowledges and agrees that the recitals set forth above in this Amendment are true and accurate and are hereby incorporated into and made a part of this Amendment.

2. Definitions. For purposes of this Amendment, the following terms will have the following meanings:

(a) “**Exchange Amount**” means the amount of the Royalty Interest that Company desires to exchange for Exchange Shares.

(b) “**Exchange Cap**” means the maximum number of Exchange Shares that could be issued to Investor without violating The Nasdaq Capital Market rules related to the aggregation of offerings under Nasdaq Listing Rule 5635(d), if applicable.

(c) “**Exchange Conditions**” means: (a) with respect to the applicable Exchange Date all of the Exchange Shares would be (i) registered for trading under applicable federal and state securities laws, (ii) freely tradable under Rule 144, or (iii) otherwise freely tradable without the need for registration under any applicable federal or state securities laws; (b) the applicable Exchange Shares would be eligible for immediate resale by Investor; (c) no Event of Default shall have occurred under the Royalty Interest; (d) if Company’s Common Stock is trading on OTCQB or OTCQX, the Exchange Amount is less than or equal to twenty-five percent (25%) of the median daily dollar trading volume of Company’s Common Stock during the ten (10) Trading Days preceding the Exchange Date; and (e) the Common Stock is trading on Nasdaq, NYSE, OTCQB or OTCQX.

(d) “**Exchange Date**” means the date that an Exchange Notice is submitted by Company to Investor.

(e) “**Exchange Notice**” means a notice delivered by Company to Investor specifying the Exchange Amount to be exchanged and the number of Exchange Shares to be issued.

(f) “**Exchange Shares**” the number of shares of Company’s Common Stock to be issued pursuant to an applicable Exchange Notice.

(g) “**Nasdaq Minimum Price**” means such term as defined in Nasdaq Listing Rule 5635(d).

3. Company Exchange Right. The Royalty Interest is hereby amended to grant Company the right to exchange from time to time at Company’s sole discretion any Exchange Amount for Exchange Shares at a price per share equal to the Nasdaq Minimum Price as of each applicable Exchange Date. Notwithstanding the foregoing, Company will not have the right to exchange any Exchange Amount and issue any Exchange Shares to Investor if: (a) the issuance of such Exchange Shares would cause Investor’s beneficial ownership to exceed 4.99% of Company’s issued and outstanding Common Stock as of such date; (b) any of the Exchange Conditions has not been satisfied as of the applicable Exchange Date; and (c) the total cumulative

number of Exchange Shares to be issued to Investor would exceed the Exchange Cap unless (i) stockholder approval is obtained to issue more than the Exchange Cap or (ii) the Common Stock is not listed for quotation on Nasdaq or NYSE American. The Exchange Cap shall be appropriately adjusted for any reorganization, recapitalization, non-cash dividend, stock split, reverse stock split or other similar transaction. Following delivery of an Exchange Notice, Company may not deliver another Exchange Notice to Investor for at least three (3) Trading Days.

4. Representations and Warranties. In order to induce Investor to enter into this Amendment, Company, for itself, and for its affiliates, successors and assigns, hereby acknowledges, represents, warrants and agrees as follows:

(a) Company has full power and authority to enter into this Amendment and to incur and perform all obligations and covenants contained herein, all of which have been duly authorized by all proper and necessary action. No consent, approval, filing or registration with or notice to any governmental authority is required as a condition to the validity of this Amendment or the performance of any of the obligations of Company hereunder.

(b) There is no fact known to Company or which should be known to Company which Company has not disclosed to Investor on or prior to the date of this Amendment which would or could materially and adversely affect the understanding of Investor expressed in this Amendment or any representation, warranty, or recital contained in this Amendment.

(c) Except as expressly set forth in this Amendment, Company acknowledges and agrees that neither the execution and delivery of this Amendment nor any of the terms, provisions, covenants, or agreements contained in this Amendment shall in any manner release, impair, lessen, modify, waive, or otherwise affect the liability and obligations of Company under the terms of the Royalty Interest.

(d) Company has no defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action of any kind or nature whatsoever against Investor, directly or indirectly, arising out of, based upon, or in any manner connected with, the transactions contemplated hereby, whether known or unknown, which occurred, existed, was taken, permitted, or begun prior to the execution of this Amendment and occurred, existed, was taken, permitted or begun in accordance with, pursuant to, or by virtue of any of the terms or conditions of the Royalty Interest. To the extent any such defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action exist or existed, such defenses, rights, claims, counterclaims, actions and causes of action are hereby waived, discharged and released. Company hereby acknowledges and agrees that the execution of this Amendment by Investor shall not constitute an acknowledgment of or admission by Investor of the existence of any claims or of liability for any matter or precedent upon which any claim or liability may be asserted.

(e) Company represents and warrants that as of the date hereof no Events of Default or other material breaches exist under the Royalty Interest, or have occurred prior to the date hereof.

5. Other Terms Unchanged. The Royalty Interest, as amended by this Amendment, remains and continues in full force and effect, constitutes legal, valid, and binding obligations of each of the parties, and is in all respects agreed to, ratified, and confirmed. Any reference to the Royalty Interest after the date of this Amendment is deemed to be a reference to the Royalty Interest as amended by this Amendment. If there is a conflict between the terms of this Amendment and the Royalty Interest, the terms of this Amendment shall control. No forbearance or waiver may be implied by this Amendment. Company acknowledges that it is unconditionally obligated to pay the remaining balance of the Royalty Interest and represents that such obligation is not subject to any deductions, defenses, rights of offset, or counterclaims of any kind. Except as expressly set forth herein, the execution, delivery, and performance of this Amendment shall not operate as a waiver of, or as an amendment to, any right, power, or remedy of Investor under the Royalty Interest, as in effect prior to the date hereof.

6. No Reliance. Company acknowledges and agrees that neither Investor nor any of its officers, directors, members, managers, equity holders, representatives or agents has made any representations or warranties to Company or any of its agents, representatives, officers, directors, or employees except as expressly set forth in this Amendment and the Royalty Interest and, in making its decision to enter into the

transactions contemplated by this Amendment, Company is not relying on any representation, warranty, covenant or promise of Investor or its officers, directors, members, managers, equity holders, agents or representatives other than as set forth in this Amendment.

7. Counterparts. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, but all of which together shall constitute one instrument. The parties hereto confirm that any electronic copy of another party's executed counterpart of this Amendment (or such party's signature page thereof) will be deemed to be an executed original thereof.

8. Further Assurances. Each party shall do and perform or cause to be done and performed, all such further acts and things, and shall execute and deliver all such other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Amendment and the consummation of the transactions contemplated hereby.

[Remainder of page intentionally left blank]

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the date set forth above.

COMPANY:

JAGUAR HEALTH, INC.

By: /s/ Lisa Conte

Lisa Conte, President and CEO

INVESTOR:

ILIAD RESEARCH AND TRADING, L.P.

By: Iliad Management, LLC, its General Partner

By: Fife Trading, Inc., its Manager

By: /s/ John M. Fife

John M. Fife, President

Appendix B-2

Amendment to December 2020 Royalty Interest

GLOBAL AMENDMENT

This Global Amendment (this “**Amendment**”) is entered into as of April 14, 2022 by and between Uptown Capital, LLC, a Utah limited liability company (f/k/a Irving Park Capital, LLC) (“**Investor**”), and Jaguar Health, Inc. a Delaware corporation (“**Company**”). Capitalized terms used in this Amendment without definition shall have the meanings given to them in the Royalty Interest (as defined below).

A. Company previously sold and issued to Investor that certain Royalty Interest dated December 22, 2020 in the original principal amount of \$12,000,000 (the “**Royalty Interest**”).

B. Investor and Company have agreed, subject to the terms, amendments, conditions and understandings expressed in this Amendment, to amend the Royalty Interest as set forth herein.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties agree as follows:

1. Recitals. Each of the parties hereto acknowledges and agrees that the recitals set forth above in this Amendment are true and accurate and are hereby incorporated into and made a part of this Amendment.

2. Definitions. For purposes of this Amendment, the following terms will have the following meanings:

(a) “**Exchange Amount**” means the amount of the Royalty Interest that Company desires to exchange for Exchange Shares.

(b) “**Exchange Cap**” means the maximum number of Exchange Shares that could be issued to Investor without violating The Nasdaq Capital Market rules related to the aggregation of offerings under Nasdaq Listing Rule 5635(d), if applicable.

(c) “**Exchange Conditions**” means: (a) with respect to the applicable Exchange Date all of the Exchange Shares would be (i) registered for trading under applicable federal and state securities laws, (ii) freely tradable under Rule 144, or (iii) otherwise freely tradable without the need for registration under any applicable federal or state securities laws; (b) the applicable Exchange Shares would be eligible for immediate resale by Investor; (c) no Event of Default shall have occurred under the Royalty Interest; (d) if Company’s Common Stock is trading on OTCQB or OTCQX, the Exchange Amount is less than or equal to twenty-five percent (25%) of the median daily dollar trading volume of Company’s Common Stock during the ten (10) Trading Days preceding the Exchange Date; and (e) the Common Stock is trading on Nasdaq, NYSE, OTCQB or OTCQX.

(d) “**Exchange Date**” means the date that an Exchange Notice is submitted by Company to Investor.

(e) “**Exchange Notice**” means a notice delivered by Company to Investor specifying the Exchange Amount to be exchanged and the number of Exchange Shares to be issued.

(f) “**Exchange Shares**” the number of shares of Company’s Common Stock to be issued pursuant to an applicable Exchange Notice.

(g) “**Nasdaq Minimum Price**” means such term as defined in Nasdaq Listing Rule 5635(d).

3. Company Exchange Right. The Royalty Interest is hereby amended to grant Company the right to exchange from time to time at Company’s sole discretion any Exchange Amount for Exchange Shares at a price per share equal to the Nasdaq Minimum Price as of each applicable Exchange Date. Notwithstanding the foregoing, Company will not have the right to exchange any Exchange Amount and issue any Exchange Shares to Investor if: (a) the issuance of such Exchange Shares would cause Investor’s beneficial ownership to exceed 4.99% of Company’s issued and outstanding Common Stock as of such date; (b) any of the Exchange Conditions has not been satisfied as of the applicable Exchange Date; and (c) the total cumulative

number of Exchange Shares to be issued to Investor would exceed the Exchange Cap unless (i) stockholder approval is obtained to issue more than the Exchange Cap or (ii) the Common Stock is not listed for quotation on Nasdaq or NYSE American. The Exchange Cap shall be appropriately adjusted for any reorganization, recapitalization, non-cash dividend, stock split, reverse stock split or other similar transaction. Following delivery of an Exchange Notice, Company may not deliver another Exchange Notice to Investor for at least three (3) Trading Days.

4. Representations and Warranties. In order to induce Investor to enter into this Amendment, Company, for itself, and for its affiliates, successors and assigns, hereby acknowledges, represents, warrants and agrees as follows:

(a) Company has full power and authority to enter into this Amendment and to incur and perform all obligations and covenants contained herein, all of which have been duly authorized by all proper and necessary action. No consent, approval, filing or registration with or notice to any governmental authority is required as a condition to the validity of this Amendment or the performance of any of the obligations of Company hereunder.

(b) There is no fact known to Company or which should be known to Company which Company has not disclosed to Investor on or prior to the date of this Amendment which would or could materially and adversely affect the understanding of Investor expressed in this Amendment or any representation, warranty, or recital contained in this Amendment.

(c) Except as expressly set forth in this Amendment, Company acknowledges and agrees that neither the execution and delivery of this Amendment nor any of the terms, provisions, covenants, or agreements contained in this Amendment shall in any manner release, impair, lessen, modify, waive, or otherwise affect the liability and obligations of Company under the terms of the Royalty Interest.

(d) Company has no defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action of any kind or nature whatsoever against Investor, directly or indirectly, arising out of, based upon, or in any manner connected with, the transactions contemplated hereby, whether known or unknown, which occurred, existed, was taken, permitted, or begun prior to the execution of this Amendment and occurred, existed, was taken, permitted or begun in accordance with, pursuant to, or by virtue of any of the terms or conditions of the Royalty Interest. To the extent any such defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action exist or existed, such defenses, rights, claims, counterclaims, actions and causes of action are hereby waived, discharged and released. Company hereby acknowledges and agrees that the execution of this Amendment by Investor shall not constitute an acknowledgment of or admission by Investor of the existence of any claims or of liability for any matter or precedent upon which any claim or liability may be asserted.

(e) Company represents and warrants that as of the date hereof no Events of Default or other material breaches exist under the Royalty Interest, or have occurred prior to the date hereof.

5. Other Terms Unchanged. The Royalty Interest, as amended by this Amendment, remains and continues in full force and effect, constitutes legal, valid, and binding obligations of each of the parties, and is in all respects agreed to, ratified, and confirmed. Any reference to the Royalty Interest after the date of this Amendment is deemed to be a reference to the Royalty Interest as amended by this Amendment. If there is a conflict between the terms of this Amendment and the Royalty Interest, the terms of this Amendment shall control. No forbearance or waiver may be implied by this Amendment. Company acknowledges that it is unconditionally obligated to pay the remaining balance of the Royalty Interest and represents that such obligation is not subject to any deductions, defenses, rights of offset, or counterclaims of any kind. Except as expressly set forth herein, the execution, delivery, and performance of this Amendment shall not operate as a waiver of, or as an amendment to, any right, power, or remedy of Investor under the Royalty Interest, as in effect prior to the date hereof.

6. No Reliance. Company acknowledges and agrees that neither Investor nor any of its officers, directors, members, managers, equity holders, representatives or agents has made any representations or warranties to Company or any of its agents, representatives, officers, directors, or employees except as expressly set forth in this Amendment and the Royalty Interest and, in making its decision to enter into the

transactions contemplated by this Amendment, Company is not relying on any representation, warranty, covenant or promise of Investor or its officers, directors, members, managers, equity holders, agents or representatives other than as set forth in this Amendment.

7. Counterparts. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, but all of which together shall constitute one instrument. The parties hereto confirm that any electronic copy of another party's executed counterpart of this Amendment (or such party's signature page thereof) will be deemed to be an executed original thereof.

8. Further Assurances. Each party shall do and perform or cause to be done and performed, all such further acts and things, and shall execute and deliver all such other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Amendment and the consummation of the transactions contemplated hereby.

[Remainder of page intentionally left blank]

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the date set forth above.

COMPANY:

JAGUAR HEALTH, INC.

By: /s/ Lisa Conte

Lisa Conte, President and CEO

INVESTOR:

UPTOWN CAPITAL, LLC

By: /s/ John M. Fife

John M. Fife, President

Appendix B-3

Amendment to March 2021 Royalty Interest

GLOBAL AMENDMENT

This Global Amendment (this “**Amendment**”) is entered into as of April 14, 2022 by and between Streeterville Capital, LLC, a Utah limited liability company (“**Investor**”), and Jaguar Health, Inc. a Delaware corporation (“**Company**”). Capitalized terms used in this Amendment without definition shall have the meanings given to them in the Royalty Interest (as defined below).

A. Company previously sold and issued to Investor that certain Royalty Interest dated March 8, 2021 in the original principal amount of \$10,000,000 (the “**Royalty Interest**”).

B. Investor and Company have agreed, subject to the terms, amendments, conditions and understandings expressed in this Amendment, to amend the Royalty Interest as set forth herein.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties agree as follows:

1. Recitals. Each of the parties hereto acknowledges and agrees that the recitals set forth above in this Amendment are true and accurate and are hereby incorporated into and made a part of this Amendment.

2. Definitions. For purposes of this Amendment, the following terms will have the following meanings:

(a) “**Exchange Amount**” means the amount of the Royalty Interest that Company desires to exchange for Exchange Shares.

(b) “**Exchange Cap**” means the maximum number of Exchange Shares that could be issued to Investor without violating The Nasdaq Capital Market rules related to the aggregation of offerings under Nasdaq Listing Rule 5635(d), if applicable.

(c) “**Exchange Conditions**” means: (a) with respect to the applicable Exchange Date all of the Exchange Shares would be (i) registered for trading under applicable federal and state securities laws, (ii) freely tradable under Rule 144, or (iii) otherwise freely tradable without the need for registration under any applicable federal or state securities laws; (b) the applicable Exchange Shares would be eligible for immediate resale by Investor; (c) no Event of Default shall have occurred under the Royalty Interest; (d) if Company’s Common Stock is trading on OTCQB or OTCQX, the Exchange Amount is less than or equal to twenty-five percent (25%) of the median daily dollar trading volume of Company’s Common Stock during the ten (10) Trading Days preceding the Exchange Date; and (e) the Common Stock is trading on Nasdaq, NYSE, OTCQB or OTCQX.

(d) “**Exchange Date**” means the date that an Exchange Notice is submitted by Company to Investor.

(e) “**Exchange Notice**” means a notice delivered by Company to Investor specifying the Exchange Amount to be exchanged and the number of Exchange Shares to be issued.

(f) “**Exchange Shares**” the number of shares of Company’s Common Stock to be issued pursuant to an applicable Exchange Notice.

(g) “**Nasdaq Minimum Price**” means such term as defined in Nasdaq Listing Rule 5635(d).

3. Company Exchange Right. The Royalty Interest is hereby amended to grant Company the right to exchange from time to time at Company’s sole discretion any Exchange Amount for Exchange Shares at a price per share equal to the Nasdaq Minimum Price as of each applicable Exchange Date. Notwithstanding the foregoing, Company will not have the right to exchange any Exchange Amount and issue any Exchange Shares to Investor if: (a) the issuance of such Exchange Shares would cause Investor’s beneficial ownership to exceed 4.99% of Company’s issued and outstanding Common Stock as of such date; (b) any of the Exchange Conditions has not been satisfied as of the applicable Exchange Date; and (c) the total cumulative

number of Exchange Shares to be issued to Investor would exceed the Exchange Cap unless (i) stockholder approval is obtained to issue more than the Exchange Cap or (ii) the Common Stock is not listed for quotation on Nasdaq or NYSE American. The Exchange Cap shall be appropriately adjusted for any reorganization, recapitalization, non-cash dividend, stock split, reverse stock split or other similar transaction. Following delivery of an Exchange Notice, Company may not deliver another Exchange Notice to Investor for at least three (3) Trading Days.

4. Representations and Warranties. In order to induce Investor to enter into this Amendment, Company, for itself, and for its affiliates, successors and assigns, hereby acknowledges, represents, warrants and agrees as follows:

(a) Company has full power and authority to enter into this Amendment and to incur and perform all obligations and covenants contained herein, all of which have been duly authorized by all proper and necessary action. No consent, approval, filing or registration with or notice to any governmental authority is required as a condition to the validity of this Amendment or the performance of any of the obligations of Company hereunder.

(b) There is no fact known to Company or which should be known to Company which Company has not disclosed to Investor on or prior to the date of this Amendment which would or could materially and adversely affect the understanding of Investor expressed in this Amendment or any representation, warranty, or recital contained in this Amendment.

(c) Except as expressly set forth in this Amendment, Company acknowledges and agrees that neither the execution and delivery of this Amendment nor any of the terms, provisions, covenants, or agreements contained in this Amendment shall in any manner release, impair, lessen, modify, waive, or otherwise affect the liability and obligations of Company under the terms of the Royalty Interest.

(d) Company has no defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action of any kind or nature whatsoever against Investor, directly or indirectly, arising out of, based upon, or in any manner connected with, the transactions contemplated hereby, whether known or unknown, which occurred, existed, was taken, permitted, or begun prior to the execution of this Amendment and occurred, existed, was taken, permitted or begun in accordance with, pursuant to, or by virtue of any of the terms or conditions of the Royalty Interest. To the extent any such defenses, affirmative or otherwise, rights of setoff, rights of recoupment, claims, counterclaims, actions or causes of action exist or existed, such defenses, rights, claims, counterclaims, actions and causes of action are hereby waived, discharged and released. Company hereby acknowledges and agrees that the execution of this Amendment by Investor shall not constitute an acknowledgment of or admission by Investor of the existence of any claims or of liability for any matter or precedent upon which any claim or liability may be asserted.

(e) Company represents and warrants that as of the date hereof no Events of Default or other material breaches exist under the Royalty Interest, or have occurred prior to the date hereof.

5. Other Terms Unchanged. The Royalty Interest, as amended by this Amendment, remains and continues in full force and effect, constitutes legal, valid, and binding obligations of each of the parties, and is in all respects agreed to, ratified, and confirmed. Any reference to the Royalty Interest after the date of this Amendment is deemed to be a reference to the Royalty Interest as amended by this Amendment. If there is a conflict between the terms of this Amendment and the Royalty Interest, the terms of this Amendment shall control. No forbearance or waiver may be implied by this Amendment. Company acknowledges that it is unconditionally obligated to pay the remaining balance of the Royalty Interest and represents that such obligation is not subject to any deductions, defenses, rights of offset, or counterclaims of any kind. Except as expressly set forth herein, the execution, delivery, and performance of this Amendment shall not operate as a waiver of, or as an amendment to, any right, power, or remedy of Investor under the Royalty Interest, as in effect prior to the date hereof.

6. No Reliance. Company acknowledges and agrees that neither Investor nor any of its officers, directors, members, managers, equity holders, representatives or agents has made any representations or warranties to Company or any of its agents, representatives, officers, directors, or employees except as expressly set forth in this Amendment and the Royalty Interest and, in making its decision to enter into the

transactions contemplated by this Amendment, Company is not relying on any representation, warranty, covenant or promise of Investor or its officers, directors, members, managers, equity holders, agents or representatives other than as set forth in this Amendment.

7. Counterparts. This Amendment may be executed in any number of counterparts, each of which shall be deemed an original, but all of which together shall constitute one instrument. The parties hereto confirm that any electronic copy of another party's executed counterpart of this Amendment (or such party's signature page thereof) will be deemed to be an executed original thereof.

8. Further Assurances. Each party shall do and perform or cause to be done and performed, all such further acts and things, and shall execute and deliver all such other agreements, certificates, instruments and documents, as the other party may reasonably request in order to carry out the intent and accomplish the purposes of this Amendment and the consummation of the transactions contemplated hereby.

[Remainder of page intentionally left blank]

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the date set forth above.

COMPANY:

JAGUAR HEALTH, INC.

By: /s/ Lisa Conte

Lisa Conte, President and CEO

INVESTOR:

STREETERVILLE CAPITAL, LLC

By: /s/ John M. Fife

John M. Fife, President

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**

Washington, DC 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2021

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

COMMISSION FILE NO. 001-36714

JAGUAR HEALTH, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

46-2956775
(I.R.S. Employer
Identification No.)

200 Pine Street, Suite 400
San Francisco, California 94104
(Address of principal executive offices)

Registrant's telephone number, including area code:
(415) 371-8300

SECURITIES REGISTERED PURSUANT TO SECTION 12(b) OF THE ACT:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, Par Value \$0.0001 Per Share	JAGX	The Nasdaq Capital Market

SECURITIES REGISTERED PURSUANT TO SECTION 12(g) OF THE ACT: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes No

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No

As of June 30, 2021, the aggregate market value of the registrant's common stock held by non-affiliates was approximately \$215,622,279 based upon the closing sales price of the registrant's common stock on The Nasdaq Capital Market on such date.

The number of shares of the registrant's common stock outstanding as of March 10, 2022 was 77,053,990 shares of voting common stock and 673 shares of non-voting common stock, par value \$0.0001 per share (convertible into equivalent shares of voting common stock).

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the proxy statement for the registrant's 2022 Annual Meeting of Stockholders, or Proxy Statement, to be filed within 120 days of the end of the fiscal year ended December 31, 2021 are incorporated by reference in Part III hereof. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as a part hereof.

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PART I

Forward-looking statements

This Form 10-K contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements other than statements of historical facts contained in this Form 10-K, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, research and development costs, timing of receipt of clinical trial, field study and other study data, and likelihood of success, commercialization plans and timing, other plans and objectives of management for future operations, and future results of current and anticipated products are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “aim,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplate,” “believe,” “estimate,” “predict,” “potential” or “continue” or the negative of these terms or other similar expressions. The forward-looking statements in this Form 10-K are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this Form 10-K and are subject to a number of risks, uncertainties and assumptions described under the sections in this Form 10-K titled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and elsewhere in this Form 10-K. Forward-looking statements are subject to inherent risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that we may face. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

Jaguar Health, our logo, Napo Pharmaceuticals, Napo Therapeutics, Mytesi, Equilevia, Canalevia, Canalevia-CA1, Canalevia-CA2, and Neonorm are our trademarks that are used in this Form 10 K. This Form 10 K also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this Form 10 K appear without the ©, ® or ™ symbols, but those references are not intended to indicate that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

ITEM 1. BUSINESS

BUSINESS

Jaguar Health, Inc. (“Jaguar” or the “Company”) is a commercial stage pharmaceuticals company focused on developing novel, plant-based, non-opioid, and sustainably derived prescription medicines for people and animals with GI distress, including chronic, debilitating diarrhea. Jaguar Animal Health is a tradename of Jaguar Health. Our wholly owned subsidiary, Napo Pharmaceuticals, Inc. (“Napo”), focuses on developing and commercializing proprietary plant-based human pharmaceuticals for the global marketplace from plants or plant products used traditionally in rainforest areas. Napo’s marketed drug Mytesi (crofelemer 125 mg delayed-release tablets) is a first-in-class oral botanical drug product approved by the U.S. Food and Drug Administration (“FDA”) for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. To date, this is the only oral plant-based botanical prescription medicine approved under the FDA’s Botanical Guidance. Jaguar Animal Health’s Canalevia-CA1 (crofelemer delayed-release tablets) drug is the first and only oral plant-based prescription product that is FDA conditionally approved to treat chemotherapy-induced diarrhea (“CID”) in dogs. Canalevia-CA1

is a canine-specific formulation of crofelemer. Napo Therapeutics S.p.A., Napo's majority owned Italian subsidiary, focuses on expanding crofelemer access in Europe.

Jaguar, formerly known as Jaguar Animal Health, Inc., was founded in San Francisco, California as a Delaware corporation on June 6, 2013 (inception). The Company was a majority-owned subsidiary of Napo until the close of the Company's initial public offering on May 18, 2015. The Company was formed to develop and commercialize first-in-class prescription and non-prescription products for companion and production animals and horses. The Company's first non-prescription commercial products, Neonorm Calf and Neonorm Foal, were launched in 2014 and 2016, respectively.

On July 31, 2017, Jaguar completed a merger with Napo pursuant to the Agreement and Plan of Merger dated March 31, 2017, by and among Jaguar, Napo, Napo Acquisition Corporation ("Merger Sub"), and Napo's representative (the "Merger Agreement"). In accordance with the terms of the Merger Agreement, upon the completion of the merger, Merger Sub merged with and into Napo, with Napo surviving as the wholly-owned subsidiary (the "Merger" or "Napo Merger"). Immediately following the Merger, Jaguar changed its name from "Jaguar Animal Health, Inc." to "Jaguar Health, Inc." Napo now operates as a wholly-owned subsidiary of Jaguar focused on human health including the ongoing development of crofelemer and commercialization of Mytesi.

On March 15, 2021, Jaguar established Napo EU S.p.A (which changed its name in January 2022 to Napo Therapeutics S.p.A. "Napo Therapeutics") based in Milan, Italy as a subsidiary of Napo. Napo Therapeutics' mission is to provide access to crofelemer in Europe to address significant rare/orphan disease indications, including, initially, two key orphan target indications: Short bowel syndrome with intestinal failure ("SBS-IF"), and congenital diarrheal disorders ("CDD"). On November 3, 2021, Napo Therapeutics merged with Dragon SPAC S.p.A. ("Dragon SPAC").

On December 13, 2021, the European Medicines Agency ("EMA") granted orphan-drug designation ("ODD") for crofelemer for short bowel syndrome ("SBS") indication in the European Union following review of the ODD application Napo submitted to the EMA in September 2021. Following this decision from the EMA, Napo Therapeutics is initiating efforts to commence clinical development of crofelemer in both adult and pediatric SBS patients in support of the company's key focus on leveraging the EMA's accelerated conditional marketing authorization pathway in Europe for these rare diseases. Napo Therapeutics has also agreed to support an investigator-initiated trial ("IIT") which will provide proof of concept ("POC") support for potential expanded access programs for crofelemer for patients with CDD and/or SBS patients with intestinal failure ("IF"). The expanded access program will be initiated following completion of this study and upon publication of POC results, potentially in 2023. Crofelemer previously received ODD in the U.S. from the FDA for SBS. SBS affects approximately 10,000 to 20,000 people in the U.S., according to the Crohn's & Colitis Foundation, and it is estimated that the population of SBS patients in Europe is approximately the same size. Despite limited treatment options, the global SBS market exceeded \$568 million in 2019 and is expected to reach \$4.6 billion by 2027, according to a report by Vision Research Reports.

On December 21, 2021, we received conditional approval from the FDA to market Canalevia-CA1 (crofelemer delayed-release tablets), our oral plant-based prescription drug and the only drug for the treatment of CID in dogs. We expect Canalevia-CA1 to be available to multiple leading veterinary distributors in the U.S. in the second quarter of 2022 after we complete a post-approval update to the chemistry, manufacturing and controls ("CMC") related to crofelemer. This update will align with the CMC requirements related to crofelemer used as the active ingredient in Mytesi.

On January 4, 2022, we announced the launch of Canalevia-CA1 (crofelemer delayed-released tablets), which is being commercialized as a prescription drug product under the Company's Jaguar Animal Health tradename. Canalevia-CA1 is a tablet that is given orally and can be prescribed for home treatment of CID. Canalevia-CA1 is a canine-specific formulation of crofelemer that is conditionally approved by the FDA under application number 141-552. Conditional approval allows for commercialization of the product while Jaguar Animal Health continues to collect the substantial evidence of effectiveness required for a full approval. We have received Minor Use in a Major Species ("MUMS") designation from the FDA for Canalevia-CA1 to treat CID in dogs. FDA has established a "small number" threshold for minor use in each of the seven major species covered by the MUMS act. The small number threshold is currently 70,000 for dogs, representing the largest number of dogs that can be affected by a disease or

condition over the course of a year and still have the use qualify as a minor use. We expect Canalevia-CA1 to be available to multiple leading veterinary distributors in the U.S. in the second quarter of 2022 after we complete a post-conditional-approval update to the CMC related to crofelemer. In the field of animal health, we are continuing limited activities related to developing and commercializing first in class gastrointestinal products for dogs, dairy calves, foals, and high value horses.

Most of the activities of the Company are focused on the commercialization of Mytesi and Canalevia-CA1 and the ongoing clinical development of crofelemer for the prophylaxis of diarrhea in adult patients receiving targeted cancer therapy. In June 2021, Napo Pharmaceuticals recruited Dr. Darlene Horton, as the Chief Medical Officer (“CMO”) of Napo Pharmaceuticals to support the ongoing clinical development activities for prescription products for human health. Dr. Horton is a 25-year veteran of the biotech and pharmaceutical industry. Prior to joining Napo, she led clinical development and regulatory strategy as CMO at Coherus Biosciences, Itero Biopharmaceuticals, and SMC Biotechnology. As Head of Clinical and Medical Affairs at Scios, she led the clinical development program that led to the approval of Natrecor® and was on the senior executive team when Scios was acquired by JNJ for \$2.4B. At JNJ, she co-led (with strategic marketing) the cardiovascular therapeutic area when JNJ in-licensed and began developing the blockbuster drug Xarelto®. She also served as CEO at Nile Therapeutics and TulangCo Inc. Dr. Horton completed her Pediatric Cardiology fellowship and Pediatrics Residency at UCSF. She holds M.D. and B.S. in Microbiology degrees from the University of Florida.

We believe Jaguar is poised to realize a number of synergistic, value adding benefits—an expanded pipeline of potential blockbuster human follow on indications of crofelemer, and a second generation anti secretory agent—upon which to build global partnerships. Jaguar, through Napo, holds global unencumbered rights for crofelemer, Mytesi, and Canalevia-CA1. Additionally, several of the drug product opportunities in Jaguar’s crofelemer pipeline are backed by Phase 2 and proof of concept evidence from human clinical trials.

Crofelemer is a novel, first in class anti secretory agent which has a normalizing effect on electrolyte and fluid balance while acting locally in the gut, and this mechanism of action has the potential to benefit multiple disorders that cause gastrointestinal distress, including diarrhea and abdominal discomfort. Crofelemer is also in development for possible follow on indications, including prophylaxis for cancer therapy related diarrhea (“CTD”); for rare disease indications for symptomatic treatment of infants and children with CDD and for adult and pediatric patients with SBS-IF. As mentioned above, crofelemer has received ODD for SBS in the US and in the European Union (“EU”). Furthermore, the drug is being evaluated for management of diarrhea and abdominal discomfort in inflammatory bowel disease (“IBD”); diarrhea-predominant irritable bowel syndrome (“IBS-D”); and for idiopathic/functional diarrhea. A second generation proprietary anti secretory agent, NP-300 (lechlemer), is undergoing preclinical development for symptomatic relief and treatment of diarrhea in patients with acute infection from cholera.

Napo has a direct sales force of 8 sales representatives and a national sales director covering U.S. geographies with the highest commercial potential. In 2019, we hired Ian Wendt, an industry veteran with a broad range of experience that includes commercializing supportive care and HIV treatments, as Vice President of Commercial Strategy. He was promoted to Chief Commercial Officer in 2020. With support provided by concomitant marketing, promotional activities, patient education programs and peer education initiatives described below, we expect continued growth in the number of patients treated with Mytesi. Mr. Wendt will lead disease state educational initiatives that will pave the way for crofelemer’s final development for the CTD market and our commercial role for this next important, potential indication for Mytesi. Additionally, he is leading commercialization activities for Canalevia-CA1 in the U.S. veterinary market.

A key component of our marketing strategies for Mytesi in 2021 was focused on the transition of Mytesi distribution to a closed network of specialty pharmacies rather than to wholesalers that resell the product to retail pharmacies. This transition was intended to help remove access barriers for patients receiving Mytesi and includes services such as a higher level of support for prior authorizations, appeals, adherence counseling, and home delivery options. While patients often visit retail pharmacies for short-term or uncomplicated medical needs, specialty pharmacies focus on serving patients with complex and chronic medical conditions like HIV. The transition to a closed network of specialty pharmacies is expected to result in a meaningful reduction in Mytesi distribution costs and

prepare our U.S. commercial distribution network for future indication expansion of cfofelemer to other populations of patients with complex medical needs. However, when we made the full transition on September 3, 2021, to selling to specialty pharmacies, it resulted in an underrepresentation of actual Mytesi utilization, as wholesalers depleted their inventory during the transition process.

The goal of Napo's sales team is to deliver a frequent and consistent selling message to targeted, high volume prescribers of HIV antiretroviral therapies ("ART") and to gastroenterologists who see large numbers of HIV patients. In 2017 we released the results of a survey of 350 people living with HIV and AIDS regarding the topic of "Talking to Your Doctor About Symptoms." The survey results show that diarrhea remains prevalent in those living with HIV/AIDS, with 27% of respondents reporting that they currently have diarrhea, and 56% reporting that they have had diarrhea in the past. Additionally, the results of a 2017 Napo sponsored survey of 271 U.S. board certified gastroenterologists indicate that the number one GI complaint for people living with HIV/AIDS is diarrhea, and 93% of U.S. gastroenterologists see patients with HIV/AIDS in their practice.

Key to the success of our sales representatives in growing Mytesi sales is segmenting and targeting the right health care providers—those HIV treaters who are high prescribers of ART and those gastrointestinal doctors who see large populations of people living with HIV/AIDS. The target list of prescribers for our sales reps includes a pool of approximately 1,300 high volume ART prescribing HIV specialists, and gastroenterologists who see the largest number of people living with HIV/AIDS, and we've strategically focused our sales force in the US geographies with the highest potential, including San Francisco, Sacramento, Seattle, southern California, Arizona, Nevada, Florida, New York City/Long Island, Connecticut, New Jersey, Pennsylvania, Maryland, Kansas, Texas, Missouri, Chicago, Michigan, Atlanta, Louisiana, DC, Virginia, North Carolina, South Carolina, Indianapolis, and Ohio.

Medical education presentations led by health care providers ("HCPs") participating in the Napo Speakers Bureau—a group that includes HIV/AIDS treaters, infectious disease specialists, gastroenterologists, colorectal surgeons, nurse practitioners, doctors of pharmacology, and physician assistants—focus on the prevalence and pathophysiology of gastrointestinal consequences of HIV infection and on the latest treatment options for HIV related diarrhea. Presentations given by patient advocate members provide information to HIV/AIDS patients about the prevalence of diarrhea in people living with HIV/AIDS ("PLWHA") and offer guidance about talking to HCPs regarding diarrhea related concerns.

With the introduction of newer antiretroviral ("ARV") drug therapies, there has been a reduction in the severity of ARV induced diarrhea. However, a significant portion of this patient population still suffers from diarrhea caused by HIV enteropathy, which is due to the direct and indirect effects of HIV on the intestinal mucosa. Chronic diarrhea remains a significant complaint of PLWHA, particularly those who are older and have lived with the virus in their gut for 10+ years. According to data from the U.S. Centers for Disease Control and Prevention, currently more than 70% of people living with HIV are over age 50 and have lived with HIV for more than 10 years.

Napo is on many AIDS Drug Assistance Program ("ADAP") formularies. ADAPs provide lifesaving HIV treatments to low income, uninsured, and underinsured individuals living with HIV/AIDS in all 50 states and the territories. The ADAP program provides Mytesi free of charge to patients who qualify and copay support for some patients who have insurance coverage. Based on data from healthcare research firm Decision Resource Group, approximately 86% of ADAP eligible US lives now have access to Mytesi, which is now on the ADAP formularies for 30 states, including the four programs with the largest enrollment.

In May 2020, Napo launched a program to educate insurance companies about the benefits of Mytesi and negotiate better access to Mytesi for commercially insured patients. We believed that our enhanced Mytesi market access strategy engaged select payors in contracting discussions with the objective of removing barriers for patients in order to allow them to more easily start on – and stay on – Mytesi. This initiative represented a commercial opportunity to employ a strategic mechanism that was well-established in the U.S. pharmaceutical industry to help patients access Mytesi.

Napo expanded the NapoCares Patient Support Program for Mytesi in April 2020 as part of the Company's enhanced market access strategy. The expansion meaningfully increased co-pay support for commercially insured patients, which also includes allowing the co-pay amount to remain the same whether a patient fills a 30-day or a 90-day prescription of Mytesi. The expansion also increased the income ceiling from two times the Federal poverty limit to five times the Federal poverty limit for our patient assistance program, which will allow more low-income patients to receive Mytesi at no cost. The co-pay program and patient assistance program are components of a comprehensive suite of patient support services Napo rolled out in the second quarter of 2020 with the support of AssistRx, a specialty therapy initiation and patient support company.

On August 2021, Napo signed a license agreement with Napo EU S.p.A. to study, develop, manufacture, and commercialize Napo's plant-based crofelemer and lechlemer drug product candidates in the European Union (excluding Russia) and in specified non-EU countries in Europe for specific indications, which rights and obligations were assumed by the combined company formed by the merger of Napo Therapeutics with Dragon SPAC (the combined company uses the Napo Therapeutics name). Per the terms of the license agreement, Napo will receive payment of up to \$10 million as the initial license fee (to be paid in two installments, the first of which has already been received) as the initial license fee and is eligible to receive additional payments related to milestones, royalties, and product transfers.

In November 2021, Napo Therapeutics appointed Mr. Massimo Mineo, a veteran of the European pharmaceutical industry for 20+ years, as general manager (the equivalent in Europe of chief executive). He has significant experience in the field of orphan-drug development and commercialization activities and his leadership is expected to be instrumental in the ongoing development and commercialization activities for crofelemer for the planned SBS-IF indication in the EU. Mr. Mineo is responsible for the strategy, planning, direction, and implementation of all Napo Therapeutics' commercial, operational, and product development activities within Europe, with success defined by bringing crofelemer to market for key initial target indications, beginning with SBS-IF and CDD.

In November 2021, Napo Therapeutics announced the appointment of Annabella Amatulli as chief regulatory officer. A recognized expert in global regulatory affairs, Ms. Amatulli is responsible for both high-level strategic planning and hands-on support for Napo Therapeutics' development programs and licensed products from a regulatory perspective and serves as the primary liaison between Napo Therapeutics and European health authorities.

In January 2022, Napo Therapeutics announced the appointment of Martire Particco, MD, a physician with 30+ years of experience in Europe's pharmaceutical industry and in clinical practice, as its CMO for the EU-related development activities of Napo Therapeutics. Dr. Particco possesses in-depth experience in the field of orphan and rare diseases, having been involved in the clinical development and launch of Pfizer's pulmonary hypertension indication for sildenafil and the clinical development of Kerdion Biopharma's ligenous conjunctivitis indication for plasminogen, with direct experience with patients and experts treating these rare pathologies.

In February 2022, Napo announced the completion of a third-party, investigator-initiated preclinical enterocyte (intestinal cell) in vitro study to evaluate the effects of crofelemer on cells with certain genetic defects that result in specific forms of CDD. Jaguar believes that these study results will support certain requests received from the Office of Orphan Products Development at the U.S. FDA in response to the ODD application Napo filed with the FDA for crofelemer for CDD in infants and children. The data from this study will support the rare disease business model that Napo Therapeutics is pursuing in Europe under its exclusive license for crofelemer from Jaguar and Napo. CDD patients have intestinal failure and morbidity resulting in a failure to thrive due to malabsorption of nutrients and need parenteral nutrition. We believe the novel mechanism of action of crofelemer may have considerable potential to manage the severe secretory loss of electrolytes and fluid resulting in dehydration. There are currently no therapies for CDD except parenteral nutrition. Thus, crofelemer may reduce the associated morbidity and mortality of CDD and lessen the need for total parenteral nutrition ("TPN").

Napo has actively ensured that its intellectual property (“IP”) filings in support of the development of crofelemer for various proposed indications are protected appropriately. The IP portfolio for crofelemer includes the relief and treatment of HIV-associated diarrhea and chemotherapy-induced diarrhea as well as planned indications for inflammatory diarrhea, IBS-D, CID and SBS, with all indications, Napo prioritizes IP protection. Napo currently holds approximately 143 patents, the majority of which do not expire until 2027 - 2031, and approximately 43 patents pending.

In October 2020, Napo initiated its pivotal Phase 3 clinical trial of crofelemer (Mytesi) for prophylaxis of diarrhea in adult cancer patients receiving targeted therapy (OnTarget study). The Phase 3 OnTarget clinical trial is a 24-week (two 12-week stages), randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of crofelemer in the prophylaxis of diarrhea in adult cancer patients with solid tumors receiving targeted cancer therapy-containing treatment regimens. Patients will be randomized to receive either crofelemer or matching placebo treatment that will start concurrently with the initiation of targeted cancer therapy regimen. The primary endpoint will be assessed at the end of the initial (Stage I) 12-week double-blind placebo-controlled primary treatment phase after the last patient has completed 12 weeks of treatment. After completing the Stage I treatment phase, the subjects will have the option to remain on their assigned treatment arm and re-consent to enter into the Stage II 12-week extension phase. The safety and efficacy of orally administered crofelemer will be evaluated for the prophylaxis of diarrhea in adult cancer patients receiving targeted cancer therapies with or without standard chemotherapy regimens. The assessment of the frequency of diarrhea will be measured by the average number of weekly loose and/or watery stools for the active (crofelemer) or placebo arms over 12-week Stage I treatment period.

A significant proportion of patients undergoing cancer therapy experience diarrhea. Novel “targeted cancer therapy” agents, such as epidermal growth factor receptor (“EGFR”) antibodies and tyrosine kinase inhibitors (“TKIs”), with or without cycle chemotherapy agents, may activate intestinal chloride ion channel-mediated secretory pathways leading to increased electrolyte and fluid content in the gut lumen, which results in passage of loose/watery stools, i.e., secretory diarrhea. With increased approval of several novel targeted therapies, it is estimated that 13.6% of cancer patients in 2020 were eligible for targeted therapies with or without standard chemotherapy regimens, according to a paper published in April 2021 in the journal *Annals of Oncology*¹. According to the National Cancer Institute, in 2020, 1,806,590 new cases of cancer were diagnosed and nearly 250,000 of these newly diagnosed patients could be eligible for available targeted therapies.

Due to the chronic dosing and toxicity associated with targeted therapies, many cancer patients on targeted therapy require drug holidays or dose reductions in their therapy, including those due to diarrhea. By improving stool consistency and reducing the frequency of watery stools, crofelemer is expected to provide improved adherence to the therapeutic dosing of any targeted therapies, potentially leading to better clinical outcomes. We have learned from business development discussions with cancer drug manufacturers that the adoption and continued use of targeted cancer therapies is directly related to the ability of patients to tolerate these therapies—highlighting the importance of supportive care drugs like crofelemer to help manage cancer treatment-related diarrhea in this patient population.

As previously announced, an abstract regarding patient outcomes associated with cancer-related diarrhea (“CRD”) by Napo and Napo's collaborators was accepted for poster presentation at the American Society of Clinical Oncology (ASCO®) Annual Meeting, which was held virtually from June 4-8, 2021. This study found that patients with CRD were 40% more likely to discontinue the chemotherapy or targeted therapy than patients without CRD. The persistence of index cancer therapy and time to switch were also lower for patients with CRD. Strategies to control CRD and continue cancer therapy are urgently needed².

In addition, two CRD-related abstracts from Napo and its collaborators were accepted for online publication at ASCO. One of these studies found that patients with CRD used significantly more resources, including outpatient services, ED visits, and hospitalizations. Effective prevention of CRD remains an unmet strategy to reduce the overall

¹A. Haslam, M.S. Kim, V. Prasad, *Updated estimates of eligibility for and response to genome-targeted oncology drugs among US cancer patients, 2006-2020*

²Pablo C. Okhuysen, M.D., Lee Schwartzberg, M.D., FACP, Eric Roeland, M.D., FAAHPM, *The impact of cancer-related diarrhea on changes in cancer therapy patterns: Real world evidence*

cost of cancer care³. Findings from the other study indicated that patients with CRD had nearly 2.9 times higher all-cause total cost than patients without CRD after adjusting for covariates. Prevention of CRD may result in a significant reduction in cancer-treatment cost⁴.

As previously announced in June 2020, the effects of crofelemer (Mytesi) were evaluated in reducing diarrhea associated with the irreversible pan-HER TKI neratinib in female dogs. The data were presented at the American Association for Cancer Research (“AACR”) Annual Meeting II in 2020. The results from the dog study provide further scientific support for the evaluation of crofelemer in providing symptomatic relief of watery diarrhea in patients receiving a targeted cancer therapy drug like neratinib with or without cycle chemotherapy, without the use of antimotility drugs like loperamide, in future clinical studies.

The dog study was conducted without the prophylaxis or concomitant use of loperamide and demonstrated that crofelemer caused an approximate 30% reduction in the incidence and severity of diarrhea associated with daily oral administration of neratinib, which was statistically significant, within the 28-day period. Crofelemer also demonstrated significant improvement in the proportion of responder dogs, and there was a trend for fewer neratinib dose reductions in both crofelemer treatment groups when compared to the control group.

The results and finding from a clinical, third-party investigator-initiated Phase 2 study (called HALT-D) evaluated the effectiveness of crofelemer for reduction of diarrhea in HER2 positive breast cancer patients receiving trastuzumab, pertuzumab, and chemotherapy agents such as docetaxel or paclitaxel with or without carboplatin. The investigators of the HALT-D study, sponsored by Georgetown University and funded by Genentech, a member of the Roche Group, were presented at the San Antonio Breast Cancer Symposium on December 10, 2021. It has been reported that these pertuzumab-containing regimens cause diarrhea in up to 80% of breast cancer patients and approximately 8 to 12% of patients reach grade 3, which often requires hospitalization. No anti-diarrheal medications are currently approved that specifically target the underlying mechanism of CID associated with pertuzumab-containing regimens. Recent studies have shown that EGFR inhibitors cause increased chloride secretion into the lumen of the gut and Crofelemer through its unique and novel mechanism of reducing the chloride-secretory actions of the cystic fibrosis transmembrane conductance regulator (“CFTR”) and calcium-activated chloride channels (CaCC), was considered to be mechanistically- and physiologically-appropriate for reducing the loss of electrolyte and fluid in breast cancer patients receiving this regimen.

The Principal Investigator (“PI”), Paula Pohlmann, MD, PhD, Associated Professor at the University of Texas MD Anderson Cancer Center and formerly from Georgetown University, reported the results of the HALT-D study. This clinical study evaluated 51 breast cancer patients that were eligible to receive at least three cycles of pertuzumab-containing regimen with chemotherapy that were randomly assigned to either crofelemer in cycles 1 and 2 or the control group, in which patients received standard of care. Breakthrough anti-diarrheal medicines (“BAM”) were permitted but not given prophylactically. Findings showed that the primary endpoint, the incidence of diarrhea for at least two consecutive days, was not statistically different for the two groups. However, crofelemer patients demonstrated significantly better outcomes compared to control group patients across a number of key secondary endpoints including reductions in the incidence and severity of diarrhea in cycle 2 based on Investigator and Patient Reported Outcomes (“PRO”) (see Jaguar Health’s November 19, 2021 press release). In the presentation, additional findings were reported that showed that CID occurred significantly lesser (by 23%) in the crofelemer group during cycle 1 and crofelemer patients were 1.8 times more likely than control patients to have their diarrhea resolved. These data provide concordance to the planned primary endpoint in Napo’s ongoing phase 3 OnTarget study.

Dr. Pohlmann commented that the HALT-D study showed benefits of crofelemer across a range of important diarrhea-related measures, including its incidence, severity and probability of resolving and that the lack of difference in the primary endpoint was because about 70% of the patients in both groups would have at least two consecutive days of diarrhea regardless of cycle or CID treatment group. The incidence of two consecutive days of diarrhea is

³Lee Schwartzberg, M.D., FACP, Eric Roeland, M.D., FAAHPM, Pablo C. Okhuysen, M.D., *Characterizing unplanned resource utilization associated with cancer-related diarrhea*

⁴Eric Roeland, M.D., FAAHPM, Pablo C. Okhuysen, M.D., Lee Schwartzberg, M.D., FACP, *Healthcare utilization and costs associated with cancer-related diarrhea*

typical in cancer patient experiences from receiving chemotherapy regimens and is thus not clinically relevant as it does not differentiate the severity nor duration of CID among treatment groups. Dr. Pohlmann also commented that the secondary endpoints provided a more relevant assessment of CID, which may guide future studies that address this significant comorbidity in cancer patients receiving such regimens.

Napo is also continuing to conduct preclinical and formulation activities to support the evaluation of its second generation, plant-based oral prescription drug product, NP-300 (lechlemer), for its planned evaluation in the symptomatic treatment of diarrhea associated with acute infections including that from *Vibrio cholerae*. Cholera produces a devastating loss of electrolytes and fluid in patients and without appropriate reduction in loss of fluid and electrolytes, patients experience significant hospitalization and mortality. Lechlemer provides the opportunity to treat cholera patients in combination with oral rehydration salts (“ORS”) and the recommended guidelines from the World Health Organization (“WHO”) for the use of appropriate antibiotics to reduce the burden of the pathogen. Appropriate preclinical toxicity studies and formulation development activities are ongoing to support the conduct of clinical studies with lechlemer.

As previously mentioned, Napo completed 7-day and 28-day preclinical toxicology and safety studies in rats and dogs with lechlemer (NP-300) following repeated daily oral dosing. Napo received partial support for preclinical services from the National Institute of Allergy and Infectious Diseases (“NIAID”) of the National Institutes of Health, and Napo is grateful for their partial support of lechlemer’s development.

Napo is currently conducting additional, prerequisite IND-enabling toxicity studies and also developing appropriate oral solid dosage forms to allow the clinical evaluation of lechlemer. The Company plans to provide appropriate regulatory documents by end of the second quarter of 2022 to support the initiation of first-in-human (“FIH”) evaluation in the third quarter of 2022.

Cholera is an acute diarrheal illness caused by infection of the intestine with the bacterium *Vibrio cholerae*. According to the Centers for Disease Control and Prevention of the U.S. Department of Health & Human Services, an estimated 3.5 million cholera cases and more than 100,000 cholera-related deaths occur each year around the world. The infection is often mild or without symptoms but can sometimes be severe. Approximately one in 10 of infected persons will have severe disease characterized by profuse watery diarrhea, vomiting, and leg cramps. In these people, rapid loss of body fluids leads to dehydration and shock. Without treatment, death can occur within hours. The largest cholera outbreak in recorded history recently occurred in Yemen. According to Oxfam, the number of cholera cases in Yemen in 2019 was the second largest ever recorded in a country in a single year, surpassed only by the numbers in Yemen in 2017. According to the Brookings Institution, cholera continues to spread in Yemen, with 180,000 new cases reported in the first eight months of 2020.

We expect that lechlemer will be significantly less expensive and would support development efforts to receive a tropical disease priority review voucher from the FDA for an indication for the symptomatic treatment of diarrhea from acute infections such as cholera. Priority review vouchers are granted by the FDA as an incentive to develop treatments for neglected diseases and rare pediatric diseases. Priority review vouchers are transferable and, in past transactions by other companies, have sold for prices ranging from \$60 million to \$350 million. Additionally, we believe lechlemer may provide a long-term pipeline opportunity as a second-generation anti-secretory agent for multiple gastrointestinal diseases—especially in resource-constrained countries.

Napo received advice from the Division of Anti-Infectives at the U.S. FDA in September 2021 as part of the pre-investigational New Drug Application (“Pre-IND”) discussion. Napo plans to include the advice in its plans for the Phase 1 clinical trial in healthy volunteers, currently planned the second half of 2022. The NP-300 (lechlemer) program is paired with funding from a promissory note related to the potential future sale of a possible TDPDV.

As previously announced, the Company also launched the Entheogen Therapeutics (“ETI”) initiative to support the discovery and development of novel, natural medicines derived from psychoactive and psychedelic plant compounds for treatment of mood disorders, neuro-degenerative diseases, addiction, and other mental health disorders. The initiative is initially focused on plants with the potential to treat depression and leverages Napo’s proprietary library of approximately 2,300 plants with medicinal properties. According to statistics available from the

National Institute of Mental Health Disorders, part of the National Institutes of Health, approximately 9.5% of American adults ages 18 and over will suffer from a depressive illness (major depression, bipolar disorder, or dysthymia) each year.

Field research collaborations have been conducted in the past by members of the scientific strategy team (“SST”) of Jaguar’s predecessor company Shaman Pharmaceuticals, who are also members of the ETI SST, yielded possible applications for a compound called alstonine. Alstonine is derived from a plant used by traditional healers in Nigeria, and has demonstrated a potential novel mechanism of action for the treatment of difficult to manage conditions such as schizophrenia.

The ETI SST consists of leading and globally renowned ethnobotanists, physicians, and pharmacologists as well as experts in the fields of natural product chemistry and neuropharmacology. We believe the wealth of expertise, experience, and commitment of the ETI SST—comprised of multiple members of the original SST that contributed to development of Jaguar's proprietary library of approximately 2,300 plants—will play an instrumental role in advancing our shared initial goal of identifying plants in our library that may have the potential to treat mood disorders and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic sclerosis. Mood disorders and neurodegenerative diseases affect hundreds of millions of people around the globe and represent classic unmet medical needs.

While Napo and Jaguar remain steadfastly focused on the commercial success of Mytesi and Canalevia-CA1, respectively, and on the development of potential crofelemer follow-on indications in the area of gastrointestinal treatments, the Company believes the same competencies and multi-disciplinary scientific strategy that led to the development of crofelemer will support collaborative efforts with potential partners to develop novel first-in-class prescription medicines derived from psychoactive plants.

Our management team has significant experience in gastrointestinal product development for both humans and animals. Napo was founded 32 years ago to perform drug discovery and development by leveraging the knowledge of traditional healers working in rainforest areas. Ten members of the Jaguar and Napo team have been together for more than 15 years. Dr. Steven King, our chief sustainable supply, ethnobotanical research and intellectual property officer, and Lisa Conte, our founder, president and CEO, have worked together for more than 30 years. We have buttressed the early founding team with the expertise and experiences of team members like Dr. Darlene Horton and Dr. Karen Brunke to support the continued development and commercialization activities of the Napo and Jaguar family. We have assembled an impressive group of scientific advisory board (SAB) members that work closely with the Chair of Jaguar’s Scientific Advisory Board, Dr. Pravin Chaturvedi, who also serves as the Chief Scientific Officer (“CSO”) of Jaguar. Together, these dedicated personnel successfully transformed crofelemer, which is extracted from trees growing in the rainforest, to Mytesi and Canalevia-CA1, which are natural, sustainably harvested, FDA-approved drugs.

As announced in February 2020, the American Botanical Council named Napo the recipient of the 2019 Varro E. Tyler Commercial Investment in Phytomedicinal Research Award in recognition of Napo’s ongoing commitment to the sustainable development and production of natural therapeutic preparations. Specifically, this award acknowledges the successful development and approval of crofelemer, which is derived from the medicinal *Croton lechleri* tree in the Amazon rainforest. Previous recipients of this award include Jaguar’s partner, Italy based Indena S.p.A., one of the world’s largest producers of clinically-tested botanical extracts for the food, dietary supplement, cosmetic, and pharmaceutical markets.

Pipeline within a product—crofelemer

Crofelemer is currently being evaluated for the prophylaxis of CTD in adult patients receiving targeted therapy. As announced in October 2020, Napo has initiated its pivotal Phase 3 clinical trial of crofelemer (Mytesi) for prophylaxis of diarrhea in adult cancer patients receiving targeted therapy (OnTarget study). A significant proportion of patients undergoing cancer therapy experience diarrhea. Novel targeted cancer therapy agents, such as epidermal growth factor receptor antibodies and tyrosine kinase inhibitors, with or without cycle chemotherapy agents, may

activate intestinal chloride secretory pathways leading to increased chloride secretion into the gut lumen, coupled with significant loss of water that would result in secretory diarrhea.

According to data appearing in “Treatment Guidelines for CID” (chemotherapy induced diarrhea) in the April 2004 issue of Gastroenterology and Endoscopy News, diarrhea is the most common adverse event reported in chemotherapy patients. Approved third-party supportive care products for chemotherapy induced nausea and vomiting (“CINV”) include Sustol, Aloxi, Akynzeo and Sancuso. According to a report published by Allied Market Research, the global CINV market was valued at \$1.66 billion in 2015 and is estimated to reach \$2.66 billion by 2022.

Diarrhea has been reported as the most common side effect of the recently approved CDK 4/6 inhibitor abemaciclib and the pan HER TKI neratinib, with occurrence ranging from 86% to >95% and grade 3 over 40%, in published studies. Diarrhea in this patient population has the potential to cause dehydration, potential infections, and non-adherence to treatment. A novel anti-diarrheal like crofelemer may hold promise for treating secretory diarrhea—and therefore also support long term cancer treatment adherence—in this population.

Napo has previously received orphan drug designation from the FDA for adult and/or pediatric SBS. The Orphan Drug Act provides for granting special status to a drug or biological product to treat a rare disease or condition upon request of a sponsor. Orphan drug designation qualifies the sponsor of the drug for various development incentives, including extended exclusivity, tax credits for qualified clinical testing, and relief of filing fees. As mentioned above, Napo Therapeutics has licensed the rights for the orphan and rare diseases associated with SBS and CDD with IF.

Napo Therapeutics expects that an IIT in pediatric patients with CDD will study crofelemer in the second half of 2022. This study will be initiated in the Middle East/North Africa (“MENA”) region with sites that treat infants and children with CDD and SBS with IF.

CDD is a group of rare, chronic intestinal channel diseases, with onset in early infancy, that are characterized by severe, lifelong diarrhea and a lifelong need for nutritional intake either parenterally or with a feeding tube. CDD is related to specific genetic defects inherited as autosomal recessive traits. The incidence of CDD is prevalent in regions where consanguineous marriage (related by blood) is part of the culture. CDD is directly associated with serious secondary conditions including dehydration, metabolic acidosis, and failure to thrive, prompting the need for immediate therapy to prevent death and limit lifelong disability. A recent preclinical study shows that crofelemer reduces the chloride secretion in intestinal cells derived from patients with CDD and these preclinical results provide additional support and rationale for the use of crofelemer in treating patients with CDD and/or SBS with IF.

As previously announced (in 2019), a clinical research study sponsored by The University of Texas Health Science Center at Houston (“UTHealth”) is being supported by Napo. This study evaluates the safety and effectiveness of crofelemer for treatment of chronic idiopathic diarrhea in patients. Chronic idiopathic diarrhea is a common complaint of patients presenting to family practitioners and internists and is one of the most common reasons for referral to gastroenterologists. It is estimated that the prevalence of chronic idiopathic diarrhea in developed countries (including the U.S.) is approximately 3-5%. It has a significant negative effect on health-related quality of life and causes a high economic burden on patients and society. The American Gastroenterological Association Burden of Illness study (2012) showed that the estimated annual direct and indirect costs associated with chronic idiopathic diarrhea is up to \$524 million per year and \$136 million per year, respectively. The principal investigator for this study is Dr. Brooks D. Cash, MD, AGAF, FACP, FASGE, Chief – Division of Gastroenterology, Hepatology and Nutrition, Sterling Professor of Medicine, McGovern Medical School at UTHealth, Co-Director, Ertan Digestive Disease Center at Memorial Hermann-Texas Medical Center. The Study is titled Yield of Diagnostic Tests and Management of Crofelemer for Chronic Idiopathic Diarrhea in Non-HIV Patients.

Crofelemer is also being evaluated in another investigator-initiated trial for the management of functional diarrhea in non-HIV patients. The principal investigator for this clinical study is Dr. Anthony Lembo, Professor, Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA. This clinical study is a randomized double-blind, placebo-controlled study in adult subjects with functional diarrhea. Eligible patients will have functional diarrhea defined by Rome IV criteria as >25% loose watery stools and <25% hard/lumpy stools. The study plans to randomize 80 patients and the subjects will be randomized 1:1 for 4 weeks to either the placebo or crofelemer 125 mg delayed-release tablets (Mytesi) arm, administered twice daily for 4 weeks. Following the four-week placebo-controlled period, all subjects will receive Mytesi for an additional four weeks in an open label extension phase. The safety and tolerability of crofelemer and the clinical response during the placebo-controlled period will be evaluated in this study. Subjects will be allowed to use limited amounts of an antimotility drug (loperamide) during the placebo-controlled and open-label extension phase to manage uncontrolled diarrhea. However, no more than 11 doses of 2 mg loperamide will be permitted during any given week per subject.

Jaguar's and Napo's portfolio development strategy involves meeting with Key Opinion Leaders ("KOLs") to identify indications that are potentially high value because they address important medical needs that are significantly or globally unmet, obtain input on protocol practicality and protocol generation, and then strategically sequencing indication development priorities, second generation product pipeline development, and partnering goals on a global basis.

Mytesi is the only antidiarrheal drug that has been approved by the US FDA for the treatment of chronic, noninfectious diarrhea in adult HIV/AIDS patients receiving ART. This approval was on the basis of the drug's safety and efficacy in reducing the number of weekly and daily watery stools in patients and improvement of stool consistency, from unformed to formed stools, over a 24-week treatment period.

Unlike other available diarrhea treatments, crofelemer does not act by inhibiting intestinal motility. It has minimal oral absorption and does not have any clinically significant food or drug interactions, thereby allowing patients to maintain their appropriate dosing of treatment to suppress their viral load and maintain adequate CD4 levels in PLWHA. Crofelemer is also the only approved antidiarrheal drug that is approved for chronic use. Moreover, it is not an opioid, like other traditionally used treatments, thus avoiding both the acute side effect of constipation and the potential for abuse.

Napo's Scientific Advisory Board has focused primarily on physician education, and community and global awareness regarding the importance and availability of solutions for neglected comorbidities, such as the first in class anti secretory mechanism of action of Mytesi for its currently approved indication.

There are significant barriers to entry for Mytesi (crofelemer). Through Napo, we hold an extensive global patent portfolio. At the present time, we hold approximately 143 issued worldwide patents, with coverage in many cases that extends until 2031. These issued patents cover multiple indications, including HIV AIDS diarrhea, irritable bowel syndrome ("IBS"), IBD, manufacturing, enteric protection from gastric juices, among others. We also have approximately 43 pending patent applications worldwide in the human health areas that are being prosecuted.

Mytesi is the first oral drug approved under the FDA's Botanical Guidance, which provides another barrier to entry from potential generic competition. The FDA requires that the manufacturer of crofelemer use a validated proprietary bioassay to release the drug substance and drug product of Mytesi. While most generic products are fashioned to meet chemical release specifications that are in the public domain, the specifics of this assay are not publicly available. There is no pathway by which a generic product can be developed for a drug approved under botanical guidance. In addition, Mytesi is minimally absorbed systemically, so the classic approach of creating a generic drug by matching pharmacokinetic blood levels is not possible. A generic player would have to conduct costly and risky clinical trials.

While Jaguar's commercial and development efforts have evolved to focus primarily on Mytesi and human pipeline indications since its merger with Napo, the Company has commenced launch initiatives related to Canalevia-CA1, our drug product which received conditional approval in December 2021 for treatment of CID in dogs. CID in dogs is typically caused by the same mechanism of action as in humans, and hence the work in dogs serves as a

preclinical proof of concept for the diarrhea in humans that is related to targeted cancer therapy. CID is an interesting model for human medical need and is being pursued as a prescription indication for animal health. We believe there is an important unmet medical need for the treatment of CID in dogs. Certain cancer treatment agents provided to dogs are human drugs or have the same mechanism of action as human cancer drugs, and these agents and mechanisms of action often have meaningful rates of diarrhea in humans as well.

As previously announced, Jaguar has received MUMS designation status from the FDA for Canalevia-CA1 for the indication of CID in dogs. MUMS designation is modeled on the orphan drug designation for human drug development and offers possible financial incentives to encourage MUMS drug development, such as the availability of grants to help with the cost of developing the MUMS drug.

For Jaguar Animal Health's second proposed indication for Canalevia, exercise induced diarrhea ("EID") in dogs, the Company is leveraging the use of many of the same major technical sections that have been submitted in support of the Company's application for Canalevia-CA1 for the indication of CID in dogs. Conditional approval of Canalevia for EID, under the name Canalevia-CA2, is expected in the fourth quarter of 2022.

Crofelemer is extracted and purified from the Croton lechleri tree, which we sustainably harvest and manage through programs that we have been developing over the past 30 years. This process has involved working with local and indigenous communities to plant trees, obtaining permits for export, and creating a supply network that is robust and reliable.

Our team continues to have relationships with partners that we began working with in the 1990s. Additionally, through the establishment of a nonprofit called the Healing Forest Conservancy, our team has created a long term mechanism for benefit sharing that recognizes the intellectual contribution of Indigenous populations. This program is intended to contribute to the continued strength and effectiveness of the valued and strategically important relationships we have carefully cultivated over the past 30+ years.

Product Pipeline

In addition to our Mytesi (crofelemer) product that is approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy, we are also developing a pipeline of prescription drug product candidates to address unmet needs in gastrointestinal health through Napo. Mytesi (crofelemer) is a novel, first in class anti secretory agent which has a basic normalizing effect locally in the gut and lumen, and this mechanism of action has the potential to benefit multiple disorders. Clinical trials demonstrated that nearly 80% of Mytesi users experienced an improvement in their diarrhea over a four week period. At week 20 of the pivotal trial, over half the patients had no watery stools, or a 100% decrease, and 83% had at least a 50% decrease in watery stools. Our Mytesi pipeline currently includes prescription drug product candidates for four follow on indications, several of which are backed by Phase 2 evidence from completed Phase 2 trials. In addition, a second generation proprietary anti secretory agent, lechlemer, is in development for cholera-related diarrhea.

Napo Prescription Drug Product Candidates

Product Candidates	Indication	Completed Milestones	Current Phase of Development	Anticipated Near-Term Milestones*
Mytesi.....	CTD	<ul style="list-style-type: none"> • Initiated pivotal Phase 3 clinical trial in October 2020 • Findings of Phase 2 HALT-D study presented in Q4 2021 	Phase 3	<ul style="list-style-type: none"> • Enrollment in Phase 3 trial ongoing
Novel lyophilized crofelemer product	Rare disease indications (SBS & CDD)	<ul style="list-style-type: none"> • Orphan drug designation for SBS granted by FDA and EMA 	Phase 2	<ul style="list-style-type: none"> • Initiate Phase 2 proof of concept (POC) study in SBS and/or CDD in 2022
Mytesi.....	IBS-D	<ul style="list-style-type: none"> • Two Phase 2 studies completed 	Phase 2	<ul style="list-style-type: none"> • Potential business development opportunities
Mytesi.....	Chronic idiopathic diarrhea	<ul style="list-style-type: none"> • Initiated clinical study at The University of Texas Health Science Center at Houston (“UTH”) 	Phase 2	<ul style="list-style-type: none"> • Top line results of UTH trial expected in 2022
Mytesi.....	Functional diarrhea	<ul style="list-style-type: none"> • Initiated clinical study at Beth Israel Deaconess Medical Center, Harvard Medical School, Boston 	Phase 2	<ul style="list-style-type: none"> • Enrollment ongoing
Mytesi	IBD	<ul style="list-style-type: none"> • Safety evidence from other chronic diarrhea indications 	Phase 2	<ul style="list-style-type: none"> • KOL discussions ongoing
NP-300 (lechlemer)	Second-generation antidiarrheal drug for infectious diarrhea including from cholera	<ul style="list-style-type: none"> • Ongoing IND-enabling toxicology studies and formulation development 	Pre IND	<ul style="list-style-type: none"> • Initiate Phase 1 trial in the second half of 2022

*Clinical trials are funding dependent

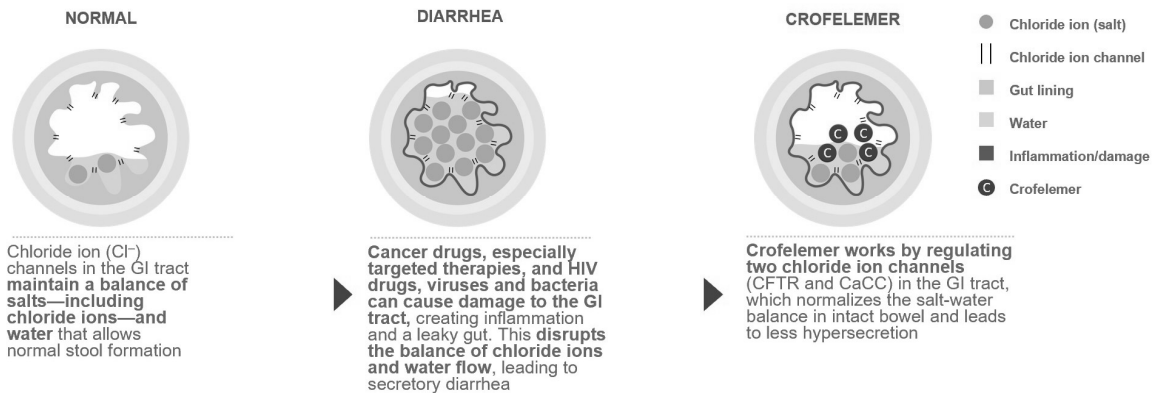
Estimated Size of Mytesi Target Markets

We believe the medical need for Mytesi is significant, compelling, and unmet, and that doctors are looking for a drug product with a mechanism of action that is distinct from the options currently available to resolve diarrhea. A growing percentage of HIV patients have lived with the virus in their gut for 10+ years, often causing gut enteropathy and chronic or chronic episodic diarrhea. According to data from the U.S. Centers for Disease Control and Prevention, by 2020 more than 70% of Americans with HIV are expected to be 50 and older and have lived with HIV for more than 10 years (1).

<u>Market</u>	<u>Competition</u>	<u>Market Size/Potential</u>
HIV-related Diarrhea.	None	We estimate the U.S. market revenue potential for Mytesi to be approximately \$50 million in gross annual sales
CTD	None	An estimated 650,000 U.S. cancer patients receive chemotherapy in an outpatient oncology clinic(2). Comparable supportive care (i.e., CINV) product sales of ~\$620 million in 2013(3). Global CINV market projected to reach a valuation of \$2.7 billion by 2022(4)
SBS/CDD	1	Financial benefits of Orphan Drug Designation. The global SBS market exceeded \$568 million in 2019 and is expected to reach \$4.6 billion by 2027, according to a report by Vision Research Reports(5)
IBS-D	3	Most IBS products have an estimated revenue potential of greater than \$1.0 billion(6)
IBD	None	Estimated 1,171,000 Americans have IBD(7)
Infectious Diarrhea from Cholera	None	In recent transactions by other companies, priority review vouchers have sold for \$67 million to \$350 million(8)

- (1) HIV Among People Aged 50 and Older (<https://www.cdc.gov/hiv/group/age/olderamericans/index.html>)
- (2) Centers for Disease Control and Prevention. Preventing Infections in Cancer Patients: Information for Health Care Providers (cdc.gov/cancer/prevent_infections/providers.htm)
- (3) Heron Therapeutics, Inc. Form 10 K for the fiscal year ended December 31, 2016
- (4) Report published by Allied Market Research, titled, "Chemotherapy-induced Nausea and Vomiting (CINV) Market-Global Opportunity Analysis and Industry Forecast, 2014-2022" (<https://www.prnewswire.com/news-releases/chemotherapy-induced-nausea-and-vomiting-cinv-market-expected-to-reach-2659-million-by-2022-611755395.html>)
- (5) Short Bowel Syndrome Market – Global Industry Analysis, Size, Share, Trends, Revenue, Forecast 2020 to 2027 (<https://www.mynewsdesk.com/us/medical-technology-news/pressreleases/short-bowel-syndrome-market-global-industry-analysis-size-share-trends-revenue-forecast-2020-to-2027-3069433>)
- (6) Merrill Lynch forecasts peak US sales of roughly \$1.5 bn for Ironwood’s Linzess (<https://247wallst.com/healthcare-business/2015/04/27/key-analyst-sees-nearly-30-upside-in-ironwood/>); Rodman & Renshaw estimate peak annual sales of Synergy Pharmaceuticals’ Trulance at \$2.3 bn in 2021 (<https://www.benzinga.com/analyst-ratings/analyst-color/17/04/9304883/what-synergys-new-patents-mean-for-its-commercial-prospe>)
- (7) Kappelman, M. et al. Recent Trends in the Prevalence of Crohn’s Disease and Ulcerative Colitis in a Commercially Insured US Population. *Dig Dis Sci.* 2013 Feb; 58(2): 519-525
- (8) In Aug. 2015, AbbVie Inc. bought a priority review voucher from United Therapeutics Corp for \$350 million (<https://www.wsj.com/articles/united-therapeutics-sells-priority-review-voucher-to-abbvie-for-350-million-1439981104>). In July 2014, BioMarin announced that it had sold a priority review voucher to Sanofi and Regeneron for \$67.5 million. (<https://investors.biomarin.com/2014-07-30-BioMarin-Sells-Priority-Review-Voucher-for-67-5-Million>).

The following diagram illustrates the mechanism of action of our human and animal gastrointestinal drug products and drug product candidates, which normalize chloride and water flow and transit time of fluids within the intestinal lumen.



Business Strategy

Our goal is to become a leading pharmaceutical company with first in class, sustainably derived products that address significant unmet gastrointestinal medical needs globally. To accomplish this goal, we plan to:

Expand Mytesi by leveraging our significant gastrointestinal product knowledge, experience and intellectual property portfolio

Mytesi is a novel, first in class anti secretory antidiarrheal agent which has a basic normalizing effect locally on the gut, and this mechanism of action has the potential to benefit multiple gastrointestinal disorders. Our Mytesi (crofelemer) product is approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. Jaguar, through Napo, holds global unencumbered rights for Mytesi. Mytesi is in development for multiple possible follow on indications, including diarrhea related to targeted cancer therapy; orphan drug indications for infants and children with congenital diarrheal disorders and short bowel syndrome; inflammatory bowel disease; irritable bowel syndrome; and for idiopathic/functional diarrhea. In addition, a second generation proprietary anti secretory agent is in development for cholera.

Our management team collectively has extensive experience in the development of prescription drugs. This experience covers all aspects of product development, including discovery, preclinical and clinical development, GMP manufacturing, regulatory affairs, and commercialization. Key members of this team successfully developed Mytesi.

Maintain commercial capabilities in Mytesi sales and marketing efforts

Napo's direct sales organization is comprised of Mytesi field sales representatives strategically positioned to cover U.S. geographies with the highest potential. With support provided by concomitant marketing, promotional activities, patient empowerment programs, including an integrated social digital campaign, and medical education initiatives described below, we expect a proportional response in the number of patients treated with Mytesi.

Leverage our relationships with Scientific Advisory Board (SAB) members for crofelemer commercialization and development in follow on indications

The Company has retained 10 SAB members that have extensive clinical experience in HIV, CTD, IBD, SBS, and CDD. In addition, the Company engages key opinion leaders (KOLs) for specific turnkey needs.

Establish partnerships to support moving pipeline indications to pivotal clinical trials

Jaguar is actively pursuing the development of a robust pipeline of potential follow on indications for crofelemer, and the Company's goal is to establish partnerships to support moving pipeline indications to pivotal clinical trials.

Strategically sequence the development of follow on indications of Mytesi and seek geographically focused licensing opportunities

As announced September 24, 2018, Jaguar and Knight Therapeutics Inc. ("Knight") entered into a Distribution, License and Supply Agreement that grants Knight the exclusive right to commercialize Mytesi and related products in Canada and Israel. The License Agreement has a term of 15 years (with automatic renewals) and provides Knight with an exclusive right to commercialize current and future Jaguar human health products (including crofelemer, Lechlemer, and any product containing a proanthocyanidin or with an anti-secretory mechanism) in Canada and Israel. Knight forfeited its right of first negotiation for expansion to Latin America. Under the License Agreement, Knight is responsible for applying for and obtaining necessary regulatory approvals in the territory of Canada and Israel, as well as marketing, sales and distribution of the licensed products. Knight will pay a transfer price for all licensed products, and upon achievement of certain regulatory and sales milestones, the Company may receive payments from Knight in an aggregate amount of up to approximately \$18 million payable throughout the initial 15-year term of the agreement. The Company did not have any license revenues since the execution of this agreement.

Although it is possible that we may enter into additional corporate partnering relationships related to Mytesi, our intention would be to retain all or co commercialization and promotional rights in the U.S., so that we do not become primarily a royalty collecting organization, and we are opposed to entering into any Mytesi partnering relationship that would require splitting indications. We are seeking to put limited geographically focused partnerships in place in the near term, while also considering possibilities for a worldwide partnership with a leading global entity (excluding the U.S. exclusive commercial rights) in the field of gastrointestinal care and cancer in the long term.

Reduce risks relating to product development

Risk reduction is a key focus of our product development planning. Mytesi is approved for chronic indication, providing us the ability to leverage this corresponding safety data when seeking approval for planned follow on indications that are also chronic or chronic episodic indications. In an effort to reduce risk further, we have implemented the following approach: first, we meet with key opinion leaders, typically at medical conferences. Next, we confirm unmet medical needs with these key opinion leaders and discuss the practicality of patient enrollment and trial implementation. We then generate protocols to discuss with the FDA, seeking, when possible, special protocol assessments. Our goal is to have de risked the program as much as we believe we possibly can, by the time we start devoting significant funds to a clinical trial, in particular the regulatory pathway. We believe this approach will lead to better long-term outcomes for our products in development.

We will continue to seek partnerships outside the United States for the above indications while focusing on development and commercial access in the United States directly. We are also focused on investigating (lechlemer) for various gastrointestinal indications. Lechlemer is a proprietary Jaguar pharmaceutical product, a standardized botanical extract distinct from crofelemer, also sustainably derived from the Croton lechleri tree.

We believe lechlemer, which has a similar mechanism of action as crofelemer and is significantly less costly to produce, may support efforts to receive a priority review voucher from the U.S. FDA for symptomatic treatment of diarrhea from cholera infection. Priority review vouchers are granted by the FDA to drug developers for tropical disease indications (TDPRV) as an incentive to develop treatments for neglected diseases and rare pediatric diseases. Additionally, we believe lechlemer represents a long-term pipeline opportunity as a second generation anti secretory agent, on a global basis, for multiple gastrointestinal diseases—especially in resource constrained countries where the cost of goods is a factor, in part, because requirements often exist in such regions for drug prices to decrease annually.

The Company has previously presented Phase 2 data on crofelemer for the treatment of diarrhea in cholera patients from a study in Bangladesh. Napo plans to follow a similar clinical study design to support the development of lechlemer (NP-300) for a cholera related indication.

Napo is conducting IND-enabling preclinical toxicology studies and developing novel NP-300 formulations that will support the initiation of clinical studies in 2022.

Our portfolio development strategy is based on identifying indications that are potentially high value because they address important medical needs that are significantly or globally unmet, and then strategically sequencing indication development priorities, second generation product pipeline development, and partnering goals on a global basis.

Our technology for proprietary gastrointestinal disease products is central to the product pipelines of both human and veterinary indications. Crofelemer is also the API in Canalevia-CA1, our prescription drug product recently conditionally approved by the FDA and launched for CID in dogs, and also expected to be approved and launched, under the name Canalevia-CA2, for EID in dogs in the fourth quarter of 2022.

Napo Therapeutics Provides New Opportunities to Treat Orphan Indications Like Short Bowel Syndrome

Jaguar is strategically pursuing multiple important shots on goal for its drug development pipeline: Crofelemer for CTD, led by Napo, and crofelemer for SBS and CDD, led by Napo Therapeutics. Jaguar's exclusive license agreement with Napo Therapeutics provides a perpetual, royalty-bearing license for Europe (excluding Russia), and includes traditional terms such as up-front fees, milestone payments, royalties on sales in Europe, and a supply agreement, and rights to utilize all data Napo Therapeutics generates for Jaguar development and approval activities globally.

Competition

There are several significantly larger pharmaceutical companies competing with us in the gastrointestinal segment.

Diarrhea in adult patients living with HIV/AIDS. We are not aware of any other FDA approved drugs for the symptomatic relief of diarrhea in HIV/AIDS patients. HIV/AIDS diarrhea patients may also use loperamide or Lomotil but these medications affect motility which can result in rebound diarrhea and are not indicated for chronic use. Other agents' patients may use include over the counter anti diarrheal remedies such as Mylanta or Kaopectate.

Cancer therapy related diarrhea. We are not aware of any FDA approved drugs specifically indicated for cancer therapy related diarrhea, including chemotherapy related diarrhea. A recent Phase 2b trial of elsiglutide for the treatment of chemotherapy induced diarrhea in colorectal cancer patients did not meet statistical significance. Opioids and over the counter drugs are commonly used to treat chemotherapy induced diarrhea, but these drugs affect motility. Certain tyrosine kinase inhibitor chemotherapy agents have diarrhea as a significant side effect. For example, FDA guidance suggests diarrhea prophylaxis prior to initiating adjuvant therapy with neratinib.

Short Bowel Syndrome and Congenital Diarrheal Disorders. We are not aware of any FDA approved drugs specifically indicated for congenital diarrheal disorders. In the U.S., Takeda Pharmaceuticals' GATTEX® (teduglutide) is indicated for the treatment of adults and pediatric patients 1 year of age and older with short bowel syndrome who are dependent on parenteral support, and Zorbtive® is a recombinant human growth hormone indicated for the treatment of short bowel syndrome in adult patients receiving specialized nutritional support.

Diarrhea predominant irritable bowel syndrome. Two drugs were approved in 2015 for the treatment of diarrhea predominant irritable bowel syndrome, Allergan plc's Virbezi and Xifaxan, which is marketed by Valeant Pharmaceuticals International. Also, Lotronex was approved by the FDA in 2000 but was withdrawn from the market and later reintroduced in 2002 under a Risk Management Program. With the exception of Lotronex, the sponsors of

Verbezi and Xifaxan employ extensive media and print promotion for the commercialization of these products. We are seeking a partner to further the clinical development and commercialization of crofelemer for IBS-D. There are currently numerous trials ongoing for IBS-D.

Inflammatory Bowel Disorders. We are not aware of any FDA approved drugs specifically indicated as an anti-secretory agent for use to address IBD.

Infectious Diarrhea from Cholera. We are not aware of any FDA approved drugs specifically indicated as an anti-secretory agent for use to address the devastating dehydration in cholera patients.

Manufacturing

The plant material used to manufacture is crude plant latex (“CPL”) extracted and purified from *Croton lechleri*, a widespread and naturally regenerating tree in the rainforest that is managed as part of sustainable harvesting programs. The tree is found in several South American countries and has been the focus of long term sustainable harvesting research and development work. Napo’s collaborating suppliers obtain CPL and arrange for the shipment of CPL to Napo’s third party contract manufacturer.

Napo’s third party contract manufacturer, India based Glenmark Life Sciences Ltd. (“Glenmark”), a research driven, global, integrated pharmaceutical company, is Napo’s manufacturer of crofelemer, the active pharmaceutical ingredient in Mytesi. Glenmark processes CPL into crofelemer utilizing a proprietary manufacturing process. The processing occurs at an FDA approved Glenmark facility. Additionally, Napo is establishing a second processing site, which will be operated by Indena S.p.A. (“Indena”), a Milan, Italy based contract manufacturer dedicated to the identification, development and production of high quality active principles derived from plants, for use in the pharmaceutical, health food and personal care industries. Indena has completed the required technology transfer and feasibility and preparing for validation activities to support commercial scale manufacturing.

We have contracts in place with all the manufacturers and third-party testing labs required to manufacture Mytesi, Canalevia-CA1, and lechlemer. We are finalizing a master service agreement with Indena for the manufacture of crofelemer. We are evaluating alternate drug substance and drug product manufacturers to establish redundancy for DP manufacturing.

Proprietary Library of Medicinal Plants

We possess a proprietary library of more than 2,300 medicinal plants.

Intellectual Property

Trademarks

We plan to market all of our products under a trademark or trademarks we select, and we will own all rights, title and interest, including all goodwill, associated with such trademarks. Mytesi is a registered trademark owned by Napo. Jaguar Animal Health is a trademark owned by Jaguar.

License Agreements

Patent Portfolio

Napo

Napo owns a portfolio of patents and patent applications covering formulations of and methods of treatment with proanthocyanidin polymers isolated from *Croton* spp. or *Calophyllum* spp., including Mytesi (crofelemer). The patent family associated with International Patent publication WO1998/16111 relates to enteric protected formulations

of proanthocyanidin polymers isolated from *Croton* spp. or *Calophyllum* spp., including crofelemer, and methods of treating watery diarrhea using these enteric protected formulations. There is one U.S. patent in force in this family, US 7,341,744, which has a term until at least June 23, 2019, which term has been extended under 35 U.S.C. 156 by 1,075 days. Based upon the June 23, 2019 expiration date, the expiration date for crofelemer is June 2, 2022, to account for the regulatory delay in obtaining human marketing approval for crofelemer.

Napo additionally owns a family of patents arising from International Patent Application Publication WO2012/058664 that cover methods of treating HIV associated diarrhea and HAART associated diarrhea with proanthocyanidin polymers isolated from *Croton* spp. or *Calophyllum* spp., including crofelemer. In the U.S., there are two issued patents, US 8,962,680 and US 9,585,868, both of which expire October 31, 2031. Outside the U.S., patent protection for methods of treating HIV associated diarrhea has been obtained in Australia, Europe, Hong Kong, Japan, Kenya, Mexico, Russia, Ukraine, South Africa, and Zimbabwe, with expiration dates of October 31, 2031, and applications are pending in Brazil, Hong Kong, and China. Napo also has patent families related to methods of treating diarrhea predominant irritable bowel syndrome, methods of treating constipation predominant irritable bowel syndrome, and methods of treating inflammatory bowel disease, familial adenomatous polyposis and colon cancer, with proanthocyanidin polymers isolated from *Croton* spp. or *Calophyllum* spp., including crofelemer. In particular, for diarrhea predominant irritable bowel syndrome, Napo has two issued U.S. patents, US 8,846,113 and US 9,980,938, which expire on February 9, 2027, as well as issued patents in Australia, Canada, Europe, Gulf States, Hong Kong, Japan, South Korea, Mexico, New Zealand, Singapore, and Taiwan and pending applications in Bangladesh, Bolivia, Chile, Paraguay, Thailand, and Venezuela, all of which are estimated to expire April 30, 2027; for constipation predominant irritable bowel syndrome, Napo has three issued U.S. patents, with terms to at least April 30, 2027, patents in Australia, Canada, Europe, Hong Kong, Mexico, New Zealand, and Singapore, all of which are estimated to expire April 30, 2027; and for inflammatory bowel disease, familial adenomatous polyposis and/or colon cancer, Napo has two issued U.S. patents, US 8,852,649 and US 9,987,250 with terms until at least January 4, 2028, as well as issued patents in Australia, Hong Kong, and Europe and Canada, which have estimated expiration dates of April 30, 2027. Napo has a pending U.S. non provisional application for the treatment of CID with crofelemer filed on March 9, 2018, as well as International and Taiwanese applications, and two International Patent Applications on other human indications including for the treatments of short bowel syndrome and congenital diarrhea disorder filed on May 31, 2018, with pending national phase applications in the United States, Australia, Canada, China, Europe, Israel, Jordan, Japan and the Gulf States.

For methods of manufacturing proanthocyanidin polymers isolated from *Croton* spp. or *Calophyllum* spp., including crofelemer, Napo owns issued patents in India, South Africa, and Eurasia with terms at least until August 26, 2029. Napo also owns issued patents in Brazil, India, Russia, and South Africa and pending applications in Argentina and Venezuela that also cover methods of manufacturing proanthocyanidin polymers isolated from *Croton* spp. or *Calophyllum* spp., including crofelemer, with terms at least until January 17, 2032. Lastly, Napo owns two U.S. patents covering a formulation of NP 500 (nordihydroguaiaretic acid (“NDGA”)) and its use in treating a metabolic disorder that have terms until April 23, 2031.

Napo grants license to Napo Therapeutics S.p.A. (formerly named Napo EU S.p.A.)

On August 2021, Napo signed a license agreement with Napo EU S.p.A. to study, develop, manufacture, and commercialize Napo’s plant-based crofelemer and lechlemer drug product candidates in the European Union (excluding Russia) and in specified non-EU countries in Europe for specific indications, which rights and obligations were assumed by the combined company formed by the merger of Napo Therapeutics with Dragon SPAC (the combined company uses the Napo Therapeutics name). The license agreement grants Napo Thera the rights for SBS-IF, HIV-related diarrhea, and the symptomatic relief and treatment of IF-related diarrhea in patients with congenital disorders. The license agreement grants Napo Thera the right to study Per the terms of the license agreement, Napo will receive payment of up to \$10 million as the initial license fee (to be paid in two installments, the first of which has already been received) as the initial license fee and is eligible to receive additional payments related to milestones, royalties, and product transfers. The license fees will be eliminated in the consolidated financial statements.

Government Regulation

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing and distribution of prescription drugs such as those Napo is that Jaguar and its subsidiaries are commercializing and/or developing. These agencies and other federal, state and local entities regulate, among other things, the research and development, testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post approval monitoring and reporting, sampling and export and import of Napo's drug product candidates. To comply with the regulatory requirements in each of the jurisdictions in which Napo is seeking to market and subsequently sell its prescription products, Napo has established processes and resources to provide oversight of the development, approval processes and launch of its products and to position those products in order to gain market share

U.S. Government Regulation

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act ("FDCA"), and it's implementing regulations.

The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending New Drug Applications ("NDAs"), withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a human or animal health prescription drug may be marketed in the United States generally involves the following:

- completion of pre-clinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or good laboratory practices ("GLPs") regulations;
- submission to the FDA of an investigational new drug application ("IND") for human clinical trials, or an investigational new animal drug ("INAD") for animal health studies;
- approval by an institutional review board ("IRB") for human trials, and appropriate animal care and use committees for animal health studies. Multiple sites may necessitate the involvement of multiple IRBs and submissions for human health products;
- performance of adequate and well controlled human clinical trials in accordance with good clinical practices ("GCPs"), requirements to establish the safety and efficacy of the proposed drug product for each indication;
- submission to the FDA of an NDA for marketing approval of human prescription drugs; and a new animal drug application ("NADA") for marketing authorization of animal health products;
- satisfactory completion of FDA advisory committees review, if applicable;
- satisfactory completion of an FDA pre-approval inspection ("PAI") of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices ("cGMPs"), requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and

- FDA review and approval of the NDA or NADA.

Pre-clinical Studies

Pre-clinical studies include laboratory evaluation of the drug product's chemistry, toxicity and formulation, as well as animal studies to assess potential safety and effectiveness. An IND sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some pre-clinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials for Human Prescription Drugs

Clinical trials involve the administration of the investigational new drug to human subjects pursuant to a clinical protocol, under the supervision of qualified investigators in accordance with GCPs requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives or endpoints of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA under the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their www.clinicaltrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness depending on the endpoints set forth in the protocol.
- Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Special Protocol Assessment for Human Health Prescription Drugs

The special protocol assessment, or SPA, process is designed to facilitate the FDA's review and approval of drugs by allowing the FDA to evaluate issues related to the adequacy of certain clinical trials, including Phase 3

clinical trials that can form the primary basis for a drug product's efficacy claim in an NDA. Upon specific request by a clinical trial sponsor, the FDA will evaluate the protocol and respond to a sponsor's questions regarding, among other things, primary efficacy endpoints, trial conduct and data analysis, within 45 days of receipt of the request.

The FDA ultimately assesses whether the protocol design and planned analysis of the trial are acceptable to support regulatory approval of the product candidate with respect to effectiveness of the indication studied. All agreements and disagreements between the FDA and the sponsor regarding a SPA must be clearly documented in a SPA letter or the minutes of a meeting between the sponsor and the FDA.

Even if the FDA agrees to the design, execution and analyses proposed in protocols reviewed under the SPA process, the FDA may revoke or alter its agreement under the following circumstances:

- public health concerns emerge that were unrecognized at the time of the protocol assessment;
- the director of the review division determines that a substantial scientific issue essential to determining safety or efficacy has been identified after testing has begun;
- a sponsor fails to follow a protocol that was agreed upon with the FDA; or
- the relevant data, assumptions, or information provided by the sponsor in a request for SPA change, are found to be false statements or misstatements, or are found to omit relevant facts.

A documented SPA may be modified, and such modification will be deemed binding on the FDA review division, except under the circumstances described above, if FDA and the sponsor agree in writing to modify the protocol and such modification is intended to improve the study.

Marketing Approval for Human Prescription Drugs

Assuming successful completion of the required clinical testing, the results of the pre-clinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act ("PDUFA"), guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a "filing" decision.

In addition, under the Pediatric Research Equity Act of 2003, as amended and reauthorized, certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations; this would include information which supports dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers from the pediatric data requirements.

The FDA may also require submission of a risk evaluation and mitigation strategy, or REMS, plan to ensure that the benefits of the drug outweigh its risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

The FDA may also require other information as part of the NDA filing, such as an environmental impact statement. The FDA can waive some or delay compliance with some of these requirements.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be

resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMPs requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA may inspect one or more clinical trial sites to assure compliance with GCPs requirements.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter must contain a statement of specific items that prevent the FDA from approving the application and will also contain conditions that must be met in order to secure final approval of the NDA and may require additional clinical or pre-clinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements for Human Prescription Drugs

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. New secondary indications must be supported by clinical trials or data. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMPs requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMPs requirements and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMPs compliance.

Once approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, include, but are not limited to:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. In addition, the FDA regulates the purity and or consistency of the approved product. Products, if deemed adulterated, can lead to serious consequences as set forth above as well as civil and criminal penalties.

Animal Health Prescription Drugs

Under the Federal Food, Drug, and Cosmetic Act (the "Act"), the term "drug" means articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary; articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles other than food intended to affect the structure or any function of the body of man or other animals. It also includes articles intended for use as a component of a drug.

Once a product is determined to be a drug for animal use, the next step is to determine whether or not it is a new animal drug. The Act defines a new animal drug (in part) as any drug intended for use for animals other than man, the composition of which is not generally recognized, among experts qualified by scientific training and experience, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling. By virtue of Supreme Court interpretations of the necessary basis for general recognition, there are, for all practical purposes, no animal drugs which are not also new animal drugs.

Under the Act, a new animal drug may not be legally introduced into interstate commerce unless it is the subject of either:

- an approved NADA or abbreviated new animal drug application (ANADA) under section 512 of the Act;
- a conditional approval under section 571 of the Act;
- a listing on the Legally Marketed Unapproved New Animal Drug Index for Minor Species (the Index) under section 572 of the Act;
- an emergency use authorization (“EUA”) under section 564 of the Act (an EUA may only be issued under very limited circumstances, more information regarding EUAs is available at this webpage: Emergency Use Authorization) ; or
- an investigational exemption under section 512(j) of the Act.

Three Regulatory Pathways in the U.S. to Legal Marketing Status for Animal Health Drugs

Approval

An approved animal drug has gone through the New Animal Drug Application (NADA) process, or for an approved generic animal drug, the Abbreviated New Animal Drug Application (ANADA) process. If the information in the application meets the requirements for approval, FDA approves the animal drug. FDA’s approval means the drug is safe and effective when it is used according to the label. FDA’s approval also ensures that the drug’s strength, quality, and purity are consistent from batch to batch, and that the drug’s labeling is truthful, complete, and not misleading.

Conditional Approval

Conditional approval is only available for some animal drugs for use in a minor species or in a major species under special circumstances. A conditionally approved animal drug has gone through FDA's drug approval process except the drug has not yet met the effectiveness standard for full approval. FDA’s conditional approval means that when used according to the label, the drug is safe and has a “reasonable expectation of effectiveness.” FDA's conditional approval also means that the drug is properly manufactured.

The conditional approval is valid for one year. The drug company can ask FDA to renew the conditional approval annually for up to four more years, for a total of five years of conditional approval. During the 5-year period, the drug company can legally sell the animal drug while collecting the remaining effectiveness data. After collecting the remaining effectiveness data, the company submits an application to FDA for full approval. The agency reviews the application and, if appropriate, fully approves the drug.

Indexing

An indexed animal drug is a drug on FDA’s Index of Legally Marketed Unapproved New Animal Drugs for Minor Species, referred to simply as “the Index.” As the name says, a drug listed on the Index is unapproved but has legal marketing status. It can be legally sold for a specific use in certain minor species. Indexing is allowed for drugs for:

- Non-food-producing minor species, such as pet birds, hamsters, and ornamental fish. These animals are typically not eaten by people or by other animals that produce food for people to eat; and
- An early non-food life stage of a food-producing minor species, such as oyster spat (immature oysters). Because people do not generally eat oyster spat, a drug to treat a disease in spat can be indexed, but a drug to treat a disease in adult oysters, which people commonly eat, cannot be indexed.

Indexing a drug is quite different from the drug approval process. Indexing relies heavily on a panel of qualified experts outside FDA. The experts review the drug's safety in the specific minor species and the drug's effectiveness for the intended use. All experts on the panel must agree that, when used according to the label, the drug's benefits outweigh the risks to the treated animal. If FDA agrees with the panel, the agency adds the drug to the Index.

Animal Health Business Regulations

The development, approval and sale of animal health products are governed by the laws and regulations of each country in which we intend to seek approval, where necessary, to market and subsequently sell our prescription drug and non-drug products. To comply with these regulatory requirements, we have established processes and resources to provide oversight of the development, approval processes and launch of our products and to position those products in order to gain market share in each respective market.

Certain U.S. federal regulatory agencies are charged with oversight and regulatory authority of animal health products in the United States. These agencies, depending on the product and its intended use, may include the FDA, the USDA and the Environmental Protection Agency. The approval of prescription drugs intended for animal use is regulated by the FDA's CVM. In addition, the Drug Enforcement Administration regulates animal therapeutics that are classified as controlled substances. In addition, the Federal Trade Commission may, in the case of non-drug products, regulate the marketing and advertising claims being made.

Labeling

The FDA plays a significant role in regulating the labeling, advertising and promotion of animal drugs. This is also true of regulatory agencies in the EU and other territories. In addition, advertising and promotion of animal health products is controlled by regulations in many countries. These rules generally restrict advertising and promotion to those claims and uses that have been reviewed and approved by the applicable agency. We will conduct a review of advertising and promotional material for compliance with the local and regional requirements in the markets where we sell our product candidates.

EMA Regulation of Human Prescription Drugs

Napo and Napo Therapeutics intend to leverage the orphan medicines marketing authorization incentives from the EMA for the short bowel syndrome and congenital diarrheal disorders indications for crofelemer for the licensed territories in the European Union. EMA has developed a regulatory procedure for sponsor eligibility for incentives available for drugs with ODD for the appropriate patient populations in an expedited manner. The EMA is responsible for scientific evaluation of centralized marketing authorization applications ("MAA"). Once granted by the European Commission, the centralized MAA is valid in all EU member states, Iceland, Norway and Liechtenstein.

Centralized authorization procedure

Under the centralized authorization procedure, pharmaceutical companies submit a single marketing authorization application to EMA. This allows the marketing-authorization holder to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorization.

EMA's Committee for Medicinal products for Human Use ("CHMP") or Committee for Medicinal products for Veterinary Use ("CVMP") carry out a scientific assessment of the application and give a recommendation on whether the medicine should be marketed or not. However, under EU law EMA has no authority to actually permit marketing in the different EU countries. The European Commission is the authorizing body for all centrally authorized product, who takes a legally binding decision based on EMA's recommendation. This decision is issued within 67 days of receipt of EMA's recommendation.

Once granted by the European Commission, the centralized marketing authorization is valid in all EU Member States as well as in the European Economic Area ("EEA") countries Iceland, Liechtenstein and Norway. Commission decisions are published in the Community Register of medicinal products for human use.

Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases.

Conditional marketing authorization

The EMA supports the development of medicines that address unmet medical needs. In the interest of public health, applicants may be granted a conditional marketing authorization for such medicines on less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

Medicines for human use are eligible if they are intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases. This includes orphan medicines. Its use is also intended for a public health emergency (e.g. a pandemic). For these medicines, less comprehensive pharmaceutical and non-clinical data may also be accepted. The legal basis is Article 14-a of Regulation (EC) No 726/2004. The provisions for granting a conditional marketing authorization are further elaborated in Regulation (EC) No 507/2006.

Criteria and conditions

EMA's CHMP may grant a conditional marketing authorization for a medicine if it finds that all of the following criteria are met:

- the benefit-risk balance of the medicine is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorization;
- the medicine fulfils an unmet medical need;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Conditional marketing authorizations are valid for one year and can be renewed annually. Once a conditional marketing authorization has been granted, the marketing authorization holder must fulfil specific obligations within defined timelines. These obligations could include completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive. EMA publishes the conditions of the marketing authorization in the medicine's European public assessment report.

The marketing authorization can be converted into a standard marketing authorization (no longer subject to specific obligations) once the marketing authorization holder fulfils the obligations imposed and the complete data confirm that the medicine's benefits continue to outweigh its risks. Initially, this is valid for 5 years. It can then be renewed for unlimited validity.

As for any medicine, if new data show that the medicine's benefits no longer outweigh its risks, EMA can take regulatory action, such as suspending or revoking the marketing authorization. EMA can also take regulatory action if the company does not comply with the imposed obligations.

Despite earlier approval, it guarantees that the medicine meets rigorous EU standards for safety, efficacy and quality and that comprehensive data is still generated post-approval. It offers a robust post-authorization regulatory framework based on legally binding obligations, safeguards and controls.

These include:

- full prescribing information and package leaflet with detailed instructions for safe use and conditions for storage;
- a robust risk-management and safety monitoring plan;

- manufacturing controls including official batch controls for vaccines, as required;
- legally binding post-approval obligations (i.e. conditions) for the marketing authorization holder and a clear legal framework for the evaluation of emerging efficacy and safety data;
- a pediatric investigation plan.

Guidance for applicants for conditional marketing authorization

EMA advises applicants to discuss their development plans with the Agency via scientific advice or protocol assistance early in the development process. Involving health technology assessment bodies early is also encouraged, which is possible via EMA's parallel consultations procedure. The applicant should indicate a request for conditional marketing authorization in their notification of intention to submit a marketing authorization application. They should submit this 6 to 7 months before submitting the application. EMA also encourages applicants to further discuss their plans with EMA as part of a pre-submission meeting. For products deemed suitable for a conditional marketing authorization, EMA encourages applicants to also consider requesting accelerated assessment.

Applicants should include a formal request for a conditional marketing authorization in their marketing authorization application. The CHMP will assess this request together with the application. Guideline on the scientific application and the practical arrangements necessary to implement Regulation (EC) No 507/2006 on the conditional marketing authorization for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.

Distinction from authorization under exceptional circumstances

EMA may also grant a marketing authorization in absence of comprehensive data under exceptional circumstances. Unlike conditional marketing authorization, where marketing approval is granted in the likelihood that the sponsor will provide such data within an agreed timeframe, EMA can grant authorization under exceptional circumstances when comprehensive data cannot be obtained even after authorization. This authorization route normally does not lead to a standard marketing authorization.

Orphan drug development incentives from EMA

Protocol assistance

The Agency provides a form of scientific advice specifically for orphan medicines called protocol assistance. This allows sponsors to get answers to their questions on the types of studies needed to demonstrate the medicine's quality, benefits and risks, and information on the significant benefit of the medicine. Protocol assistance is available at a reduced charge for designated orphan medicines, linked to a fee-reduction scale that depends on the status of the sponsor. There is no restriction on the number of times a sponsor can request protocol assistance.

The Agency encourages sponsors to consider coordinating the timing of protocol assistance from the Agency with request for scientific advice from the United States Food and Drug Administration (FDA). Parallel scientific advice with the FDA is available.

Access to the centralized authorization procedure

All designated orphan medicines are assessed for marketing authorization centrally in the European Union. This allows companies to make a single application to the European Medicines Agency, resulting in a single opinion and a single decision from the European Commission, valid in all EU Member States. Sponsors may also have access via orphan designation to conditional approval, which is conducted under the centralized procedure.

Ten years of market exclusivity

Authorized orphan medicines benefit from ten years of protection from market competition with similar medicines with similar indications once they are approved. This period of protection is extended by two years for

medicines that also have complied with an agreed pediatric investigation plan granted at the time of review of the orphan medicine designation.

Additional incentives for micro, small and medium-sized enterprises (“SMEs”)

Companies classified as SMEs benefit from further incentives when developing medicines with orphan designation. These include administrative and procedural assistance from the Agency's SME office and fee reductions.

Fee reductions

Companies applying for designated orphan medicines pay reduced fees for regulatory activities. This includes reduced fees for protocol assistance, marketing-authorization applications, inspections before authorization, applications for changes to marketing authorizations made after approval, and reduced annual fees. Fee reductions are revised each year in relation to the budget available.

EMA Grants

The Agency does not offer research grants for sponsors of orphan medicines, but funding is available from the European Commission and other sources:

- Horizon 2020, the EU Framework Programme for Research and Innovation;
- E-Rare, a transnational project for research programs on rare diseases.
- Grants are also available for sponsors considering research in the United States or Japan:
- United States: Food and Drug Administration: Orphan products grants program
- Japan: National Institute of Biomedical Innovation: Services to promote development of medicinal products for rare diseases

Incentives in Member States

Details on incentives available for designated orphan medicines in EU Member States are available in the European Commission's Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products.

Activities after orphan designation

Orphan designation makes the sponsor eligible for a number of orphan incentives. Sponsors need to comply with various activities that take place after a designation has been granted. Sponsors should submit all post-designation activities, including annual reports. For information and guidance on using IRIS, see the IRIS homepage. Sponsors must submit an annual report on development to the Agency summarizing the status of development of the medicine.

Sponsors of medicines with orphan designation should also remember to apply for a pediatric investigation plan (“PIP”), deferral or waiver at the appropriate time, as specified in the Pediatric regulation.

Sponsors also need to submit an application for maintenance of the orphan designation at the time of marketing authorization, in order to be eligible for the ten-year market exclusivity incentive.

A valid and completed PIP could make the sponsor eligible for the two-year marketing exclusivity extension to the ten-year marketing exclusivity which is granted at the time of review of the orphan medicinal designation. Transfers of orphan designation from one sponsor to another are possible. Transfers are free of charge. Sponsors can also request removal of an orphan designation.

EMA Compassionate Use Program

Compassionate use is a treatment option that allows the use of an unauthorized medicine. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorized therapies and who cannot enter clinical trials. The EMA provides recommendations through the Committee for Medicinal Products for Human Use (“CHMP”), but these do not create a legal framework. Compassionate use programs are coordinated and implemented by Member States, which set their own rules and procedures.

Established by Article 83 of Regulation (EC) No 726/2004, this tool is designed to:

- facilitate and improve access to compassionate use programs by patients in the EU;
- favor a common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorized new medicines;
- increase transparency between Member States in terms of treatment availability.

These programs are only put in place if the medicine is expected to help patients with life-threatening, long-lasting or seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorized medicine. The medicine must be undergoing clinical trials or have entered the marketing-authorization application process and while early studies will generally have been completed, its safety profile and dosage guidelines may not be fully established.

How to request an opinion for Compassionate Use

National competent authorities can ask EMA for an opinion on how to administer, distribute and use certain medicines for compassionate use. The CHMP also identifies which patients would benefit, and Member States should take note of these recommendations when making decisions.

Manufacturers and marketing-authorization applicants should not contact EMA to request an opinion, but they may wish to inform the Agency of applications underway at national level. National competent authorities will inform the Agency if they are making a product available to a group of patients for compassionate use.

Comparison to individual basis treatment (Named Patient Program)

Compassionate use should not be confused with 'named-patient basis' treatments, which see doctors obtain medicines directly from manufacturers before authorization. This is done on an individual basis under the direct responsibility of the doctor, and the Agency does not need to be informed.

In general, medicines that are not yet authorized are first made available through clinical trials and patients should always be considered for inclusion in trials before being offered compassionate use programs.

Compassionate use recommendations

EMA's recommendations cover how a medicine should be used in compassionate use programs across the EU, and the type of patient who may benefit from treatment. EMA does not update its recommendations after a medicine receives marketing authorization, as all relevant information on the medicine's use is available in its European public assessment report (“EPAR”). However, compassionate use programs may continue in certain Member States until the medicine becomes available on the market.

Rewards and incentives for pediatric medicines

Several rewards and incentives for the development of pediatric medicines for children are available in the EU. Medicines authorized across the EU with the results of studies from a pediatric investigation plan included in the

product information are eligible for an extension of their supplementary protection certificate by six months. This is the case even when the studies' results are negative.

For orphan medicines, the incentive is an additional two years of market exclusivity.

Scientific advice and protocol assistance at the Agency are free of charge for questions relating to the development of pediatric medicines. Medicines developed specifically for children that are already authorized but are not protected by a patent or supplementary protection certificate are eligible for a pediatric-use marketing authorization (“PUMA”). If a PUMA is granted, the product will benefit from 10 years of market protection as an incentive. The above can be complemented by other incentives to support the research, development and availability of medicinal products for pediatric use.

Market exclusivity: Orphan medicines

Orphan medicines benefit from ten years of market exclusivity once they receive a marketing authorization in the EU. This measure is intended to encourage the development of medicines for rare diseases, by protecting them from competition from similar medicines with similar indications, which cannot be marketed during the exclusivity period. Market exclusivity is an orphan incentive awarded by the European Commission to a specific clinical indication with an orphan designation.

Each indication with an orphan designation confers ten years' market exclusivity for the particular indication. A medicine that has multiple orphan designations for different conditions will benefit from separate market exclusivity periods pertaining to its different orphan designations.

To benefit from market exclusivity, a medicine must maintain its orphan designation at the time of marketing authorization.

Extension of market exclusivity period

The market exclusivity period is extended by two additional years for an orphan-designated condition when the results of specific studies are reflected in the summary of product characteristics (“SmPC”) addressing the pediatric population and completed in accordance with a fully compliant PIP.

The European Commission grants the extension based on a positive compliance check from the Pediatric Committee and opinion from the Committee for Medicinal Products for Human Use (“CHMP”), and includes this information in the Community register of orphan medicinal products.

Review of market exclusivity period

Article 8(2) of the Orphan Regulation establishes the possibility for Member States to request that the market exclusivity be reduced from ten to six years, under certain circumstances.

Expiry of market exclusivity

When the period of market exclusivity for an indication ends, the orphan designation for that indication expires and the European Commission removes it from the Community register of orphan medicinal products.

Once all of the orphan designations associated with an approved medicine have expired or been withdrawn by the sponsor, the medicine ceases to be classified as an orphan medicine and no longer benefits from the orphan incentives.

European Union new chemical entity exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from referencing the innovator's data to assess a

generic application for eight years, after which a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

European Union orphan designation and exclusivity

In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the European Union Community and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the medicinal product.

In the European Union, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

European Union Pediatric Plan

In the EEA, marketing authorization applications for new medicinal products not authorized have to include the results of studies conducted in the pediatric population, in compliance with a pediatric investigation plan, or PIP, agreed with the EMA's Pediatric Committee ("PDCO"). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which marketing authorization is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the marketing authorization is obtained in all Member States of the EU and study results are included in the product information, even when negative, the product is eligible for six months' supplementary protection certificate extension. For orphan drug designated medicinal products, the 10 year period of market exclusivity is extended to 12 years.

Clinical Trials Regulation in Europe

In the EU, pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on GCP, a system for the approval of clinical trials in the EU has been implemented through national legislation of the EU member states. Under this system, an applicant must obtain approval from the national competent authority of an EU member state in which the clinical trial is to be conducted, or in multiple member states if the clinical trial is to be conducted in a number of member states. Furthermore, the applicant may only start a clinical trial at a specific study site after the independent ethics committee for each site has issued a favorable opinion. The clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and corresponding national laws of the individual EU member states and further detailed in applicable guidance documents. In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. It is anticipated that the new Clinical Trials Regulation (EU) No 536/2014 may come into effect in late 2021 with a three-year transition period for some types of clinical trials. It will overhaul the current system of

approvals for clinical trials in the EU. Specifically, the new regulation, which will be directly applicable in all EU member states, aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single-entry point and strictly defined deadlines for the assessment of clinical trial applications

Other U.S. Healthcare Laws

In addition to FDA restrictions on marketing of pharmaceutical and biological products, other U.S. federal and state healthcare regulatory laws restrict business practices in the pharmaceutical industry, which include, but are not limited to, state and federal anti-kickback, false claims, data privacy and security and physician payment and drug pricing transparency laws.

The U.S. federal Anti-Kickback Statute prohibits, among other things, any person or entity from knowingly and willfully offering, paying, soliciting, receiving or providing any remuneration, directly or indirectly, overtly or covertly, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any good, facility, item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federal healthcare programs. The term “remuneration” has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, formulary managers and beneficiaries on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not meet the requirements of a statutory or regulatory exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the U.S. federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case by case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute’s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

Additionally, the intent standard under the U.S. federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, to a stricter standard such that a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA codified case law that a claim including items or services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. The majority of states also have Anti-Kickback laws, which establish similar prohibitions and, in some cases, may apply to items or services reimbursed by any third-party payor, including commercial insurers.

The federal false claims and civil monetary penalties laws, including the civil False Claims Act, prohibit any person or entity from, among other things, knowingly presenting, or causing to be presented, a false, fictitious or fraudulent claim for payment to, or approval by, the federal government, knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. A claim includes “any request or demand” for money or property presented to the U.S. government. Actions under the civil False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the civil False Claims Act can result in very significant monetary penalties and treble damages. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies’ marketing of products for unapproved, or off label, uses. Companies also have been prosecuted for allegedly violating the Anti-Kickback Statute and False Claims Act as a result of impermissible arrangements between companies and healthcare practitioners or as a result of the provision of remuneration by the companies to the healthcare practitioners. In addition, the civil monetary penalties statute imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health

program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. Many states also have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Violations of fraud and abuse laws, including federal and state Anti-Kickback and false claims laws, may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid), disgorgement and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties, as well as imprisonment, also can be imposed upon executive officers and employees of such companies. Given the significant size of actual and potential settlements, it is expected that the government authorities will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act ("HIPAA") of 1996 created additional federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the U.S. federal Anti-Kickback Statute, the ACA broadened the reach of certain criminal healthcare fraud statutes created under HIPAA by amending the intent requirement such that a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and certain other healthcare providers. The ACA imposed, among other things, new annual reporting requirements through the Physician Payments Sunshine Act for covered manufacturers for certain payments and "transfers of value" provided to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit timely, accurately and completely the required information for all payments, transfers of value and ownership or investment interests may result in civil monetary penalties of up to an aggregate of \$150,000 per year and up to an aggregate of \$1 million per year for "knowing failures." Covered manufacturers must submit reports by the 90th day of each subsequent calendar year. In addition, certain states require the implementation of compliance programs and compliance with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, impose restrictions on marketing practices and/or tracking and reporting of gifts, compensation and other remuneration or items of value provided to physicians and other healthcare professionals and entities.

Napo may also be subject to data privacy and security regulation by both the federal government and the states in which Napo conducts its business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act ("HITECH"), and their respective implementing regulations, including the Final HIPAA Omnibus Rule, published on January 25, 2013, impose specified requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. Among other things, HITECH made HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating compliance efforts.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any pharmaceutical products for which Napo obtains regulatory approval. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use Napo's products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of Napo's products. Sales of any products for which Napo receives regulatory approval for commercial sale will, therefore depend, in part, on the availability of coverage and adequate reimbursement from third party payors. Third party payors include government authorities, managed care plans, private health insurers and other organizations. In the United States, the process for determining whether a third party payor will provide coverage for a pharmaceutical or biological product typically is separate from the process for setting the price of such product or for establishing the reimbursement rate that the payor will pay for the product once coverage is approved. Third party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA approved products for a particular indication. A decision by a third party payor not to cover Napo's product candidates could reduce physician utilization of Napo's products once approved and have a material adverse effect on Napo's sales, results of operations and financial condition. Moreover, a third party payor's decision to provide coverage for a pharmaceutical or biological product does not imply that an adequate reimbursement rate will be approved. Adequate third party reimbursement may not be available to enable Napo to maintain price levels sufficient to realize an appropriate return on Napo's investment in product development. Additionally, coverage and reimbursement for products can differ significantly from payor to payor. One third party payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. As a result, the coverage determination process will require Napo to provide scientific and clinical support for the use of Napo's products to each payor separately and will be a time consuming process.

In the EEA, governments influence the price of products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription products, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross border imports from low priced markets exert commercial pressure on pricing within a country.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of pharmaceutical or biological products have been a focus in this effort. Third party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical or biological products, medical devices and medical services, in addition to questioning safety and efficacy. If these third party payors do not consider Napo's products to be cost effective compared to other available therapies, they may not cover Napo's products after FDA approval or, if they do, the level of payment may not be sufficient to allow Napo to sell its products at a profit.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in March 2010, the ACA was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to the utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for

certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs covered under Medicare Part D; subjected drug manufacturers to new annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; creation of the Independent Payment Advisory Board, once empaneled, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs; and establishment of a Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending. Since its enactment, the U.S. federal government has delayed or suspended the implementation of certain provisions of the ACA.

Napo expects that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement and additional downward pressure on the price that Napo receives for any approved product. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. Moreover, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. The implementation of cost containment measures or other healthcare reforms may prevent Napo from being able to generate revenue, attain profitability or commercialize Napo's drugs.

Additionally, on August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013, and due to subsequent legislative amendments to the statute, will stay in effect through 2025 unless additional action is taken by Congress. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, there has been heightened governmental scrutiny recently over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products.

Napo expects that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for Napo's products once approved or additional pricing pressures.

Other Regulatory Considerations

We believe regulatory rules relating to human food safety, food additives, or drug residues in food will not apply to the products we currently are developing because our animal prescription drug product candidates are not intended for use in production animals, with the exception of horses, which qualify as food animals in Europe and Canada; and our nonprescription products are not regulated by section 201(g) of the Federal Food, Drug, and Cosmetic Act, which the FDA is authorized to administer.

We do not believe that our animal nonprescription products are currently subject to regulation in the United States. The CVM only regulates those animal supplements that fall within the FDA's definition of an animal drug, food or feed additive. The Federal Food Drug and Cosmetic Act defines food as "articles used for food or drink for man or other animals and articles used as components of any such article." Animal foods are not subject to pre-market approval and are designed to provide a nutritive purpose to the animals that receive them. Feed additives are defined as those articles that are added to an animal's feed or water, as illustrated by the guidance documents. Our nonprescription products are not added to food, are not ingredients in food, nor are they added to any animal's drinking water. There is no intent to make our nonprescription products a component of an animal food, either directly

or indirectly. We do not believe that our nonprescription products fit the definition of an animal drug, food or food additive and therefore are not regulated by the FDA at this time.

In addition to the foregoing, we may be subject to state, federal and foreign healthcare and/or veterinary medicine laws, including but not limited to anti-kickback laws, as we may from time to time enter consulting and other financial arrangements with veterinarians, who may prescribe or recommend our products. If our financial relationships with veterinarians are found to be in violation of such laws that apply to us, we may be subject to penalties.

Legal Proceedings

From time to time, we may become involved in litigation relating to claims arising from the ordinary course of business. Other than as set forth in “Item 3. LEGAL PROCEEDINGS”, there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

Corporate Information

We were incorporated in the State of Delaware on June 6, 2013. Our principal executive office is located at 200 Pine Street, Suite 400, San Francisco, CA 94104 for human health prescription drugs and the telephone number is (415) 371 8300. We have an additional office at 200 Pine Street, Suite 600, San Francisco, CA 94104 for Jaguar Animal Health. Our website for the corporation is <https://jaguar.health>. The information contained on, or that can be accessed through, our website is not part of this annual report. Our voting common stock is listed on the NASDAQ Capital Market and trades under the symbol “JAGX.” On July 31, 2017, we completed the acquisition of Napo pursuant to the Agreement and Plan of Merger, dated March 31, 2017, by and among the Company, Napo, Napo Acquisition Corporation, and Napo’s representative (the “Merger”).

Employees

As of December 31, 2021, we had 52 employees. Ten employees hold M.D., D.V.M and/or Ph.D. degrees. Twenty-one of our employees are engaged in research and development activities and 17 employees are engaged in sales and marketing. We have two employees within Napo Therapeutics in Italy. None of our employees are represented by labor unions or covered by collective bargaining agreements.

Description of Properties

Our corporate headquarters are located in San Francisco, California, where we currently lease 10,526 rentable square feet of office space from M & E, LLC.

ITEM 1A. RISK FACTORS

The business, financial condition and operating results of the Company may be affected by a number of factors, whether currently known or unknown, including but not limited to those described below. Anyone or more of such factors could directly or indirectly cause the Company’s actual results of operations and financial condition to vary materially from past or anticipated future results of operations and financial condition. Any of these factors, in whole or in part, could materially and adversely affect the Company’s business, financial condition, results of operations and stock price. The following information should be read in conjunction with Part II, Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and the consolidated financial statements and related notes in Part II, Item 8, “Financial Statements and Supplementary Data” of this Annual Report.

Risk Factor Summary

The following is a summary of the principal risks that could adversely affect our business, operations and financial results.

Risks Related to Our Business

- We have a limited operating history, expect to incur further losses as we grow and may be unable to achieve or sustain profitability.
- We expect to incur significant additional costs as we continue commercialization efforts for current prescription drug candidates or other product candidates, and undertake the clinical trials necessary to obtain any necessary regulatory approvals, which will increase our losses.
- We will need to raise substantial additional capital in the future in the event that we conduct clinical trials for new indications and we may be unable to raise such funds when needed and on acceptable terms, which would force us to delay, limit, reduce or terminate one or more of our product development programs.
- We are substantially dependent on the success of Mytesi, our current lead prescription drug product, and Canalevia-CA1, our conditionally approved prescription drug product for CID in dogs, and Canalevia-CA2, our candidate for EID in dogs. We cannot be certain that necessary approvals will be received for planned Mytesi, Canalevia-CA1 or Canalevia-CA2 follow-on indications or that these product candidates will be successfully commercialized, either by us or any of our partners.
- If we are not successful in identifying, licensing, developing and commercializing additional product candidates and products, our ability to expand our business and achieve our strategic objectives could be impaired.
- Mytesi faces significant competition from other pharmaceutical companies, both for its currently approved indication and for planned follow-on indications, and our operating results will suffer if we fail to compete effectively.
- We may be unable to obtain, or obtain on a timely basis, regulatory approval for our existing or future human or animal prescription drug product candidates under applicable regulatory requirements, which would harm our operating results.
- The results of our earlier studies of Mytesi may not be predictive of the results in any future clinical trials and species-specific formulation studies, respectively, and we may not be successful in our efforts to develop or commercialize line extensions of Mytesi.
- Development of prescription drug products is inherently expensive, time-consuming and uncertain, and any delay or discontinuance of our current or future pivotal trials would harm our business and prospects.
- We will partially rely on third parties to conduct our development activities. If these third parties do not successfully carry out their contractual duties, we may be unable to obtain regulatory approvals or commercialize our current or future human or animal product candidates on a timely basis, or at all.
- Even if we obtain regulatory approval for planned follow-on indications of crofelemer, Canalevia or our other product candidates, they may never achieve market acceptance. Further, even if we are successful in the ongoing commercialization of Mytesi and Canalevia, we may not achieve commercial success.
- Human and animal gastrointestinal health products are subject to unanticipated post-approval safety or efficacy concerns, which may harm our business and reputation.
- Future federal and state legislation may result in increased exposure to product liability claims, which could result in substantial losses.
- If we fail to retain current members of our senior management, or to identify, attract, integrate and retain additional key personnel, our business will be harmed.
- We are dependent on two suppliers for the raw material used to produce the active pharmaceutical ingredient in Mytesi and Canalevia. The termination of either of these contracts would result in a disruption to product development and our business will be harmed.
- We are dependent upon third-party contract manufacturers, both for the supply of the active pharmaceutical ingredient in Mytesi and Canalevia-CA1, as well as for the supply of finished products for commercialization.
- If we are unable to establish sales capabilities on our own or through third parties, we may not be able to market and sell our current or future human products and product candidates, if approved, and generate

product or other revenue.

- We will need to increase the size of our organization and may not successfully manage such growth.
- Canalevia-CA1 and, our animal health prescription drug product candidates, if approved may be marketed in the United States only in the target animals and for the indications for which they are approved, and if we want to expand the approved animals or indications, it will need to obtain additional approvals, which may not be granted.
- The misuse or extra-label use of Mytesi, Canalevia, and our human or animal prescription drug product candidates if approved by regulatory authorities, may harm our reputation or result in financial or other damages.
- We may be unable to obtain, or obtain on a timely basis, a renewal of conditional approval for Canalevia-CA1, or to eventually obtain full regulatory approval of Canalevia-CA1, which would harm our operating results.
- We may not maintain the benefits associated with MUMS designation, including market exclusivity.
- The market for our human and animal products, and the gastrointestinal health market as a whole, is uncertain and may be smaller than we anticipate, which could lead to lower revenue and harm our operating results.
- Insurance coverage for Mytesi for its current approved indication could decrease or end, or Mytesi might not receive insurance coverage for any approved follow-on indications, which could lead to lower revenue and harm our operating results.
- We may engage in future acquisitions that increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.
- Certain of the countries in which we plan to commercialize our products in the future are developing countries, some of which have potentially unstable political and economic climates.
- Fluctuations in the exchange rate of foreign currencies could result in currency transactions losses.
- Laws and regulations governing global trade compliance could adversely impact our business.
- There are other gastrointestinal-focused human pharmaceutical companies, and we face competition in the marketplaces in which we operate or plan to operate.
- Our obligations to Streeterville are secured by a security interest in all of Napo's lechlemer assets, so if we default on those obligations, Streeterville could foreclose on our assets.
- Our royalty interests require us to make minimum royalty payments, even if we do not sell a sufficient amount of products to cover the amount of such payments, which may strain our cash resources.
- Failure in our information technology systems, including by cyber-attacks or other data security incidents, could significantly disrupt our operations.
- The novel coronavirus global pandemic could adversely impact our business, including our supply chain, clinical trials and commercialization of Mytesi and Canalevia.
- Long-term remote work arrangements may adversely affect our business.
- Substantially all of our revenue for recent periods has been received from three customers.
- We are subject to state laws in California that require gender and diversity quotas for boards of directors of public companies headquartered in California.

Risks Related to Our Intellectual Property

- We cannot be certain that our patent strategy will be effective to protect against competition
- Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.
- Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, which would be costly, time-consuming and, if successfully asserted against us, delay or prevent the development and commercialization of our current or future products and product candidates.
- Our proprietary position depends upon the botanical guidance of our drug approval and patents that are formulation or method-of-use patents, which do not prevent a competitor from using the same human or animal drug for another use.
- We may be involved in lawsuits to protect or enforce our patents, which could be expensive, time-

consuming and unsuccessful, and third parties may challenge the validity or enforceability of our patents and they may be successful.

- If we are unable to prevent disclosure of our trade secrets or other confidential information to third parties, our competitive position may be impaired.
- Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.
- We may not be able to protect our intellectual property rights throughout the world, which could impair our business.
- Our business could be harmed if we fail to obtain certain registered trademarks in the United States or in other countries.
- We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.
- Even if we receive any of the required regulatory approvals for our current or future prescription drug product candidates and non-prescription products, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense.
- Any of our current or future prescription drug product candidates or non-prescription products may cause or contribute to adverse medical events that we would be required to report to regulatory authorities and, if we fail to do so, we could be subject to sanctions that would harm our business.
- Legislative or regulatory reforms with respect to animal health may make it more difficult and costly for us to obtain regulatory clearance or approval of any of our current or future product candidates and to produce, market, and distribute our products after clearance or approval is obtained.
- We believe that our non-prescription products are not subject to regulation by regulatory agencies in the United States, but there is a risk that regulatory bodies may disagree with our interpretation, or may redefine the scope of their regulatory reach in the future, which would result in additional expense and could delay or prevent the commercialization of these products.
- Even if we receive the required regulatory approvals for our current or future prescription drug product candidates and non-prescription products, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense

Risks Related to Our Common Stock

- Our failure to meet the continued listing requirements of The Nasdaq Capital Market could result in a delisting of our common stock.
- If we issue all shares available for issuance pursuant to the ATM Agreement, we will have no shares of common stock available for new securities issuances, which may restrict us from accessing additional capital through the sale of new securities.
- If our shares become subject to the penny stock rules, it would become more difficult to trade our shares.
- The price of our common stock could be subject to volatility related or unrelated to our operations, and purchasers of our common stock could incur substantial losses.
- A possible “short squeeze” due to a sudden increase in demand of our common stock that largely exceeds supply may lead to further price volatility in our common stock.
- You may not be able to resell our common stock when you wish to sell them or at a price that you consider attractive or satisfactory.
- If securities or industry analysts do not publish research or reports about our company, or if they issue adverse or misleading opinions regarding us or our stock, our stock price and trading volume could decline.
- You may be diluted by conversions of outstanding shares of non-voting common stock, exercises of outstanding options and warrants and issuances of securities pursuant to our ATM Agreement.
- Provisions in our charter documents and under Delaware law could discourage a takeover that stockholders may consider favorable and may lead to entrenchment of management.
- Our amended and restated bylaws designate the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain actions and proceedings that may be initiated by our stockholders, which could limit our stockholders’ ability to obtain a favorable judicial forum for disputes with us or our directors, officers or other employees.
- We do not intend to pay dividends on our common stock, and your ability to achieve a return on your

investment will depend on appreciation in the market price of our common stock.

- The requirements of being a public company, including compliance with the reporting requirements of the Exchange Act and the requirements of the Sarbanes-Oxley Act, may strain our resources, increase our costs and distract management, and we may be unable to comply with these requirements in a timely or cost-effective manner.
- We are a smaller reporting company and the reduced reporting requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

Risks Related to Our Business

We have a limited operating history, expect to incur further losses as we grow and may be unable to achieve or sustain profitability.

Since the consummation of our merger with Napo Pharmaceuticals Inc. in 2017, our operations have been primarily focused on research, development and the ongoing commercialization of our lead prescription drug product, Mytesi, which is approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. As a result, we have limited meaningful historical operations upon which to evaluate our business and prospects and have not yet demonstrated an ability to broadly commercialize any of our human health products beyond Mytesi for HIV-related diarrhea or animal health products, obtain any required marketing approval for any of our animal prescription drug product candidates or successfully overcome the risks and uncertainties frequently encountered by companies in emerging fields such as the animal health industry or the gastrointestinal health industry in general. Our revenues to date have been insufficient to offset our expenses, and we expect to continue to incur significant research and development and other expenses. Our net loss and comprehensive loss for the years ended December 31, 2021 and 2020 was \$52.6 million and \$33.8 million, respectively. As of December 31, 2021, we had total stockholders' equity of \$11.9 million. We expect to continue to incur losses for the foreseeable future, which will increase significantly from historical levels as we expand our product development activities, seek necessary approvals for our human and veterinary drug product candidates, conduct species-specific formulation studies for our non-prescription products and increase commercialization activities. Even if we succeed in developing and broadly commercializing one or more of our products or product candidates, we expect to continue to incur losses for the foreseeable future, and we may never become profitable. If we fail to achieve or maintain profitability, then we may be unable to continue our operations at planned levels and be forced to reduce or cease operations.

As more fully discussed in Note 1 to our consolidated financial statements, we believe there is substantial doubt about our ability to continue as a going concern as we do not currently have sufficient cash resources to fund our operations through March 11, 2023, or one year from the filing date of our Form 10-K. Our financial statements do not include any adjustments that may result from the outcome of this uncertainty. If we are unable to continue as a viable entity, our stockholders may lose their investment.

We expect to incur significant additional costs as we continue commercialization efforts for current prescription drug candidates or other product candidates, and undertake the clinical trials necessary to obtain any necessary regulatory approvals, which will increase our losses.

Napo commenced sales of Mytesi for adults with HIV/AIDS on antiretroviral therapy in September 2016. Jaguar launched Canalevia-CA1 for chemotherapy-induced diarrhea in dogs in December 2021. We will need to continue to invest in developing our internal and third-party sales and distribution network and outreach efforts to key opinion leaders in the gastrointestinal health industry, including physicians and veterinarians as applicable.

We are actively identifying additional products for development and commercialization, and will continue to expend substantial resources for the foreseeable future to develop Mytesi, lechlemer and Canalevia-CA1. These expenditures will include costs associated with:

- identifying additional potential prescription drug product candidates and non-prescription products;

- formulation studies;
- conducting pilot, pivotal and toxicology studies;
- completing other research and development activities;
- payments to technology licensors;
- maintaining our intellectual property;
- obtaining necessary regulatory approvals;
- establishing commercial supply capabilities; and
- sales, marketing and distribution of our commercialized products.

We also may incur unanticipated costs in connection with developing and commercializing our products. Because the outcome of our development activities and commercialization efforts is inherently uncertain, the actual amounts necessary to successfully complete the development and commercialization of our current or future products and product candidates may be greater than we anticipate.

Because we anticipate incurring significant costs for the foreseeable future, if we are not successful in broadly commercializing any of our current or future products or product candidates or raising additional funding to pursue our research and development efforts, we may never realize the benefit of our development efforts and our business may be harmed.

We will need to raise substantial additional capital in the future in the event that we conduct clinical trials for new indications and we may be unable to raise such funds when needed and on acceptable terms, which would force us to delay, limit, reduce or terminate one or more of our product development programs.

We are forecasting continued losses and negative cash flows as we continue to fund our operating and marketing activities and research and development programs, and to complete the development of all the current products in our pipeline, or any additional products we may identify. We will need to seek additional funds through public or private equity or debt financings or other sources such as strategic collaborations. Any such financings or collaborations may result in dilution to our stockholders, the imposition of debt covenants and repayment obligations or other restrictions that may harm our business or the value of our common stock. We may also seek from time to time to raise additional capital based upon favorable market conditions or strategic considerations such as potential acquisitions or potential license arrangements.

Our future capital requirements depend on many factors, including, but not limited to:

- the scope, progress, results and costs of researching and developing our current and future prescription drug product candidates and non-prescription products;
- the timing of, and the costs involved in, obtaining any regulatory approvals for our current and any future products;
- the number and characteristics of the products we pursue;
- the cost of manufacturing our current and future products and any products we successfully commercialize;
- the cost of commercialization activities for Mytesi and Canalevia, if approved, including sales,

marketing and distribution costs;

- the expenses needed to attract and retain skilled personnel;
- the costs associated with being a public company;
- our ability to establish and maintain strategic collaborations, distribution or other arrangements and the financial terms of such agreements; and
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing possible patent claims, including litigation costs and the outcome of any such litigation.

Additional funds may not be available when we need them on terms that are acceptable to us, or at all or we may not have sufficient authorized shares to raise additional capital. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate one or more of our product development programs or future commercialization efforts.

We are substantially dependent on the success of Mytesi, our current lead prescription drug product, and Canalevia-CA1, our conditionally approved prescription drug product for CID in dogs, and Canalevia-CA2, our candidate for EID in dogs. We cannot be certain that necessary approvals will be received for planned Mytesi and Canalevia-CA1 follow-on indications or that these product candidates will be successfully commercialized, either by us or any of our partners.

Other than Mytesi and Canalevia-CA1 (for which we have conditional approval), we currently do not have regulatory approval for any of our prescription drug product candidates. Our current efforts are primarily focused on the ongoing commercialization of Mytesi and Canalevia-CA1, and development efforts related to Mytesi and Canalevia-CA1. With regard to Mytesi, we are focused on marketing the product in the United States as well as on development efforts related to a follow-on indication for Mytesi in CTD, an important supportive care indication for patients undergoing primary or adjuvant chemotherapy for cancer treatment, and symptomatic relief of COVID-related diarrhea. Mytesi is also in development for other possible follow-on indications, including orphan drug indications for symptomatic relief of diarrhea in infants and children with CDD and for adult and pediatric patients with SBS; and for supportive care for diarrhea relief in IBD; IBS-D; and for idiopathic/functional diarrhea. With regard to Canalevia-CA1, we are focused on the launch of the product in the United States for chemotherapy-induced diarrhea in dogs. In addition, a second-generation proprietary anti-secretory agent is in development for cholera. Mytesi previously received orphan-drug designation for SBS. Accordingly, our near term prospects, including our ability to generate material product revenue, obtain any new financing if needed to fund our business and operations or enter into potential strategic transactions, will depend heavily on the success of Mytesi and Canalevia-CA1.

Substantial time and capital resources have been previously devoted by third parties in the development of crofelemer, the active pharmaceutical ingredient, or API, in Mytesi and Canalevia, and the development of the botanical extract used in Equilevia and Neonorm. Both crofelemer and the botanical extract used in Equilevia and Neonorm were originally developed at Shaman Pharmaceuticals, Inc. (“Shaman”), by certain members of our management team, including Lisa A. Conte, our chief executive officer and president, and Steven R. King, Ph.D., our executive vice president of sustainable supply, ethnobotanical research and intellectual property and secretary. Shaman spent significant development resources before voluntarily filing for bankruptcy in 2001 pursuant to Chapter 11 of the U.S. Bankruptcy Code. The rights to crofelemer and the botanical extract used in Equilevia and Neonorm, as well as other intellectual property rights, were subsequently acquired by Napo from Shaman in 2001 pursuant to a court approved sale of assets. Ms. Conte founded Napo in 2001 and was the current interim chief executive officer of Napo and a member of Napo’s board of directors prior to the Merger. While at Napo, certain members of our management team, including Ms. Conte and Dr. King, continued the development of crofelemer. Following the merger of Jaguar and Napo in July 2017, Napo became Jaguar’s wholly-owned subsidiary. If we are not successful in the development and commercialization of Mytesi, our business and our prospects will be harmed.

The successful development and commercialization of Mytesi and Canalevia-CA1 will depend on a number of factors, including the following:

- our ability to demonstrate to the satisfaction of the FDA and any other regulatory bodies, the safety and efficacy of Canalevia;
- our ability and that of our contract manufacturers to manufacture supplies of Mytesi and Canalevia-CA1 and to develop, validate and maintain viable commercial manufacturing processes that are compliant with current good manufacturing practices, or cGMPs, if required;
- our ability to successfully market Mytesi and Canalevia-CA1, whether alone or in collaboration with others;
- the availability, perceived advantages, relative cost, relative safety and relative efficacy of our prescription drug product candidates compared to alternative and competing treatments;
- the acceptance of our prescription drug product candidates and non-prescription products as safe and effective by physicians, veterinarians, patients, animal owners and the human and animal health community, as applicable;
- our ability to achieve and maintain compliance with all regulatory requirements applicable to our business; and
- our ability to obtain and enforce our intellectual property rights and obtain marketing exclusivity for our prescription drug product candidates and non-prescription products, and avoid or prevail in any third-party patent interference, patent infringement claims or administrative patent proceedings initiated by third parties or the U.S. Patent and Trademark Office (“USPTO”).

Many of these factors are beyond our control. Accordingly, we may not be successful in developing or commercializing Mytesi, Neonorm, Equilevia, Canalevia or any of our other potential products. If we are unsuccessful or are significantly delayed in commercializing Mytesi, our business and prospects will be harmed and you may lose all or a portion of the value of your investment in our common stock.

If we are not successful in identifying, licensing, developing and commercializing additional product candidates and products, our ability to expand our business and achieve our strategic objectives could be impaired.

Although a substantial amount of our efforts is focused on the commercial performance of Mytesi and Canalevia-CA1, a key element of our strategy is to identify, develop and commercialize a portfolio of products to serve the gastrointestinal health market. Most of our potential products are based on our knowledge of medicinal plants. Our current focus is primarily on product candidates whose active pharmaceutical ingredient or botanical extract has been successfully commercialized or demonstrated to be safe and effective in human or animal trials. In some instances, we may be unable to further develop these potential products because of perceived regulatory and commercial risks. Even if we successfully identify potential products, we may still fail to yield products for development and commercialization for many reasons, including the following:

- competitors may develop alternatives that render our potential products obsolete;
- an outside party may develop a cure for any disease state that is the target indication for any of our planned or approved drug products;
- potential products we seek to develop may be covered by third-party patents or other exclusive rights;
- a potential product may on further study be shown to have harmful side effects or other characteristics

that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;

- a potential product may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a potential product may not be accepted as safe and effective by physicians, veterinarians, patients, animal owners, key opinion leaders and other decision-makers in the gastrointestinal health market, as applicable.

While we are developing specific formulations, including flavors, methods of administration, new patents and other strategies with respect to our current potential products, we may be unable to prevent competitors from developing substantially similar products and bringing those products to market earlier than we can. If such competing products achieve regulatory approval and commercialization prior to our potential products, our competitive position may be impaired. If we fail to develop and successfully commercialize other potential products, our business and future prospects may be harmed and we will be more vulnerable to any problems that we encounter in developing and commercializing our current potential products.

Mytesi faces significant competition from other pharmaceutical companies, both for its currently approved indication and for planned follow-on indications, and our operating results will suffer if we fail to compete effectively.

The development and commercialization of products for human gastrointestinal health is highly competitive and our success depends on our ability to compete effectively with other products in the market. During the ongoing commercialization of Mytesi for its currently approved indication, and during the future commercialization of Mytesi for any planned follow-on indications, if such follow-on indications receive regulatory approval, we expect to compete with major pharmaceutical and biotechnology companies that operate in the gastrointestinal space, such as Takeda Pharmaceuticals, Allergan, Inc., Ironwood Pharmaceuticals, Inc., Synergy Pharmaceuticals Inc., Sebela Pharmaceuticals, Inc. and Salix Pharmaceuticals.

Many of our competitors and potential competitors in the human gastrointestinal space have substantially more financial, technical and human resources and greater ability to lower costs of manufacturing and sales and marketing than we do. Many also have more experience in the development, manufacture, regulation and worldwide commercialization of human gastrointestinal health products.

For these reasons, we cannot be certain that we and Mytesi can compete effectively.

We may be unable to obtain, or obtain on a timely basis, regulatory approval for our existing or future human or animal prescription drug product candidates under applicable regulatory requirements, which would harm our operating results.

The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of human and animal health products are subject to extensive regulation. We are typically not permitted to market our prescription drug product candidates in the United States until we receive approval of the product from the FDA through the filing of an NDA or NADA, as applicable. To gain approval to market a prescription drug, we must provide the FDA with safety and efficacy data from pivotal trials that adequately demonstrate that our prescription drug product candidates are safe and effective for the intended indications. Likewise, to gain approval to market an animal prescription drug for a particular species, we must provide the FDA with safety and efficacy data from pivotal trials that adequately demonstrate that our prescription drug product candidates are safe and effective in the target species (e.g., dogs, cats or horses) for the intended indications. In addition, we must provide manufacturing data evidencing that we can produce our product candidates in accordance with cGMPs. For the FDA, we must also provide data from toxicology studies, also called target animal safety studies, and in some cases environmental impact data. In addition to our internal activities, we will partially rely on contract research organizations (“CROs”), and other third parties to conduct our toxicology studies and for certain other product development activities. The results of toxicology studies, other initial development activities, and/or any previous studies in humans or animals conducted by us or third parties

may not be predictive of future results of pivotal trials or other future studies, and failure can occur at any time during the conduct of pivotal trials and other development activities by us or our CROs. Our pivotal trials may fail to show the desired safety or efficacy of our prescription drug product candidates despite promising initial data or the results in previous human or animal studies conducted by others. Success of a prescription drug product candidate in prior animal studies, or in the treatment of humans, does not ensure success in subsequent studies. Clinical trials in humans and pivotal trials in animals sometimes fail to show a benefit even for drugs that are effective because of statistical limitations in the design of the trials or other statistical anomalies. Therefore, even if our studies and other development activities are completed as planned, the results may not be sufficient to obtain a required regulatory approval for a product candidate.

Regulatory authorities can delay, limit or deny approval of any of our prescription drug product candidates for many reasons, including:

- if they disagree with our interpretation of data from our pivotal studies or other development efforts;
- if we are unable to demonstrate to their satisfaction that our product candidate is safe and effective for the target indication and, if applicable, in the target species;
- if they require additional studies or change their approval policies or regulations;
- if they do not approve of the formulation, labeling or the specifications of our current and future product candidates; and
- if they fail to approve the manufacturing processes of our third-party contract manufacturers.

Further, even if we receive a required approval, such approval maybe for a more limited indication than we originally requested, and the regulatory authority may not approve the labeling that we believe is necessary or desirable for successful commercialization.

Any delay or failure in obtaining any necessary regulatory approval for the intended indications of our human or animal product candidates would delay or prevent commercialization of such product candidates and would harm our business and our operating results.

The results of our earlier studies of Mytesi may not be predictive of the results in any future clinical trials and species-specific formulation studies, respectively, and we may not be successful in our efforts to develop or commercialize line extensions of Mytesi.

Our human and animal product pipeline includes a number of potential indications of Mytesi, our lead prescription product. The results of our studies and other development activities and of any previous studies in humans or animals conducted by us or third parties may not be predictive of future results of these clinical studies and formulation studies, respectively. Failure can occur at any time during the conduct of these trials and other development activities. Even if our formulation/clinical studies and other development activities are completed as planned, the results may not be sufficient to pursue a particular line extension for Mytesi. Further, even if we obtain promising results from our clinical trials or species-specific formulation studies, as applicable, we may not successfully commercialize any line extension. Because line extensions are developed for a particular market, we may not be able to leverage our experience from the commercial launch of Mytesi in new markets. If we are not successful in developing and successfully commercializing these line extension products, we may not be able to grow our revenue and our business may be harmed.

Development of prescription drug products is inherently expensive, time-consuming and uncertain, and any delay or discontinuance of our current or future pivotal trials would harm our business and prospects.

Development of prescription drug products for human and animal gastrointestinal health remains an inherently lengthy, expensive and uncertain process, and our development activities may not be successful. We do not

know whether our current or planned pivotal trials for any of our product candidates will begin or conclude on time, and they may be delayed or discontinued for a variety of reasons, including if we are unable to:

- address any safety concerns that arise during the course of the studies;
- complete the studies due to deviations from the study protocols or the occurrence of adverse events;
- add new study sites;
- address any conflicts with new or existing laws or regulations; or
- reach agreement on acceptable terms with study sites, which can be subject to extensive negotiation and may vary significantly among different sites.

Further, we may not be successful in developing new indications for Mytesi and Canalevia-CA1, and Neonorm may be subject to the same regulatory regime as prescription drug products in jurisdictions outside the United States. Any delays in completing our development efforts will increase our costs, delay our development efforts and approval process and jeopardize our ability to commence product sales and generate revenue. Any of these occurrences may harm our business, financial condition and prospects. In addition, factors that may cause a delay in the commencement or completion of our development efforts may also ultimately lead to the denial of regulatory approval of our product candidates, which, as described above, would harm our business and prospects.

We will partially rely on third parties to conduct our development activities. If these third parties do not successfully carry out their contractual duties, we may be unable to obtain regulatory approvals or commercialize our current or future human or animal product candidates on a timely basis, or at all.

We will partially rely upon CROs to conduct our toxicology studies and for other development activities. We intend to rely on CROs to conduct one or more of our planned pivotal trials. These CROs are not our employees, and except for contractual duties and obligations, we have limited ability to control the amount or timing of resources that they devote to our programs or manage the risks associated with their activities on our behalf. We are responsible for ensuring that each of our studies is conducted in accordance with the development plans and trial protocols presented to regulatory authorities. Any deviations by our CROs may adversely affect our ability to obtain regulatory approvals, subject us to penalties or harm our credibility with regulators. The FDA and foreign regulatory authorities also require us and our CROs to comply with regulations and standards, GCPs or GLPs, for conducting, monitoring, recording and reporting the results of our studies to ensure that the data and results are scientifically valid and accurate.

Agreements with CROs generally allow the CROs to terminate in certain circumstances with little or no advance notice. These agreements generally will require our CROs to reasonably cooperate with us at our expense for an orderly winding down of the CROs' services under the agreements. If the CROs conducting our studies do not comply with their contractual duties or obligations, or if they experience work stoppages, do not meet expected deadlines, or if the quality or accuracy of the data they obtain is compromised, we may need to secure new arrangements with alternative CROs, which could be difficult and costly. In such event, our studies also may need to be extended, delayed or terminated as a result, or may need to be repeated. If any of the foregoing were to occur, regulatory approval, if required, and commercialization of our product candidates may be delayed and we may be required to expend substantial additional resources.

Even if we obtain regulatory approval for planned follow-on indications of crofelemer, Canalevia or our other product candidates, they may never achieve market acceptance. Further, even if we are successful in the ongoing commercialization of Mytesi and Canalevia, we may not achieve commercial success.

If we obtain necessary regulatory approvals for planned follow-on indications of crofelemer or our other product candidates, such products may still not achieve market acceptance and may not be commercially successful. Market acceptance of Mytesi, Canalevia, and any of our other products depends on a number of factors, including:

- the safety of our products as demonstrated in our target animal studies;
- the indications for which our products are approved or marketed;
- the potential and perceived advantages over alternative treatments or products, including generic medicines and competing products currently prescribed by physicians or veterinarians, as applicable, and, in the case of animal products, products approved for use in humans that are used extra-label in animals;
- the acceptance by physicians, veterinarians, companion animal owners, as applicable, of our products as safe and effective;
- the cost in relation to alternative treatments and willingness on the part of physicians, veterinarians, patients and animal owners, as applicable, to pay for our products;
- the prevalence and severity of any adverse side effects of our products;
- the relative convenience and ease of administration of our products; and
- the effectiveness of our sales, marketing and distribution efforts.

Any failure by Mytesi or Canalevia to achieve market acceptance or commercial success would harm our financial condition and results of operations.

Human and animal gastrointestinal health products are subject to unanticipated post-approval safety or efficacy concerns, which may harm our business and reputation.

The success of our commercialization efforts will depend upon the perceived safety and effectiveness of human and animal gastrointestinal health products, in general, and of our products, in particular. Unanticipated safety or efficacy concerns can subsequently arise with respect to approved prescription drug products, such as Mytesi, or non-prescription products, such as Neonorm, which may result in product recalls or withdrawals or suspension of sales, as well as product liability and other claims. Any safety or efficacy concerns, or recalls, withdrawals or suspensions of sales of our products could harm our reputation and business, regardless of whether such concerns or actions are justified.

Future federal and state legislation may result in increased exposure to product liability claims, which could result in substantial losses.

Under current federal and state laws, companion and production animals are generally considered to be the personal property of their owners and, as such, the owners' recovery for product liability claims involving their companion and production animals may be limited to the replacement value of the animal. Companion animal owners and their advocates, however, have filed lawsuits from time to time seeking non-economic damages such as pain and suffering and emotional distress for harm to their companion animals based on theories applicable to personal injuries to humans. If new legislation is passed to allow recovery for such non-economic damages, or if precedents are set allowing for such recovery, we could be exposed to increased product liability claims that could result in substantial losses to us if successful. In addition, some horses can be worth millions of dollars or more, and product liability for horses may be very high. While we currently have product liability insurance, such insurance may not be sufficient to cover any future product liability claims against us.

If we fail to retain current members of our senior management, or to identify, attract, integrate and retain additional key personnel, our business will be harmed.

Our success depends on our continued ability to attract, retain and motivate highly qualified management and scientific personnel. We are highly dependent upon our senior management, particularly Lisa A. Conte, our president and Chief Executive Officer. The loss of services of any of our key personnel would cause a disruption in our ability to develop our current or future product pipeline and commercialize our products and product candidates. Although we have offer letters with these key members of senior management, such agreements do not prohibit them from resigning at any time. For example, the resignation of our former Chief Financial Officer and Treasurer, Karen Wright, in August 2019, caused us to incur additional expenses and expend resources to ensure a smooth transition with her successor, which diverted management attention away from executing our operational plan during this period. To help attract, retain, and motivate qualified management and other personnel, we use share-based incentive awards such as employee stock options and restricted stock units. However, given the volatility in our stock price, it may be more difficult and expensive to recruit and retain employees, particularly senior management, through grants of stock or stock options. If our share-based compensation ceases to be viewed as a valuable benefit, our ability to attract, retain, and motivate qualified management and other personnel could be weakened, which could harm our results of operations and adversely affect the timing or outcomes of our current and planned studies, as well as the prospects for commercializing our products.

In addition, competition for qualified personnel in the human gastrointestinal health field is intense because there are a limited number of individuals who are trained or experienced in the field. We will need to hire additional personnel as we expand our product development and commercialization activities. Even if we are successful in hiring qualified individuals, as we are a growing organization, we do not have a track record for integrating and retaining individuals. If we are not successful in identifying, attracting, integrating or retaining qualified personnel on acceptable terms, or at all, our business will be harmed.

We are dependent on two suppliers for the raw material used to produce the active pharmaceutical ingredient in Mytesi and Canalevia. The termination of either of these contracts would result in a disruption to product development and our business will be harmed.

The raw material used to manufacture Mytesi and Canalevia-CA1 is CPL derived from the Croton lechleri tree, which is found in countries in South America, principally Peru. The ability of our contract suppliers to harvest CPL is governed by the terms of their respective agreements with local government authorities. Although CPL is available from multiple suppliers, we only have contracts with two suppliers to obtain CPL and arrange the shipment to our contract manufacturer. Accordingly, if our contract suppliers do not or are unable to comply with the terms of our respective agreements, and we are not able to negotiate new agreements with alternate suppliers on terms that we deem commercially reasonable, it may harm our business and prospects. The countries from which we obtain CPL could change their laws and regulations regarding the export of the natural products or impose or increase taxes or duties payable by exporters of such products. Restrictions could be imposed on the harvesting of the natural products or additional requirements could be implemented for the replanting and regeneration of the raw material. Such events could have a significant impact on our cost and ability to produce Mytesi, Canalevia-CA1 and anticipated line extensions.

We are dependent upon third-party contract manufacturers, both for the supply of the active pharmaceutical ingredient in Mytesi and Canalevia-CA1, as well as for the supply of finished products for commercialization.

We are in negotiations with Indena for the purification of the CPL received from our suppliers into the API used to manufacture Canalevia-CA1 and Mytesi, as well as the botanical extract in Neonorm. Indena has never manufactured either such ingredient to commercial scale. Glenmark is the current manufacturer of crofelemer, the active API in Canalevia-CA1 and Mytesi. As announced in October of 2015, we have entered into an agreement with Patheon, a provider of drug development and delivery solutions, under which Patheon provides enteric-coated tablets to us for use in humans and animals. We also may contract with additional third parties for the formulation and supply of finished products, which we will use in our planned studies and commercialization efforts.

We are dependent upon our contract manufacturers for the supply of the API in Mytesi and Canalevia-CA1. We currently have sufficient quantities of the API used in Mytesi and Canalevia to support our projected sales efforts. We are working with our contract manufacturers to increase API manufacturing capacity of the API to support the sales forecast for 2022 and beyond. If our contract manufacturer cannot manufacture sufficient quantities of the API in a timely manner, we could suffer losses due to lost sales opportunities. We currently have sufficient quantities of the botanical extract used in Neonorm and Equilevia to support planned commercialization efforts for Neonorm and Equilevia. If we are not successful in reaching agreements with third parties on terms that we consider commercially reasonable for manufacturing and formulation of Mytesi and Canalevia-CA1, or if our contract manufacturer and formulator are not able to produce sufficient quantities or quality of the Mytesi and Canalevia-CA1 API or finished product under their agreements, it could delay our plans and harm our business prospects. For example, as a result of the outbreak in 2020 of SARS-CoV-2, the virus that causes COVID-19, that originated in Wuhan, China and then spread globally, our suppliers and contract manufacturer could be disrupted by worker absenteeism, quarantines, or other travel or health-related restrictions or could incur increased costs associated with ensuring the safety and health of their personnel. If our suppliers or contract manufacturer is so affected, our supply chain could be disrupted, our product shipments could be delayed, our costs could be increased and our business could be adversely affected.

The facilities used by our third-party contractors are subject to inspections, including by the FDA, and other regulators, as applicable. We also depend on our third-party contractors to comply with cGMPs. If our third-party contractors do not maintain compliance with these strict regulatory requirements, they and we will not be able to secure or maintain regulatory approval for their facilities, which would have an adverse effect on our operations. In addition, in some cases, we also are dependent on our third-party contractors to produce supplies in conformity to our specifications and maintain quality control and quality assurance practices and not to employ disqualified personnel. If the FDA or a comparable foreign regulatory authority does not approve the facilities of our third-party contractors if so required, or if it withdraws any such approval in the future, we may need to find alternative manufacturing or formulation facilities, which could result in delays in our ability to develop or commercialize our products, if at all. We and our third-party contractors also may be subject to penalties and sanctions from the FDA and other regulatory authorities for any violations of applicable regulatory requirements. The European Medicines Agency (the “EMA”), employ different regulatory standards than the FDA, so we may require multiple manufacturing processes and facilities for the same product candidate or any approved product. We are also exposed to risk if our third-party contractors do not comply with the negotiated terms of our agreements, or if they suffer damage or destruction to their facilities or equipment.

If we are unable to establish sales capabilities on our own or through third parties, we may not be able to market and sell our current or future human products and product candidates, if approved, and generate product or other revenue.

We currently have limited sales, marketing or distribution capabilities, and prior to Napo’s launch of Mytesi for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy, and our launch of Neonorm for pre-weaned dairy calves and Canalevia for chemotherapy-induced diarrhea in dogs, we had no experience in the sale, marketing and distribution of human or animal health products. There are significant risks involved in building and managing a sales organization, including our potential inability to attract, hire, retain and motivate qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively oversee a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities and entry into adequate arrangements with distributors or other partners would adversely impact the commercialization of Mytesi, and Canalevia-CA1. If we are not successful in commercializing Mytesi and/or Canalevia-CA1, for their respective currently approved or conditionally approved indications or for any potential follow-on indications, either on our own or through one or more distributors, or in generating upfront licensing or other fees, including through the previously announced licensing arrangement between Napo Pharmaceuticals, Inc. and Napo Therapeutics S.p.A., we may never generate significant revenue and may continue to incur significant losses, which would harm our financial condition and results of operations.

We will need to increase the size of our organization and may not successfully manage such growth.

As of December 31, 2021, we had 52 employees. Our ability to manage our growth effectively will require us to hire, train, retain, manage and motivate additional employees and to implement and improve our operational, financial and management systems. These demands also may require the hiring of additional senior management personnel or the development of additional expertise by our senior management personnel. If we fail to expand and enhance our operational, financial and management systems in conjunction with our potential future growth, it could harm our business and operating results.

Canalevia-CA1 and, our animal health prescription drug product candidates, if approved, may be marketed in the United States only in the target animals and for the indications for which they are approved, and if we want to expand the approved animals or indications, it will need to obtain additional approvals, which may not be granted.

We may market or advertise Canalevia-CA1 and our animal health prescription drug product candidates are approved by regulatory authorities, only in the specific species and for treatment of the specific indications for which they were approved, which could limit use of the products by veterinarians and animal owners. We intend to develop, promote and commercialize approved products for new animal treatment indications in the future, but we cannot be certain whether or at what additional time and expense we will be able to do so. If we do not obtain marketing approvals for new indications, our ability to expand our animal health business may be harmed.

Under the Animal Medicinal Drug Use Clarification Act of 1994, veterinarians are permitted to prescribe extra-label uses of fully approved animal drugs and approved human drugs for animals under certain conditions. While veterinarians may in the future prescribe and use human-approved products or use our products for extra-label uses, we may not promote our animal health products for extra-label uses. We note that extra-label uses are uses for which the product has not received approval. If the FDA determines that any of our marketing activities constitute promotion of an extra-label use, we could be subject to regulatory enforcement, including seizure of any misbranded or mislabeled drugs, and civil or criminal penalties, any of which could have an adverse impact on our reputation and expose us to potential liability. We will continue to spend resources ensuring that our promotional claims for our animal health products and product candidates remain compliant with applicable FDA laws and regulations, including materials we post or link to on our website. For example, in 2012, our Chief Executive Officer received an “untitled letter” from the FDA while at Napo regarding preapproval promotion statements constituting misbranding of crofelemer, which was then an investigational drug. These statements were included in archived press releases included on Napo’s website. Napo was required to expend time and resources to revise its website to remove the links in order to address the concerns raised in the FDA’s letter.

The misuse or extra-label use of Mytesi, Canalevia and our human or animal prescription drug product candidates approved by regulatory authorities, may harm our reputation or result in financial or other damages.

If our human or animal prescription drug product candidates are approved by regulatory authorities, there may be increased risk of product liability if physicians, veterinarians, patients, animal owners or others, as applicable, attempt to use such products extra-label, including the use of our products for indications or in species for which they have not been approved. Furthermore, the use of an approved human or animal drug such as Mytesi and Canalevia for indications other than those indications for which such products have been approved may not be effective, which could harm our reputation and lead to an increased risk of litigation. If we are deemed by a governmental or regulatory agency to have engaged in the promotion of any approved human or animal product for extra-label use, such agency could request that we modify our training or promotional materials and practices and we could be subject to significant fines and penalties, and the imposition of these sanctions could also affect our reputation and position within the gastrointestinal health industry. Any of these events could harm our reputation and our operating results.

We may be unable to obtain, or obtain on a timely basis, a renewal of conditional approval for Canalevia-CA1, or to eventually obtain full regulatory approval of Canalevia-CA1, which would harm our operating results.

On December 21, 2021, the FDA conditionally approved Canalevia-CA1 (crofelemer delayed-release tablets) for the treatment of CID in dogs under application number 141-552. FDA's conditional approval allows the Company to legally sell Canalevia-CA1 before proving it meets the "substantial evidence" standard of effectiveness for full approval. The Company may request renewal of the conditional approval annually for up to four more years, for a total of five years of conditional approval. To receive a renewal from FDA, the Company must show active progress toward proving "substantial evidence of effectiveness" for full approval.

If FDA grants all four annual renewals, the Company has up to four-and-a-half years to develop and submit the necessary data to complete the effectiveness requirement. If the Company does not submit all necessary information to support full approval of Canalevia-CA1 by this four-and-a-half-year deadline, the conditional approval terminates immediately. The Company would then be required to stop marketing the drug because it would be considered to be unapproved.

If the Company submits the necessary information before the four-and-a-half-year deadline, the conditional approval period runs another six months, for a total of five years, while FDA reviews the application for full approval. The conditional approval automatically terminates five years after the date of the initial conditional approval. If FDA does not fully approve the drug before the five-year termination date, the Company would then have to stop marketing the drug because it would be considered to be unapproved.

We may not maintain the benefits associated with MUMS designation, including market exclusivity.

Although we have received MUMS designation for Canalevia-CA1 for the treatment of CID in dogs, we may not maintain the benefits associated with MUMS designation. MUMS designation is a status similar to "orphan drug" status for human drugs. When we were granted MUMS designation for Canalevia-CA1 for the indication of CID in dogs, we became eligible for incentives to support the approval or conditional approval of the designated use. This designation does not allow us to commercialize a product until such time as we obtain approval or conditional approval of the product.

Because Canalevia-CA1 has received MUMS designation for the identified particular intended use, we are eligible to obtain seven years of exclusive marketing rights upon approval (or conditional approval) of Canalevia-CA1 for that intended use and become eligible for grants to defray the cost of our clinical work. Each designation that is granted must be unique, i.e., only one designation can be granted for a particular API in a particular dosage form for a particular intended use. The intended use includes both the target species and the disease or condition to be treated.

At some point, we could lose MUMS designation. The basis for a lost designation can include but is not limited to, our failure to engage with due diligence in moving forward with a non-conditional approval. In addition, MUMS designation may be withdrawn for a variety of reasons such as where the FDA determines that the request for designation was materially defective, or if the manufacturer is unable to assure sufficient quantity of the prescription drug product to meet the needs of animals with the rare disease or condition. If this designation is lost, it could have a negative impact on the product and us, which includes but is not limited to, market exclusivity related to MUMS designation, or eligibility for grants as a result of MUMS designation.

The market for our human and animal products, and the gastrointestinal health market as a whole, is uncertain and may be smaller than we anticipate, which could lead to lower revenue and harm our operating results.

It is very difficult to estimate the commercial potential of any of our human or animal products because the gastrointestinal health market continues to evolve and it is difficult to predict the market potential for our products. The market will depend on important factors such as safety and efficacy compared to other available treatments, changing standards of care, preferences of physicians, as applicable, the willingness of patients, as applicable, to pay for such products, and the availability of competitive alternatives that may emerge either during the product development process or after commercial introduction. If the market potential for our human or animal products is less

than we anticipate due to one or more of these factors, it could negatively impact our business, financial condition and results of operations. Further, the willingness of patients to pay for our products may be less than we anticipate, and may be negatively affected by overall economic conditions.

Insurance coverage for Mytesi for its current approved indication could decrease or end, or Mytesi might not receive insurance coverage for any approved follow-on indications, which could lead to lower revenue and harm our operating results.

For its current approved indication, Mytesi is currently reimbursed by almost all of commercial and Medicare insurance plans. Mytesi is currently covered on Medicaid in all 50 states. However, the nature or extent of coverage for Mytesi by any of these plans or programs could change or be terminated, or Mytesi might not receive insurance coverage for any approved follow-on indications. Either outcome could lead to significantly lower revenue and significantly harm our operating results.

We may engage in future acquisitions that increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.

We may evaluate various strategic transactions, including licensing or acquiring complementary products, technologies or businesses. Any potential acquisitions may entail numerous risks, including increased operating expenses and cash requirements, assimilation of operations and products, retention of key employees, diversion of our management's attention and uncertainties in our ability to maintain key business relationships of the acquired entities. In addition, if we undertake acquisitions, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. Moreover, we may not be able to locate suitable acquisition opportunities and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business.

Certain of the countries in which we plan to commercialize our products in the future are developing countries, some of which have potentially unstable political and economic climates.

We may commercialize our products in jurisdictions that are developing and emerging countries. This may expose us to the impact of political or economic upheaval, and we could be subject to unforeseen administrative or fiscal burdens. At present, we are not insured against the political and economic risks of operating in these countries. Any significant changes to the political or economic climate in any of the developing countries in which we operate or plan to sell products either now or in the future may have a substantial adverse effect on our business, financial condition, trading performance and prospects.

Fluctuations in the exchange rate of foreign currencies could result in currency transactions losses.

As we expand our operations, we expect to be exposed to risks associated with foreign currency exchange rates. We anticipate that we may commercialize Mytesi and Canalevia-CA1 and its line extensions in jurisdictions outside the United States. As a result, we may also be further affected by fluctuations in exchange rates in the future to the extent that sales are denominated in currencies other than U.S. dollars. We do not currently employ any hedging or other strategies to minimize this risk, although we may seek to do so in the future.

Laws and regulations governing global trade compliance could adversely impact our business.

The U.S. Department of the Treasury's Office of Foreign Assets Control ("OFAC"), and the Bureau of Industry and Security ("BIS") at the U.S. Department of Commerce, administer certain laws and regulations that restrict U.S. persons and, in some instances, non-U.S. persons, in conducting activities, transacting business with or making investments in certain countries, governments, entities and individuals subject to U.S. economic sanctions. In addition, engaging in sales activities to foreign governments introduces additional compliance risks, including risks specific to anti-bribery regulations, including the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.K. Bribery Act 2010 and other similar statutory requirements prohibiting bribery and corruption in the jurisdictions in which we operate. The FCPA prohibits U.S. corporations and their representatives from offering,

promising, authorizing or making payments to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business abroad. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Other countries have enacted similar anti-corruption laws and/or regulations.

Our international operations subject us to these laws and regulations, which are complex, restrict our business dealings with certain countries, governments, entities, and individuals, and are constantly changing. Further restrictions may be enacted, amended, enforced or interpreted in a manner that materially impacts our operations.

Violations of these regulations are punishable by civil penalties, including fines, denial of export privileges, injunctions, asset seizures, debarment from government contracts and revocations or restrictions of licenses, as well as criminal fines and imprisonment. We have established policies and procedures designed to assist with our compliance with such laws and regulations. However, there can be no assurance that our policies and procedures will prevent us from violating these regulations in every transaction in which we may engage, or that any businesses that we may acquire have complied with such regulations, and such a violation could adversely affect our reputation, business, financial condition, results of operations and cash flows.

There are other gastrointestinal-focused human pharmaceutical companies, and we face competition in the marketplaces in which we operate or plan to operate.

Our commercial success in the human drug arena remains dependent on maintaining or establishing a competitive position in the market for the current, approved specialty indication of Mytesi as well as for planned Mytesi follow-on indications. In the IBS-D market in particular, several competitors have commercially available products approved for our planned IBS-D indication. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any drug candidate we develop. The inability to compete with existing or subsequently introduced drug candidates would have a material adverse impact on our business, financial condition and prospects.

Our obligations to Streeterville are secured by a security interest in all of Napo's lechlemer assets, so if we default on those obligations, Streeterville could foreclose on our assets.

Our obligations under the secured promissory note issued to Streeterville Capital, LLC ("Streeterville") are secured by a first priority security interest in all existing and future lechlemer technology held by Napo, including intellectual property, as provided in the Security Agreement, dated January 19, 2021 between Napo and Streeterville. As a result, if we default on our obligations under these agreements, Streeterville could foreclose on its security interests and liquidate some or all of these assets, which would harm our plans to develop and commercialize lechlemer, financial condition and results of operations and could require us to reduce or cease operations with respect to lechlemer.

Our royalty interests require us to make minimum royalty payments, even if we do not sell a sufficient amount of products to cover such payments, which may strain our cash resources.

Since March 2020, we have sold royalty interests to certain lenders that entitle such lenders to receive future royalties on sales of our products. These royalty interests require us to make minimum royalty payments beginning 2021, even if we do not sell a sufficient amount of product to cover such payments, which may strain our cash resources. The total minimum royalty payments will be \$6.0 million in 2022, \$18.0 million in 2023, \$13.9 million in 2024, \$7.10 million 2025, and \$3.9 million in 2026.

Failure in our information technology systems, including by cyber-attacks or other data security incidents, could significantly disrupt our operations.

Our operations depend, in part, on the continued performance of our information technology systems. Our information technology systems are potentially vulnerable to physical or electronic break-ins, computer viruses, phishing attacks and other types of disruptions. We have and continue to experience cyber-attacks of varying degrees.

Our security measures may also be breached due to employee error, malfeasance, system errors or other vulnerabilities. Such breach or unauthorized access or attempts by outside parties to fraudulently induce employees or users to disclose sensitive information in order to gain access to our data could result in significant legal and financial exposure, and damage to our reputation that could potentially have an adverse effect on our business. Because the techniques used to obtain unauthorized access, or sabotage systems change frequently, become more sophisticated, and often are not recognized until launched against a target, we may be unable to anticipate these techniques or to implement adequate preventative measures. Additionally, cyber-attacks could also compromise trade secrets and other sensitive information and result in such information being disclosed to others and becoming less valuable, which could negatively affect our business. Although we have information technology security systems, a successful cybersecurity attack or other data security incident could result in the misappropriation and/or loss of confidential or personal information, create system interruptions, deploy malicious software that attacks our systems, or result in financial losses. It is possible that a cybersecurity attack might not be noticed for some period of time. The occurrence of a cyber security attack or incident could result in business interruptions from the disruption of our information technology systems, or negative publicity resulting in reputational damage with our shareholders and other stakeholders and/or increased costs to prevent, respond to or mitigate cybersecurity events. In addition, the unauthorized dissemination of sensitive personal information or proprietary or confidential information could expose us or other third-parties to regulatory fines or penalties, litigation and potential liability, or otherwise harm our business.

The novel coronavirus global pandemic could adversely impact our business, including our supply chain, clinical trials and commercialization of Mytesi and Canalevia.

As a result of the outbreak of SARS-CoV-2, the virus that causes COVID-19, we may experience disruptions that could severely impact our supply chain, ongoing and future clinical trials and commercialization of Mytesi and Canalevia. For example, COVID-19 has resulted in increased travel restrictions and the shutdown or delay of business activities in various regions, including certain activities of our contract manufacturers in India and in Italy. To the extent our suppliers and contract manufacturer are unable to comply with their obligations under our agreements with them or they are otherwise unable to deliver or are delayed in delivering raw materials, Mytesi and Canalevia API or finished products to us due to COVID-19, our ability to continue meeting commercial demand for Mytesi and Canalevia in the United States or advancing development of our product candidates may become impaired. Travel restrictions and shutdowns in business operations as a result of the outbreak may also limit our ability to pursue business development activities, including limiting onsite diligence of manufacturing facilities owned or operated by the Company and our contractors.

Such travel restrictions and shutdowns in business operations may also adversely impact our commercialization of Mytesi and Canalevia, including limiting the ability of our marketing and sales force to engage with healthcare providers and patient groups, and could result in patients postponing visits to healthcare provider facilities, healthcare providers temporarily closing their offices or restricting patient visits, pharmacies being closed or suffering supply chain disruptions, healthcare provider and/or pharmacy employees being unavailable and general disruptions in the operations of payors, distributors, logistics providers and other third parties that are necessary for Mytesi to be prescribed and reimbursed.

COVID-19 continues to rapidly evolve. The extent to which COVID-19, and mutated variants of SARS-CoV-2 – the virus that causes COVID-19, may impact our business, including our supply chain, clinical trials, commercialization of Mytesi and Canalevia and distribution channels, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the pandemic, the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the pandemic.

Long-term remote work arrangements may adversely affect our business.

Many of our employees have been working remotely the past year and will continue to do so this year. An extended period of remote work arrangements could strain our business continuity plans, introduce operational risk, including but not limited to cyber-security risks, impair the effectiveness of our internal controls over financial reporting and impact our ability to manage our business.

Substantially all of our revenue for recent periods has been received from three customers.

Substantially all of our revenue has been derived from three customers. Except for the shelter-in-place mandate, we have not been made aware by our customers if they have experienced other issues arising due to COVID-19 that may materially impact our financial condition, liquidity or results of operations. We will continue to have dialogues with our customers.

We are subject to state laws in California that require gender and diversity quotas for boards of directors of public companies headquartered in California.

In September 2018, California enacted SB 826, requiring public companies headquartered in California to maintain minimum female representation on their boards of directors as follows: by December 31, 2019, public company boards must have a minimum of one female director; by December 31, 2021, public company boards with five members will be required to have at least two female directors, and public company boards with six or more members will be required to have at least three female directors.

Additionally, on September 30, 2020, California enacted AB 979, requiring public companies with principal executive offices in California to each have at least one director from an underrepresented community based on ethnicity and sexual orientation by December 31, 2021. By December 31, 2022, each of these companies will be required to have at least two directors from such underrepresented communities if such company has more than four but fewer than nine directors, or at least three directors from underrepresented communities if the company has nine or more directors.

Our board of directors currently includes one female director. As a result, we are currently not in compliance with either law. An initial violation of either law can result in a fine from the California Secretary of State in the amount of \$100,000, with each subsequent violation resulting in a fine of \$300,000. We cannot assure that we can recruit, attract and/or retain qualified members of the board and continue to meet gender and diversity quotas as required by California law, which may cause certain investors to divert their holdings in our securities and expose us to financial penalties and/or reputational harm.

Risks Related to Intellectual Property

We cannot be certain that our patent strategy will be effective to protect against competition.

Our commercial success depends in large part on obtaining and maintaining patent, trademark and trade secret protection of our human or animal products, both prescription and non-prescription, our current human or animal product candidates and any future human or animal product candidates, and their respective components, formulations, methods used to manufacture them and methods of treatment, as well as successfully defending our patents and other intellectual property rights against third-party challenges. Our ability to stop unauthorized third parties from making, using, selling, offering to sell or importing our products or our product candidates is dependent upon the extent to which we have rights under valid and enforceable patents, trade secrets and other similar intellectual property that cover these activities. The patent prosecution process is expensive and time-consuming, and we may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of inventions made in the course of development and commercialization activities in time to obtain patent protection on them.

We have a portfolio of United States and foreign issued patents and pending applications related to our products and product candidates. We have three issued United States patents listed in the FDA's Orange Book for Mytesi. We plan to rely on certain of these issued patents as protection for Canalevia. The strength of patents in the field of pharmaceuticals and animal health involves complex legal and scientific questions and can be uncertain. We cannot be certain that pending applications will issue as patents. For those patents that are already issued and even if other patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed, invalidated or held unenforceable. Furthermore, even if they are unchallenged, our patents may not adequately protect our intellectual property or prevent others from designing around their claims. If the patents we have are not maintained or their scope is significantly narrowed or if we are not able to obtain issued patents from pending applications, our business and prospects would be harmed.

The Leahy-Smith America Invents Act, patent reform legislation enacted in 2011, could increase the uncertainties and costs surrounding the prosecution of any patent applications and the enforcement or defense of any patents that issue. The Leahy-Smith Act introduced significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art, may affect patent litigation, and switch the U.S. patent system from a "first-to-invent" system to a "first-to-file" system. Under a "first-to-file" system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally is entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO developed regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first-to-file provisions, became effective on March 16, 2013. Among some of the other changes to the patent laws are changes that limit where a patentee may file a patent infringement suit and that provide opportunities for third parties to challenge any issued patent in the USPTO. The Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our patents and any other patents that issue, all of which could harm our business and financial condition.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance and annuity fees on any issued patent and, in certain jurisdictions, pending applications, are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our prescription drug products, prescription drug product candidates and non-prescription products, our competitors might be able to enter the market, which would harm our business.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, which would be costly, time-consuming and, if successfully asserted against us, delay or prevent the development and commercialization of our current or future products and product candidates.

Our research, development and commercialization activities may infringe or otherwise violate or be claimed to infringe or otherwise violate patents owned or controlled by other parties. There may be patents already issued of which we are unaware that might be infringed by a product or one of our current or future prescription drug product candidates or non-prescription products. Moreover, it is also possible that patents may exist that we are aware of, but that we do not believe are relevant to our current or future prescription drug product candidates or non-prescription products, which could nevertheless be found to block our freedom to market these products. Because patent applications can take many years to issue and may be confidential for 18 months or more after filing, there may be

applications now pending of which we are unaware and which may later result in issued patents that may be infringed by our current or future prescription drug product candidates or non-prescription products. We cannot be certain that our products, current or future prescription drug product candidates or non-prescription products will not infringe these or other existing or future third-party patents. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents.

To the extent we become subject to future third-party claims against us or our collaborators, we could incur substantial expenses and, if any such claims are successful, we could be liable to pay substantial damages, including treble damages and attorney's fees if we or our collaborators are found to be willfully infringing a third party's patents. If a patent infringement suit were brought against us or our collaborators, we or they could be forced to stop or delay research, development, manufacturing or sales of the human or animal prescription drug or non-prescription product that is the subject of the suit. Even if we are successful in defending such claims, infringement and other intellectual property claims can be expensive and time-consuming to litigate and divert management's attention from our business and operations. As a result of or in order to avoid potential patent infringement claims, we or our collaborators may be compelled to seek a license from a third party for which we would be required to pay license fees or royalties, or both. Moreover, these licenses may not be available on acceptable terms, or at all. Even if we or our collaborators were able to obtain such a license, the rights may be nonexclusive, which could allow our competitors access to the same intellectual property. Any of these events could harm our business and prospects.

Our proprietary position depends upon the botanical guidance of our drug approval and patents that are formulation or method-of-use patents, which do not prevent a competitor from using the same human or animal drug for another use.

Composition-of-matter patents on the API in prescription drug products are generally considered to be the strongest form of intellectual property protection because such patents provide protection without regard to any particular method of use or manufacture or formulation of the API used. The composition-of-matter patents for crofelemer, the API in Mytesi and Canalevia-CA1, have expired, and the issued patents and applications relevant to our products and product candidates cover methods of use for crofelemer and the botanical extract in Neonorm and Equilevia.

Method-of-use patents protect the use of a product for the specified method and formulation patents cover formulations of the API or botanical extract. These types of patents do not prevent a competitor from developing or marketing an identical product for an indication that is outside the scope of the patented method or from developing a different formulation that is outside the scope of the patented formulation. Moreover, with respect to method-of-use patents, even if competitors do not actively promote their product for our targeted indications or uses for which we may obtain patents, physicians may recommend that patients use our products extra-label, and veterinarians may recommend that animal owners use these products extra-label, or animal owners may do so themselves. Although extra-label use may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute.

We may be involved in lawsuits to protect or enforce our patents, which could be expensive, time-consuming and unsuccessful, and third parties may challenge the validity or enforceability of our patents and they may be successful.

We intend to rely upon a combination of regulatory exclusivity periods, patents, trade secret protection, and confidentiality agreements to protect the intellectual property related to Mytesi, our current prescription drug product candidates, non-prescription products and our development programs.

If the breadth or strength of protection provided by any patents, patent applications or future patents we may own, license, or pursue with respect to any of our current or future product candidates or products is threatened, it could threaten our ability to commercialize any of our current or future human or animal product candidates or products. Further, if we encounter delays in our development efforts, the period of time during which we could market any of our current or future product candidates or products under any patent protection we obtain would be reduced.

Given the amount of time required for the development, testing and regulatory review of new product candidates or products, patents protecting such candidates might expire before or shortly after such product candidates or products are commercialized. The United States Patent and Trademark Office has issued a patent term extension certificate extending the term of US 7,341,744 by 1075 days under 35 USC 156. With respect to requests for patent term extensions, the applicable authorities, including the USPTO and the FDA, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to patents, or may grant more limited extensions than requested. If this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

Even where laws provide protection or we are able to obtain patents, costly and time-consuming litigation may be necessary to enforce and determine the scope of our proprietary rights, and the outcome of such litigation would be uncertain. Moreover, any actions we may bring to enforce our intellectual property against our competitors could provoke them to bring counterclaims against us, and some of our competitors have substantially greater intellectual property portfolios than we have. To counter infringement or unauthorized use of any patents we may obtain, we may be required to file infringement claims, which can be expensive and time-consuming to litigate. In addition, if we or one of our future collaborators were to initiate legal proceedings against a third party to enforce a patent covering one of our products, current product candidates, or one of our future products, the defendant could counterclaim that the patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace and challenges to validity of patents in certain foreign jurisdictions is common as well. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or lack of statutory subject matter. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant material information from the USPTO, or made a materially misleading statement, during prosecution. Under the Hatch-Waxman Act, a competitor seeking to market a generic form of Mytesi before the expiration of any of the patents listed in the FDA's Orange Book for Mytesi could file an ANDA with a certification under 21 U.S.C. § 3559(j)(2)(A)(iv) that each of these patents (except for those which the ANDA filer states it will market only after its expiration) is either invalid, unenforceable or not infringed. We may assert the patents in Hatch-Waxman litigation against the party filing the ANDA to keep the competing product off of the market until the patents expire but there is a risk that we will not succeed. The party filing the ANDA may also counterclaim in the litigation that our patents are not valid or unenforceable, and the court may find one or more claims of our patents invalid or unenforceable. If this occurs, a competing generic product could be marketed prior to expiration of our patents listed in the Orange Book, which would harm our business.

Third parties may also raise similar validity claims before the USPTO in post-grant proceedings such as *ex parte* reexaminations, *inter partes* review, or post-grant review, or oppositions or similar proceedings outside the United States, in parallel with litigation or even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of any future patent protection on one or more of our products or our current or future product candidates. Such a loss of patent protection could harm our business. We cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution or other basis for a finding of invalidity. Litigation proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be unsuccessful, it could have an adverse effect on the price of our common stock. Finally, we may not be able to prevent, misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the United States.

If we are unable to prevent disclosure of our trade secrets or other confidential information to third parties, our competitive position may be impaired.

We also rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or for which we have not filed patent applications, processes for which patents are difficult to enforce and other elements of our product development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we require all of our employees to assign their inventions to us, and endeavor to execute confidentiality agreements with all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology, we cannot be certain that we have executed such agreements with all parties who may have helped to develop our intellectual property or had access to our proprietary information, or that our agreements will not be breached. We cannot guarantee that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. If we are unable to prevent disclosure of our intellectual property to third parties, we may not be able to maintain a competitive advantage in our market, which would harm our business.

Any disclosure to or misappropriation by third parties of our confidential proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, and erode our competitive position in our market.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other human or animal pharmaceutical product companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the human and animal health industries involves both technological and legal complexity. Therefore, obtaining and enforcing patents is costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and implemented wide-ranging patent reform legislation. The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce patents that we have or that we might obtain in the future.

We may not be able to protect our intellectual property rights throughout the world, which could impair our business.

Filing, prosecuting and defending patents on human and animal drug products, product candidates and non-prescription products throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we may obtain patent protection, but where patent enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued or licensed patents and any future patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to animal health products, which could make it difficult for us to stop the infringement of our future patents, if any, or patents we have in licensed, or marketing of competing products in violation of our proprietary rights generally. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. Proceedings to enforce our future patent rights, if any, in foreign

jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

Our business could be harmed if we fail to obtain certain registered trademarks in the United States or in other countries.

Our registered and pending U.S. trademarks include MYTESI®, JAGUAR HEALTH®, the Jaguar Health Logo®, NAPO®, Napo Logo®, Napo Therapeutics, CANALEVIA, CANALEVIA-CA1, CANALEVIA-CA2, EQUILEVIA, NEONORM®, JAGUAR ANIMAL HEALTH®, and the Jaguar Animal Health Logo®. We also own registered and pending applications for the CANALEVIA mark in a number of foreign countries. During trademark registration proceedings, we may receive rejections of our trademark applications. If so, we will have an opportunity to respond, but we may be unable to overcome such rejections. In addition, the USPTO and comparable agencies in many foreign jurisdictions may permit third parties to oppose pending trademark applications and to seek to cancel registered trademarks. If opposition or cancellation proceedings are filed against any of our trademark applications or any registered trademarks, our trademarks may not survive such proceedings. Moreover, any name we propose to use with our prescription drug product candidates in the United States, including CANALEVIA and CANALEVIA-CA1, must be approved by the FDA, regardless of whether we have registered or applied to register as a trademark. The FDA typically conducts a review of proposed prescription drug product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from third parties. In addition, we employ individuals who were previously employed at other biotechnology, pharmaceutical or animal health companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise improperly used or disclosed confidential information of these third parties or our employees' former employers. Litigation may be necessary to defend against any such claims. Even if we were successful in defending against any such claims, such litigation could result in substantial cost and be a distraction to our management and employees.

Even if we receive any of the required regulatory approvals for our current or future prescription drug product candidates and non-prescription products, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense and delays.

If the FDA or any other regulatory body approves any of our current or future prescription drug product candidates, or if necessary, our non-prescription products, the manufacturing processes, clinical development, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product may be subject to extensive and ongoing regulatory requirements. These requirements could include, but are not limited to, submissions of efficacy and safety and other post-marketing information and reports, establishment registration, and product listing, compliance with new rules promulgated under the FSMA, as well as continued compliance with cGMPs, GLPs and GCPs for any studies that we conduct post-approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our contract manufacturers or manufacturing processes, or failure to comply with regulatory requirements, are reportable events to the FDA and may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, revised labeling, or voluntary or involuntary product recalls;
- additional clinical studies, fines, warning letters or holds on target animal studies;
- refusal by the FDA, or other regulators to approve pending applications or supplements to approved applications filed by us or our strategic collaborators related to the unknown problems, or suspension or

revocation of the problematic product's license approvals;

- product seizure or detention, or refusal to permit the import or export of products; and
- injunctions and/or the imposition of civil or criminal penalties.

The FDA or other regulatory agency's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates or require certain changes to the labeling or additional clinical work concerning safety and efficacy of the product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would harm our business. In addition, failure to comply with these regulatory requirements could result in significant penalties and delays.

In addition, from time to time, we may enter into consulting and other financial arrangements with physicians or veterinarians, who prescribe or recommend our products, once approved. As a result, we may be subject to state, federal and foreign healthcare and/or veterinary medicine laws. If our financial relationships with veterinarians are found to be in violation of such laws that apply to us, we may be subject to penalties.

Further, our commercial supply is regulated by the FDA, which requires regular filings, annual reports, and may include modifications by the Company to our approvals. Failure to gain agreement from the FDA on a timely basis could adversely affect our commercial supply of product.

Lastly, if we obtain conditional approval for our current or future drug product candidates, this conditional approval is renewable annually for five years and may be withdrawn or terminated under certain circumstances either during or at the end of the five-year period. For example, even though we have obtained conditional approval for Canalevia-CA1, if we do not undertake substantial efforts to do additional clinical research each year for the next five years, the FDA could terminate such conditional approval by refusing to renew the conditional approval.

Any of our current or future prescription drug product candidates or non-prescription products may cause or contribute to adverse medical events that we would be required to report to regulatory authorities and, if we fail to do so, we could be subject to sanctions that would harm our business.

If we are successful in commercializing any of our current or future prescription drug product candidates or non-prescription products, certain regulatory authorities will require that we report certain information about adverse medical events if those products may have caused or contributed to those adverse events. The timing of our obligation to report would be triggered by the date we become aware of the adverse event as well as the nature of the event. We may fail to report adverse events we become aware of within the prescribed timeframe. We may also fail to appreciate that we have become aware of a reportable adverse event, especially if such event is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our products. If we fail to comply with our reporting obligations, the regulatory authorities could take action including, but not limited to, criminal prosecution, seizure of our products, facility inspections, removal of our products from the market, recalls of certain lots or batches, or cause a delay in approval or clearance of future products.

Legislative or regulatory reforms with respect to animal health may make it more difficult and costly for us to obtain regulatory clearance or approval of any of our current or future product candidates and to produce, market, and distribute our products after clearance or approval is obtained.

From time to time, legislation is drafted and introduced in the U.S. Congress or other jurisdictions in which we intend to operate that could significantly change the statutory provisions governing the testing, regulatory clearance or approval, manufacture, and marketing of regulated products. In addition, the FDA's regulations and guidance are often revised or reinterpreted by the FDA and such other regulators in ways that may significantly affect our business and our products and product candidates. Similar changes in laws or regulations can occur in other countries. Any new regulations or revisions or reinterpretations of existing regulations in the United States or in other countries may impose additional costs or lengthen review times of any of our current or future products and product candidates. We cannot determine what effect changes in regulations, statutes, legal interpretation or policies, when and if promulgated, enacted or adopted may have on our business in the future. Such changes could, among other things, require:

- changes to manufacturing methods;
- additional clinical trials or testing;
- new requirements related to approval to enter the market;
- recall, replacement, or discontinuance of certain products; and
- additional record keeping or the development of certain regulatory required hazard identification plans.

Each of these would likely entail substantial time and cost and could harm our financial results. In addition, delays in receipt of or failure to receive regulatory clearances or approvals for any future products would harm our business, financial condition, and results of operations.

We believe that our non-prescription products are not subject to regulation by regulatory agencies in the United States, but there is a risk that regulatory bodies may disagree with our interpretation, or may redefine the scope of their regulatory reach in the future, which would result in additional expense and could delay or prevent the commercialization of these products.

The FDA retains jurisdiction over all animal prescription drug products however, in many instances, the Federal Trade Commission will exercise primary or concurrent jurisdiction with FDA on non-prescription products as to post marketing claims made regarding the product. On April 22, 1996, the FDA published a statement in the Federal Register, 61 FR 17706, that it believes that the Dietary Supplement and Health Education Act ("DSHEA"), does not apply to animal health supplement products, such as our non-prescription products. Accordingly, the FDA's Center for Veterinary Medicine only regulates those animal supplements that fall within the FDA's definition of an animal drug, animal food or animal feed additive. The Federal Food Drug and Cosmetic Act defines food as "articles used for food or drink for man or other animals and articles used as components of any such article." Animal foods are not subject to pre-market approval and are designed to provide a nutritive purpose to the animals that receive them. Feed additives are defined as those articles that are added to an animal's feed or water as illustrated by the guidance documents. Our non-prescription products are not added to food, are not ingredients in food nor are they added to any animal's drinking water. Therefore, our non-prescription products do not fall within the definition of a food or feed additive. In light of the pronouncement by the FDA that the DSHEA was not intended to apply to animals, the FDA seeks to regulate such supplements as food or food additives depending on the intended use of the product. The intended use is demonstrated by how the article is included in a food, or added to the animals' intake (i.e., through its drinking water). If the intended use of the product does not fall within the proscribed use making the product a food, it cannot be regulated as a food. There is no intent to make our non-prescription products a component of an animal food, either directly or indirectly. A feed additive is a product that is added to a feed for any reason including the top dressing of an already prepared feed. Some additives, such as certain forage, are deemed to be Generally Recognized as Safe, or GRAS, and therefore, not subject to a feed Additive Petition approval prior to use. However, the

substances deemed GRAS are generally those that are recognized as providing nutrients as a food does. We do not believe that our non-prescription products fit within this framework either. Finally, a new animal drug refers to drugs intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in animals. Our non-prescription Neonorm Foal and Neonorm Calf products are not intended to diagnose, cure, mitigate, treat or prevent disease and therefore, do not fit within the definition of an animal drug. Additionally, because a previously marketed human formulation of the botanical extract in our non-prescription products was regulated as a human dietary supplement subject to the DSHEA (and not regulated as a drug by the FDA), we do not believe that the FDA would regulate the animal formulation used in our non-prescription products in a different manner. We do not believe that our non-prescription products fit the definition of an animal drug, food or food additive and therefore are not regulated by the FDA at this time.

However, despite many such unregulated animal supplements currently on the market, the FDA may choose in the future to exercise jurisdiction over animal supplement products in which case, we may be subject to unknown regulations thereby inhibiting our ability to launch or to continue marketing our non-prescription products. In the past, the FDA has redefined or attempted to redefine some non-prescription non-feed products as falling within the definition of drug, feed or feed additive and therefore subjected those products to the relevant regulations. We have not discussed with the FDA its belief that the FDA currently does not exercise jurisdiction over our non-prescription products. Should the FDA assert regulatory authority over our non-prescription products, we would take commercially reasonable steps to address the FDA's concerns, potentially including but not limited to, seeking registration for such products, reformulating such products to further distance such products from regulatory control, or ceasing sale of such products. Further, the Animal and Plant Health Inspection Service, an agency of the USDA, may at some point choose to exercise jurisdiction over certain non-prescription products that are not intended for production animals. We do not believe we are currently subject to such regulation, but could be in the future. If the FDA or other regulatory agencies, such as the USDA, try to regulate our non-prescription products, we could be required to seek regulatory approval for our non-prescription products, which would result in additional expense and could delay or prevent the commercialization of these products.

Even if we receive the required regulatory approvals for our current or future prescription drug product candidates and non-prescription products, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense.

If the FDA or any other regulatory body approves any of our current or future prescription drug product candidates, or if necessary, our non-prescription products, the manufacturing processes, clinical development, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product is subject to extensive and ongoing regulatory requirements. These requirements could include, but are not limited to, submissions of efficacy and safety and other post-marketing information and reports, establishment registration, and product listing, compliance with new rules promulgated under the FSMA, as well as continued compliance with cGMPs, GLPs and GCPs for any studies that Napo conducts post-approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our contract manufacturers or manufacturing processes, or failure to comply with regulatory requirements, are reportable events to the FDA and may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, revised labeling, or voluntary or involuntary product recalls;
- additional clinical studies fines, warning letters or holds on studies;
- refusal by the FDA, or other regulators to approve pending applications or supplements to approved applications filed by Napo or Napo's strategic collaborators related to the unknown problems, or suspension or revocation of the problematic product's license approvals;
- product seizure or detention, or refusal to permit the import or export of products; and
- injunctions or the imposition of civil or criminal penalties.

The FDA or other regulatory agency's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates or require certain changes to the labeling or require additional clinical work concerning safety and efficacy of the product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would harm our business. In addition, failure to comply with these regulatory requirements could result in significant penalties.

In addition, from time to time, we may enter into consulting and other financial arrangements with physicians, who prescribe or recommend our products, once approved. As a result, we may be subject to state, federal and foreign healthcare laws, including but not limited to anti-kickback laws. If our financial relationships with physicians or veterinarians are found to be in violation of such laws that apply to us, we may be subject to penalties.

Risks Related to Our Common Stock

Our failure to meet the continued listing requirements of The Nasdaq Capital Market could result in a delisting of our common stock.

If we fail to satisfy the continued listing requirements of The Nasdaq Capital Market, such as the minimum closing bid price requirement, Nasdaq may take steps to delist our common stock. The closing bid price for our common stock must remain at or above \$1.00 per share to comply with Nasdaq's minimum bid requirement for continued listing. If the closing bid price for our common stock is less than \$1.00 per share for 30 consecutive business days, Nasdaq may send us a notice stating that we will be provided a period of 180 days to regain compliance with the minimum bid requirement or else Nasdaq may make a determination to delist our common stock. Our common stock traded for less than \$1.00 for 30 consecutive trading days, and we received notice of this from the Listing Qualifications Staff of The Nasdaq Stock Market LLC on February 17, 2022. Under Nasdaq Listing Rule 5810(c)(3)(A), the Company has been granted a 180 calendar day grace period, or until August 16, 2022, to regain compliance with the minimum bid price requirement. The minimum bid price requirement will be met if our common stock has a minimum closing bid price of at least \$1.00 per share for a minimum of 10 consecutive business days during the 180 calendar day grace period. We are diligently working to evidence compliance with the minimum bid requirement for continued listing on Nasdaq; however, there can be no assurance that we will be able to regain compliance or that Nasdaq will grant us a further extension of time to regain compliance, if necessary.

The Company may be eligible for additional time to comply if it does not achieve compliance with the minimum bid price requirement by August 16, 2022. In order to be eligible for consideration for such additional time, the Company will be required to meet the continued listing requirement for market value of publicly held shares and all other initial listing standards for The Nasdaq Capital Market, with the exception of the minimum bid price requirement, and must notify Nasdaq in writing of its intention to cure the deficiency during the second compliance period.

The delisting of our common stock from Nasdaq may make it more difficult for us to raise capital on favorable terms in the future. Such a delisting would likely have a negative effect on the price of our common stock and would impair your ability to sell or purchase our common stock when you wish to do so. Further, if we were to be delisted from The Nasdaq Capital Market, our common stock would cease to be recognized as covered securities and we would be subject to regulation in each state in which we offer our securities. Moreover, there is no assurance that any actions that we take to restore our compliance with the Nasdaq minimum bid requirement would stabilize the market price or improve the liquidity of our common stock, prevent our common stock from falling below the Nasdaq minimum bid price required for continued listing again or prevent future non-compliance with Nasdaq's listing requirements.

If we issue all shares available for issuance pursuant to the ATM Agreement, we will have no shares of common stock available for new securities issuances, which may restrict us from accessing additional capital through the sale of new securities.

Our Third Amended and Restated Certificate of Incorporation, as amended, authorizes us to issue up to 150,000,000 shares of voting common stock, 77,053,990 of which are issued and outstanding and 6,634,077 of which are reserved for issuance upon exercise of options, warrants, vesting of RSUs, and shares to consultants as of March 10, 2022. Accordingly, assuming the sale by us under our ATM Agreement at a price of \$0.72 per share, which was the closing price of our Common Stock on The Nasdaq Capital Market on January 28, 2022, the maximum amount of shares that we could issue in this offering pursuant to the ATM Agreement without exceeding our total authorized but unissued shares is approximately \$68.1 million. If we were to issue the maximum amount of shares in this offering pursuant to the ATM Agreement, we will have no shares of voting common stock available for additional issuances. Our failure to increase our authorized shares may restrict our ability to access additional capital through the sale of new securities, which may harm our financial position and business prospects.

If our shares become subject to the penny stock rules, it would become more difficult to trade our shares.

The SEC has adopted rules that regulate broker-dealer practices in connection with transactions in penny stocks. Penny stocks are generally equity securities with a price of less than \$5.00, other than securities registered on certain national securities exchanges or authorized for quotation on certain automated quotation systems, provided that current price and volume information with respect to transactions in such securities is provided by the exchange or system. If we do not retain a listing on The Nasdaq Capital Market and if the price of our common stock is less than \$5.00, our common stock will be deemed a penny stock. The penny stock rules require a broker-dealer, before a transaction in a penny stock not otherwise exempt from those rules, to deliver a standardized risk disclosure document containing specified information. In addition, the penny stock rules require that before effecting any transaction in a penny stock not otherwise exempt from those rules, a broker-dealer must make a special written determination that the penny stock is a suitable investment for the purchaser and receive (i) the purchaser's written acknowledgment of the receipt of a risk disclosure statement; (ii) a written agreement to transactions involving penny stocks and (iii) a signed and dated copy of a written suitability statement. These disclosure requirements may have the effect of reducing the trading activity in the secondary market for our common stock, and therefore stockholders may have difficulty selling their shares.

The price of our common stock could be subject to volatility related or unrelated to our operations, and purchasers of our common stock could incur substantial losses.

We have experienced and may continue to experience significant volatility in the price of our common stock. From January 29, 2021 through January 28, 2022, the share price of our common stock ranged from a high of \$10.74 to a low of \$0.70. The reason for the volatility in our stock is not well understood and may continue. Factors that may have contributed to such volatility include, but are not limited to, those discussed previously in this "Risk Factors" section of this report and others, such as:

- delays in the commercialization of Mytesi, Neonorm, Canalevia-CA1, Equilevia or our other current or future prescription drug product candidates and non-prescription products;
- any delays in, or suspension or failure of, our current and future studies;
- announcements of regulatory approval or disapproval of any of our current or future product candidates or of regulatory actions affecting our company or our industry;
- manufacturing and supply issues that affect product candidate or product supply for our studies or commercialization efforts;
- quarterly variations in our results of operations or those of our competitors;

- changes in our earnings estimates or recommendations by securities analysts;
- the payment of licensing fees or royalties in shares of our common stock;
- announcements by us or our competitors of new prescription drug products or product candidates or non-prescription products, significant contracts, commercial relationships, acquisitions or capital commitments;
- announcements relating to future development or license agreements including termination of such agreements;
- adverse developments with respect to our intellectual property rights or those of our principal collaborators;
- commencement of litigation involving us or our competitors;
- any major changes in our board of directors or management;
- new legislation in the United States relating to the prescription, sale, distribution or pricing of gastrointestinal health products;
- product liability claims, other litigation or public concern about the safety of our prescription drug product or product candidates and non-prescription products or any such future products;
- market conditions in the human or animal industry, in general, or in the gastrointestinal health sector, in particular, including performance of our competitors;
- future issuances of shares of common stock or other securities;
- uncertainties related to COVID-19;
- general economic conditions in the United States and abroad; and
- market speculation regarding

In addition, the stock market, in general, or the market for stocks in our industry, in particular, may experience broad market fluctuations, which may adversely affect the market price or liquidity of our common stock. Any sudden decline in the market price of our common stock could trigger securities class-action lawsuits against us. If any of our stockholders were to bring such a lawsuit against us, we could incur substantial costs defending the lawsuit and the time and attention of our management would be diverted from our business and operations. We also could be subject to damages claims if we were found to be at fault in connection with a decline in our stock price.

A possible “short squeeze” due to a sudden increase in demand of our common stock that largely exceeds supply may lead to further price volatility in our common stock.

Investors may purchase shares of our common stock to hedge existing exposure in our common stock or to speculate on the price of our common stock. Speculation on the price of our common stock may involve long and short exposures. To the extent aggregate short exposure exceeds the number of shares of our common stock available for purchase in the open market, investors with short exposure may have to pay a premium to repurchase our common stock for delivery to lenders of our common stock. Those repurchases may in turn, dramatically increase the price of our common stock until investors with short exposure are able to purchase additional shares of common stock to cover their short position. This is often referred to as a “short squeeze.” A short squeeze could lead to volatile price movements in shares of our common stock that are not directly correlated to the performance or prospects of our

company and once investors purchase the shares necessary to cover their short position the price of our common stock may decline.

You may not be able to resell our common stock when you wish to sell them or at a price that you consider attractive or satisfactory.

The listing of our common stock on The Nasdaq Capital Market does not assure that a meaningful, consistent and liquid trading market exists. Although our common stock is listed on The Nasdaq Capital Market, trading volume in our common stock has been limited and an active trading market for our shares may never develop or be sustained. If an active market for our common stock does not develop, you may be unable to sell your shares when you wish to sell them or at a price that you consider attractive or satisfactory. The lack of an active market may also adversely affect our ability to raise capital by selling securities in the future, or impair our ability to license or acquire other product candidates, businesses or technologies using our shares as consideration.

If securities or industry analysts do not publish research or reports about our company, or if they issue adverse or misleading opinions regarding us or our stock, our stock price and trading volume could decline.

The trading market for our common stock depends in part on the research and reports that industry or financial analysts publish about us or our business. We do not influence or control the reporting of these analysts. If one or more of the analysts who do cover us downgrade or provide a negative outlook on our company or our industry, or the stock of any of our competitors, the price of our common stock could decline. If one or more of these analysts ceases coverage of our company, we could lose visibility in the market, which in turn could cause the price of our common stock to decline.

You may be diluted by conversions of outstanding shares of non-voting common stock, exercises of outstanding options and warrants and issuances of securities pursuant to our ATM Agreement.

As of March 10, 2022, we had (i) outstanding options to purchase an aggregate of 2,327,368 shares of our common stock at a weighted average exercise price of \$9.83 per share, (ii) outstanding options to purchase an aggregate of 127,949 shares of our common stock issuable upon exercise of outstanding inducement options, with a weighted-average exercise price of \$4.42 per share, (iii) 563,108 shares of our common stock issuable upon exercise of warrants outstanding, with weighted-average exercise price of \$7.17, (iv) 465,194 shares of our common stock issuable upon vesting of outstanding RSUs, (v) 38,333 shares of our common stock issuable to third parties upon exercise of those shares, and (vi) 673 shares of our non-voting common stock issuable at an equivalent share of voting common stock. The exercise of such options, warrants, vesting of RSUs, and conversion of the non-voting common stock will result in further dilution of your investment.

In addition, you may experience further dilution if we issue common stock in the future, including common stock issued pursuant to our existing At The Market Offering Agreement (the "ATM Agreement"). Pursuant to the ATM Agreement with Ladenburg Thalmann & Co. Inc. ("Ladenburg"), we may offer and sell up to \$75.0 million of our common stock from time to time through Ladenburg as our sales agent. During the year ended December 31, 2021, we sold 2,261,596 shares of common stock pursuant to the ATM Agreement for gross proceeds of \$3.5 million.

As a result of this dilution, you may receive significantly less in net tangible book value than the full purchase price you paid for the shares in the event of liquidation.

Provisions in our charter documents and under Delaware law could discourage a takeover that stockholders may consider favorable and may lead to entrenchment of management.

Our third amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could delay or prevent changes in control or changes in our management without the consent of our board of directors. These provisions include the following:

- a classified board of directors with three-year staggered terms, which may delay the ability of stockholders to change the membership of a majority of our board of directors;
- no cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates;
- the exclusive right of our board of directors to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors;
- the ability of our board of directors to authorize the issuance of shares of preferred stock and to determine the terms of those shares, including preferences and voting rights, without stockholder approval, which could adversely affect the rights of our common stockholders or be used to deter a possible acquisition of our company;
- the ability of our board of directors to alter our bylaws without obtaining stockholder approval;
- the required approval of the holders of at least 75% of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws or repeal the provisions of our third amended and restated certificate of incorporation regarding the election and removal of directors;
- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;
- the requirement that a special meeting of stockholders may be called only by the chairman of the board of directors, the chief executive officer, the president or the board of directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and
- advance notice procedures that stockholders must comply with in order to nominate candidates to our board of directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of us.

These provisions could inhibit or prevent possible transactions that some stockholders may consider attractive.

We are also subject to the anti-takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation generally may not engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the board of directors has approved the transaction.

Our amended and restated bylaws designate the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or other employees.

Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employees to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, (iv) any action asserting a claim that is governed by the internal affairs doctrine or (v) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws. Any person purchasing or otherwise acquiring any interest in any shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our amended and restated bylaws. This choice-of-forum provision may limit our stockholders' ability to bring a claim in a judicial forum that they find favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits. Alternatively, if a court were to find this provision of our amended and restated bylaws inapplicable or unenforceable with respect to one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could harm our business and financial condition.

We do not intend to pay dividends on our common stock, and your ability to achieve a return on your investment will depend on appreciation in the market price of our common stock.

We currently intend to invest our future earnings, if any, to fund our growth and not to pay any cash dividends on our common stock. Because we do not intend to pay dividends, your ability to receive a return on your investment will depend on any future appreciation in the market price of our common stock. We cannot be certain that our common stock will appreciate in price.

The requirements of being a public company, including compliance with the reporting requirements of the Exchange Act and the requirements of the Sarbanes-Oxley Act, may strain our resources, increase our costs and distract management, and we may be unable to comply with these requirements in a timely or cost-effective manner.

Our initial public offering had a significant, transformative effect on us. Prior to our initial public offering, our business operated as a privately-held company, and we were not required to comply with public reporting, corporate governance and financial accounting practices and policies required of a publicly-traded company. As a publicly-traded company, we incur significant additional legal, accounting and other expenses compared to historical levels. In addition, new and changing laws, regulations and standards relating to corporate governance and public disclosure, including the Dodd-Frank Wall Street Reform and Consumer Protection Act and the rules and regulations thereunder, as well as under the Sarbanes-Oxley Act, the JOBS Act and the rules and regulations of the SEC and The Nasdaq Capital Market, may result in an increase in our costs and the time that our board of directors and management must devote to our compliance with these rules and regulations. These rules and regulations have substantially increased our legal and financial compliance costs and diverted management time and attention from our product development and other business activities.

The Sarbanes-Oxley Act requires, among other things, that we assess the effectiveness of our internal control over financial reporting annually and the effectiveness of our disclosure controls and procedures quarterly. In particular, Section 404 of the Sarbanes-Oxley Act, or Section 404, requires us to perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on, and our independent registered public accounting firm potentially to attest to, the effectiveness of our internal control over financial reporting. We have needed to expend time and resources on documenting our internal control over financial reporting so that we are in a position to perform such evaluation when required. As a smaller reporting company ("SRC"), we expect to avail ourselves of the exemption from the requirement that our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting under Section 404. However, we may no longer avail ourselves of this exemption when we cease to be an SRC. When our independent registered

public accounting firm is required to undertake an assessment of our internal control over financial reporting, the cost of our compliance with Section 404 will correspondingly increase. Our compliance with applicable provisions of Section 404 requires that we incur substantial accounting expense and expend significant management time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements. Moreover, if we are not able to comply with the requirements of Section 404 applicable to us in a timely manner, or if we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources.

We are a smaller reporting company and the reduced reporting requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are a smaller reporting company (“SRC”) and a non-accelerated filer, which allows us to take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not SRCs or non-accelerated filers, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, reduced disclosure obligations regarding executive compensation in our Annual Report and our periodic reports and proxy statements and providing only two years of audited financial statements in our Annual Report and our periodic reports. We will remain an SRC so long as (a) the aggregate market value of our outstanding common stock held by non-affiliates as of the last business day our most recently completed second fiscal quarter is less than \$250 million or (b) (1) we have less than \$100 million in annual revenues and (2) the aggregate market value of our outstanding common stock held by non-affiliates as of the last business day our most recently completed second fiscal quarter is less than \$700 million. We cannot predict whether investors will find our common stock less attractive if we rely on certain or all of these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile and may decline.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our corporate headquarters are located at 200 Pine Street, Suite 400, San Francisco, California.

ITEM 3. LEGAL PROCEEDINGS

May 2020 Letter from the Committee on Oversight and Reform of the U.S. House of Representatives

On May 4, 2020, Jaguar Health, Inc. received a letter from the Committee on Oversight and Reform of the U.S. House of Representatives (the “Committee”) regarding the list price adjustment of Mytesi. Among other things, the Committee expressed an interest in understanding whether the price adjustment was connected to the Company’s expectation that it could market crofelemer to treat coronavirus patients given the Company’s submission of a request to the U.S. Food and Drug Administration for Emergency Use Authorization (“EUA”) for crofelemer for the symptomatic relief of diarrhea and other gastrointestinal symptoms in patients with COVID-19 and for patients with COVID-19 who have diarrhea associated with certain antiviral treatments, which submission was denied by the FDA on April 7, 2020 as previously disclosed.

The Company has cooperated with the Committee’s inquiry and has prepared a public statement regarding the price adjustment, which is available on the Company’s website at <https://jaguarhealth.gcs-web.com/company-statement>. In its statement, the Company explains that the decision to adjust the price for crofelemer was made in December 2019 as part of expanding the Company’s comprehensive patient access program, and had the Company received EUA, it would have deferred the price adjustment until after the emergency use period ended.

July 2017 Complaint Relating to the Merger

On July 20, 2017, a putative class action complaint was filed in the United States District Court, Northern District of California, Civil Action No. 3:17 cv 04102, by Tony Plant (the “Plaintiff”) on behalf of shareholders of the Company who held shares on April 12, 2017 and were entitled to vote at the 2017 Special Shareholders Meeting, against the Company and certain individuals who were directors as of the date of the vote (collectively, the “Defendants”), in a matter captioned Tony Plant v. Jaguar Animal Health, Inc., et al. (Jaguar Health, Inc. was formerly known as Jaguar Animal Health, Inc.), making claims arising under Section 14(a) and Section 20(a) of the Exchange Act and Rule 14a 9, 17 C.F.R. § 240.14a 9, promulgated thereunder by the SEC. The claims alleged false and misleading information provided to investors in the Joint Proxy Statement/Prospectus on Form S 4 (File No. 333 217364) declared effective by the Commission on July 6, 2017 related to the solicitation of votes from shareholders to approve the merger and certain transactions related thereto.

Following the completion of document discovery, the parties engaged in a mediation that resulted in an agreement in principle to settle the litigation on a class-wide basis for \$2.6 million, subject to court approval.

On May 27, 2021, the court gave the final approval to the proposed settlement and the entire settlement consideration was provided by the Company’s director and officer liability insurance carrier. Under the loss recovery model in ASC 450 and in reference to ASC 410, the ultimate net income effect of the recognized loss and the insurance proceeds directly related to the recognized loss is zero.

As of December 31, 2021 and 2020, the Company concluded not to record any loss contingency and insurance recovery.

Other than as described above, there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

ITEM 4. MINE SAFETY DISCLOSURE

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our common stock trades on The Nasdaq Capital Market under the symbol "JAGX."

Holders

As of March 10, 2022 there were approximately 28 stockholders of record of our common stock. These figures do not reflect the beneficial ownership or shares held in nominee name, nor do they include holders of any RSUs.

Dividend Policy

We have never paid any cash dividends on our common stock to date. We currently anticipate that we will retain all future earnings, if any, to fund the development and growth of our business and do not anticipate paying any cash dividends for at least the next five years, if ever.

Recent Sales of Unregistered Securities

Other than as provided on our quarterly reports on Form 10-Q filed with the SEC on May 17, 2021, August 13, 2021 and November 17, 2021 and our current reports on Form 8 K filed with the SEC on January 8, 2021, January 22, 2021, March 11, 2021, April 8, 2021, September 17, 2021, there were no unregistered sales of equity securities during the period.

The offers, sales, and issuances of the securities described above were deemed to be exempt from registration under the Securities Act in reliance on Section 3(a)(9) of the Securities Act, Section 4(a)(2) of the Securities Act, or Regulation D or Regulation S promulgated thereunder as transactions by an issuer not involving a public offering. The recipients of securities in each of these transactions acquired the securities for investment only and not with a view to or for sale in connection with any distribution thereof and appropriate legends were affixed to the securities issued in these transactions. Each of the recipients of securities in these transactions was an accredited or sophisticated person and had adequate access, through employment, business or other relationships, to information about us.

ITEM 6. SELECTED FINANCIAL DATA

Not Applicable.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis should be read together with our financial statements and the related notes appearing elsewhere in this report.

Overview

Jaguar Health, Inc. ("Jaguar" or the "Company") is a commercial stage pharmaceuticals company focused on developing novel, plant-based, non-opioid, and sustainably derived prescription medicines for people and animals with GI distress, including chronic, debilitating diarrhea. Jaguar Animal Health is a tradename of Jaguar Health. Our wholly owned subsidiary, Napo Pharmaceuticals, Inc. ("Napo"), focuses on developing and commercializing proprietary plant-based human pharmaceuticals for the global marketplace from plants or plant products used traditionally in rainforest areas. Napo's marketed drug Mytesi (crofelemer 125 mg delayed-release tablets) is a first-in-class oral botanical drug product approved by the U.S. Food and Drug Administration ("FDA") for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. To date, this is the only oral plant-based botanical prescription medicine approved under the FDA's Botanical Guidance. Jaguar Animal Health's Canalevia-CA1 (crofelemer delayed-release tablets) drug is the first and only oral plant-based prescription product that is FDA conditionally approved to treat chemotherapy-induced diarrhea (CID) in dogs. Canalevia-CA1 is a canine-specific formulation of crofelemer. Napo Therapeutics S.p.A., Napo's majority owned Italian subsidiary, focuses on expanding crofelemer access in Europe.

Jaguar, formerly known as Jaguar Animal Health, Inc., was founded in San Francisco, California as a Delaware corporation on June 6, 2013 (inception). The Company was a majority-owned subsidiary of Napo until the close of the Company's initial public offering on May 18, 2015. The Company was formed to develop and commercialize first-in-class prescription and non-prescription products for companion and production animals and horses. The Company's first non-prescription commercial products, Neonorm Calf and Neonorm Foal, were launched in 2014 and 2016, respectively.

On July 31, 2017, Jaguar completed a merger with Napo pursuant to the Agreement and Plan of Merger dated March 31, 2017, by and among Jaguar, Napo, Napo Acquisition Corporation ("Merger Sub"), and Napo's representative (the "Merger Agreement"). In accordance with the terms of the Merger Agreement, upon the completion of the merger, Merger Sub merged with and into Napo, with Napo surviving as the wholly-owned subsidiary (the "Merger" or "Napo Merger"). Immediately following the Merger, Jaguar changed its name from "Jaguar Animal Health, Inc." to "Jaguar Health, Inc." Napo now operates as a wholly-owned subsidiary of Jaguar focused on human health including the ongoing development of crofelemer and commercialization of Mytesi.

On March 15, 2021, Jaguar established Napo EU S.p.A (which changed its name in December 2021 to "Napo Therapeutics") based in Milan, Italy as a subsidiary of Napo. Napo Therapeutics' mission is to provide access to crofelemer in Europe to address significant rare/orphan disease indications, including, initially, two key orphan target indications: Short bowel syndrome with intestinal failure (SBS-IF), and congenital diarrheal disorders (CDD). On November 3, 2021, Napo Therapeutics merged with Dragon SPAC S.p.A. ("Dragon SPAC").

Most of the activities of the Company are focused on the commercialization of Mytesi and Canalevia-CA1 and the ongoing clinical development of crofelemer for the prophylaxis of diarrhea in adult patients receiving targeted cancer therapy. In the field of animal health, we are continuing limited activities related to developing and commercializing first in class gastrointestinal products for dogs, dairy calves, foals, and high value horses.

We believe Jaguar is poised to realize a number of synergistic, value adding benefits—an expanded pipeline of potential blockbuster human follow on indications of crofelemer, and a second generation anti secretory agent—upon which to build global partnerships. Jaguar, through Napo, holds global unencumbered rights for crofelemer, Mytesi, and Canalevia-CA1. Additionally, several of the drug product opportunities in Jaguar's crofelemer pipeline are backed Phase 2 and proof of concept evidence from human clinical trials.

Crofelemer is a novel, first in class anti secretory agent which has a normalizing effect on electrolyte and fluid balance while acting locally in the gut, and this mechanism of action has the potential to benefit multiple disorders that cause gastrointestinal distress, including diarrhea and abdominal discomfort. Crofelemer is also in development for possible follow on indications, including prophylaxis for cancer therapy related diarrhea (“CTD”); for rare disease indications for symptomatic treatment of infants and children with congenital diarrheal disorders (“CDD”) and for adult and pediatric patients with short bowel syndrome with intestinal failure (“SBS-IF”). Crofelemer has received orphan drug designation (ODD) for short bowel syndrome (SBS) in the US and in EU. Furthermore, the drug is being evaluated for management of diarrhea and abdominal discomfort in inflammatory bowel disease (“IBD”); diarrhea-predominant irritable bowel syndrome (“IBS-D”); and for idiopathic/functional diarrhea. A second generation proprietary anti secretory agent, NP-300 (lechlemer), is undergoing preclinical development for symptomatic relief and treatment of diarrhea in patients with acute infection from cholera.

Financial Operations Overview

On a consolidated basis, we have not yet generated enough revenue to date to achieve break even or positive cash flow, and we expect to continue to incur significant research and development and other expenses. Our net loss was \$52.6 million and \$33.8 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had total stockholders' equity of \$11.9 million, an accumulated deficit of \$219.5 million, and cash of \$17.1 million. We expect to continue to incur losses and experience increased expenditures for the foreseeable future as we expand our product development activities, seek necessary approvals for our product candidates, conduct species-specific formulation studies for our non-prescription products, establish API manufacturing capabilities and begin additional commercialization activities.

Revenue

Our product and collaboration revenue consists of the following:

- Revenues from the sale of our human drug Mytesi, which is sold through distributors and wholesalers.
- Revenues from the sale of our animal products branded as Neonorm Calf and Neonorm Foal. Our Neonorm and Botanical extract products are primarily sold to distributors, who then sell the products to the end customers.
- Our policy typically permits returns if the product is damaged, defective, or otherwise cannot be used when received by the customer if the product has expired. Returns are accepted for product that will expire within six months or that have expired up to one year after their expiration dates. Estimates for expected returns of expired products are based primarily on an ongoing analysis of our historical return patterns.

See “Results of Operations” below for more detailed discussion on revenues

Cost of Revenue

Cost of revenue consists of direct drug substance and drug product materials expense, direct labor, distribution fees, royalties and other related expenses associated with the sale of our products.

Research and Development Expense

Research and development expenses consist primarily of clinical and contract manufacturing expense, personnel and related benefit expense, stock-based compensation expense, employee travel expense and reforestation expenses. Clinical and contract manufacturing expense consists primarily of costs to conduct stability, safety and efficacy studies, and manufacturing startup expenses at an outsourced API provider in Italy. It also includes expenses with a third-party provider for the transfer of the Mytesi manufacturing process, and the related feasibility and validation activities.

We typically use our employee and infrastructure resources across multiple development programs. We track outsourced development costs by prescription drug product candidate and non-prescription product but do not allocate personnel or other internal costs related to development to specific programs or development compounds.

The timing and amount of our research and development expenses will depend largely upon the outcomes of current and future trials for our prescription drug product candidates as well as the related regulatory requirements, the outcomes of current and future species-specific formulation studies for our non-prescription products, manufacturing costs and any costs associated with the advancement of our line extension programs. We cannot determine with certainty the duration and completion costs of the current or future development activities.

The duration, costs and timing of trials, formulation studies and development of our prescription drug and non-prescription products will depend on a variety of factors, including:

- the scope, rate of progress, and expense of our ongoing, as well as any additional clinical trials, formulation studies and other research and development activities;
- future clinical trial and formulation study results;
- potential changes in government regulations; and
- the timing and receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of a prescription drug product candidate or non-prescription product could mean a significant change in the costs and timing associated with our development activities.

We expect research and development expense to increase due to the start-up costs associated with our clinical trials for other indications.

Sales and Marketing Expense

Sales and marketing expenses consist of personnel and related benefit expense, stock-based compensation expense, direct sales and marketing expense, employee travel expense, and management consulting expense. We currently incur sales and marketing expenses to promote Mytesi. We do not currently have any marketing or promotional expenses related to Neonorm Calf or Neonorm Foal for the years ended December 31, 2021 and 2020.

We expect sales and marketing expense to increase going forward as we focus on expanding our market access activities and commercial partnerships for the development of follow-on indications of Mytesi and crofelemer.

General and Administrative Expense

General and administrative expenses consist of personnel and related benefit expense, stock-based compensation expense, employee travel expense, legal and accounting fees, rent and facilities expense, and management consulting expense.

In the near term, we expect general and administrative expense to remain flat as we focus on our pipeline development and market access expansion. This will include efforts to grow the business.

Interest Expense

Interest expense consists primarily of non-cash and cash interest costs related to our borrowings.

Critical Accounting Policies and Significant Judgments and Estimates

The preparation of financial statements in conformity with U.S. generally accepted accounting principles (“U.S. GAAP”) requires the use of estimates and assumptions that affect the reported amounts of assets and liabilities, revenues and expenses, and related disclosures in the financial statements. Critical accounting policies are those accounting policies that may be material due to the levels of subjectivity and judgment necessary to account for highly uncertain matters or the susceptibility of such matters to change, and that have a material impact on financial condition or operating performance. While we base our estimates and judgments on our experience and on various other factors that we believe to be reasonable under the circumstances, actual results may differ from these estimates under different assumptions or conditions. We believe the following critical accounting policies used in the preparation of our financial statements require significant judgments and estimates. For additional information relating to these and other accounting policies, see Note 2 to the consolidated financial statements, appearing elsewhere in this report.

Results of Operations

Comparison of the Years Ended December 31, 2021 and 2020

The following table summarizes the Company's results of operations with respect to the items set forth in such table for the years ended December 31, 2021 and 2020 together with the change in such items in dollars and as a percentage.

(in thousands)	Year Ended December 31,		Variance	Variance %
	2021	2020		
Product revenue	\$ 4,335	\$ 9,385	\$ (5,050)	(53.8)%
Total revenue	4,335	9,385	(5,050)	(53.8)%
Operating Expenses				
Cost of product revenue	2,333	3,280	(947)	(28.9)%
Research and development	15,079	6,413	8,666	135.1 %
Sales and marketing	8,894	6,609	2,285	34.6 %
General and administrative	17,103	14,387	2,716	18.9 %
Series 3 warrants inducement expense	1,462	3,696	(2,234)	(60.4)%
ELOC warrants inducement expense	172	—	172	100.0 %
Series B convertible preferred stock inducement expense	—	1,647	(1,647)	(100.0)%
Total operating expenses	45,043	36,032	9,011	25.0 %
Loss from operations	(40,708)	(26,647)	(14,061)	52.8 %
Interest expense	(8,421)	(2,792)	(5,629)	201.6 %
Loss on extinguishment of debt and exchange of Series D perpetual preferred stock	(753)	(1,864)	1,111	(59.6)%
Change in fair value of financial instruments and instrument designated at Fair Value Option	(1,953)	(2,696)	743	(27.6)%
Other expense, net	(765)	190	(955)	(502.6)%
Loss before income tax	(52,600)	(33,809)	(18,791)	55.6 %
Income tax expense	—	—	—	100.0 %
Net loss and comprehensive loss	(52,600)	(33,809)	(18,791)	55.6 %
Deemed dividend attributable to Series C perpetual preferred stock	—	(2,521)	2,521	(100)%
Deemed dividend attributable to accretion of Series A redeemable convertible preferred stock	—	(1,332)	1,332	(100)%
Deemed dividend attributable to Series 1, Series 2 and Bridge warrant holders	—	(856)	856	(100)%
Stock dividend attributable to Series C perpetual preferred stock	—	(130)	130	(100)%
Adjusted net loss and comprehensive loss	\$ (52,600)	\$ (38,648)	\$ (13,952)	36.1 %
Net loss attributable to noncontrolling interest	\$ (5)	\$ —	\$ (5)	100 %
Net loss attributable to common shareholders	\$ (52,595)	\$ (38,648)	\$ (13,947)	36.1 %

Revenue

Product revenue

We transitioned from selling to the wholesalers that resell the product to retail pharmacies to the closed Specialty Pharmacy distribution networks throughout the year 2021 and we fully transitioned in the fourth quarter of the same year. The transition caused a one-time inventory draw-down of approximately 1,300 bottles of Mytesi across

our third-party logistics warehouse, wholesalers, distributors, and retail stores. This significantly contributed to the decrease of \$4.8 million of Mytesi gross revenue for the year 2021 compared to 2020.

Medicaid and AIDS Drug Assistance Program (“ADAP”) rebates accounted for \$3.5 million and \$1.7 million for the year ended December 31, 2021 and 2020, respectively, an increase of \$1.7 million primarily due to the WAC increase implemented by the Company in April 2020 which resulted in higher government rebates from Medicaid, ADAP, public health services programs, and includes approximately \$800,000 in chargebacks from the State of California. Sales discounts were \$6.2 million and \$7.0 million for the year ended December 31, 2021 and 2020, respectively, a decrease of \$778,000. We expect the wholesaler fees to decline in line with our switch to the closed Specialty Pharmacy distribution network.

Due to the Company’s arrangements, including elements of variable consideration, gross product sales are reduced in order to reflect the expected consideration to arrive at net product sales. Deductions to reduce gross product sales to net product sales for the years ended December 31, 2021 and 2020 are as follows:

<u>(in thousands)</u>	<u>Year Ended December 31,</u>		<u>Variance</u>	<u>Variance %</u>
	<u>2021</u>	<u>2020</u>		
Gross product sales				
Mytesi	\$ 15,657	\$ 20,434	\$ (4,777)	(23.4)%
Neonorm	62	77	(15)	(19.5)%
Total gross product sales	15,719	20,511	(4,792)	(23.4)%
Medicaid rebates	(3,484)	(1,738)	(1,746)	100.5 %
Sales discounts	(6,268)	(7,046)	778	(11.0)%
Sales returns	(104)	(273)	169	(61.9)%
Wholesaler fee	(1,528)	(2,069)	541	(26.1)%
Net product sales	\$ 4,335	\$ 9,385	\$ (5,050)	(53.8)%

Our gross product revenues were \$15.7 million and \$20.5 million for the year ended December 31, 2021 and 2020, respectively. These periods reflect revenue from the sale of our human drug Mytesi and our animal products branded as Neonorm Calf and Neonorm Foal. This contributed to the decrease of \$4.8 million of Mytesi gross revenue for the year 2021 compared to 2020.

Our Neonorm product revenues were \$62,000 and \$77,000 for the year ended December 31, 2021 and 2020, respectively. Sales and marketing expenses for Neonorm products are not significant during 2021 and none during the same period in 2020.

Cost of Product Revenue

<u>(in thousands)</u>	<u>Year Ended December 31,</u>		<u>Variance</u>	<u>Variance %</u>
	<u>2021</u>	<u>2020</u>		
<i>Cost of Product Revenue</i>				
Material cost	\$ 998	\$ 1,800	\$ (802)	(44.6)%
Direct labor	996	724	272	37.6 %
Distribution fees	199	430	(231)	(53.7)%
Other	140	326	(186)	(57.1)%
Total	\$ 2,333	\$ 3,280	\$ (947)	(28.9)%

The change in cost of product revenue of \$947,000 for the year ended December 31, 2021 compared to 2020 was primarily due to:

- Material costs decreased \$802,000 from \$1.8 million for the year ended December 31, 2020 to \$998,000 in 2021, largely attributable to lower sales resulting in less cost of materials for bottles sold and to non-

recurring write-off of non-conforming inventory in the year ended December 31, 2020. There was no write-off in 2021.

- Distribution fees decreased \$231,000 from \$430,000 for the year ended December 31, 2020 to \$199,000 in 2021 in line with our transition from Title model to Specialty Pharmacy distribution network.
- Other costs decreased \$186,000 from \$326,000 for the year ended December 31, 2020 to \$140,000 in 2021 mainly consisting of \$118,000 less in write-offs of non-conforming inventory, and a decrease in equipment maintenance of \$9,000 in 2020.
- Direct labor increased \$272,000 from \$724,000 for the year ended December 31, 2020 to \$996,000 in 2021, due to increased resources in manufacturing.

Research and Development Expense

The following table presents the components of research and development (“R&D”) expense for the years ended December 31, 2021 and 2020:

<u>(in thousands)</u>	<u>Year Ended December 31,</u>		<u>Variance</u>	<u>Variance %</u>
	<u>2021</u>	<u>2020</u>		
<i>Research and Development:</i>				
Clinical and contract manufacturing	\$ 6,257	\$ 1,674	\$ 4,583	273.8 %
Personnel and related benefits	3,954	1,771	2,183	123.3 %
Stock-based compensation	1,319	749	570	76.1 %
Materials expense and tree planting.	361	94	267	284.0 %
Travel, other expenses	40	45	(5)	(11.1)%
Other.	3,148	2,080	1,068	51.3 %
Total	<u>\$ 15,079</u>	<u>\$ 6,413</u>	<u>\$ 8,666</u>	<u>135.1 %</u>

The change in R&D expense of \$8.7 million for the year ended December 31, 2021 compared to 2020 was primarily due to:

- Clinical and contract manufacturing expenses increased \$4.6 million from \$1.7 million for the year ended December 31, 2020 to \$6.3 million in 2021 largely due to increased clinical trial activities related to the start-up of CTD and other indications, additional CMC manufacturing, consulting and contractors’ expenses, and cholera/lechlemer research expenses.
- Personnel and related benefits increased \$2.2 million from \$1.8 million for the year ended December 31, 2020 to \$4.0 million in 2021 due to increased resources, salary increases in April 2021 and an increase in bonus.
- Other expenses increased \$1.1 million from \$2.1 million for the year ended December 31, 2020 to \$3.1 million in 2021 mainly consisting of consulting, formulation and regulatory fees. Consulting expenses increased due to increase in clinical trial consultants while direct R&D testing costs also increased due to an increase in R&D work.
- Stock-based compensation increased \$570,000 from \$749,000 for the year ended December 31, 2020 to \$1.3 million in 2021 primarily due to new options granted in April 2021.
- Material expense and tree planting increased \$267,000 from \$94,000 for the year ended December 31, 2020 to \$361,000 in 2021 due to increased clinical trials.

Sales and Marketing Expense

The following table presents the components of sales and marketing (“S&M”) expense for the years ended December 31, 2021 and 2020:

(in thousands)	Year Ended December 31,		Variance	Variance %
	2021	2020		
<i>Sales and Marketing:</i>				
Personnel and related benefits	\$ 3,916	\$ 3,323	\$ 593	17.8 %
Direct marketing fees and expense . . .	3,415	2,187	1,228	56.1 %
Stock-based compensation	319	220	99	45.0 %
Other	1,244	879	365	41.5 %
Total	<u>\$ 8,894</u>	<u>\$ 6,609</u>	<u>\$ 2,285</u>	<u>34.6 %</u>

The change in S&M expense of \$2.3 million for the year ended December 31, 2021 compared to 2020 was primarily due to:

- Direct marketing fees and expense increased \$1.2 million from \$2.2 million for the year ended December 31, 2020 to \$3.4 million in 2021 due to an increase in marketing programs for Mytesi related to the expanding market access through specialty pharmacy channels.
- Personnel and related benefits increased \$593,000 from \$3.3 million for the year ended December 31, 2020 to \$3.9 million in 2021 due to the addition of four new personnel within Commercial Operations, increase in bonus, and salary increases in April 2021.
- Other expenses increased \$365,000 from \$879,000 for the year ended December 31, 2020 to \$1.2 million in 2021 largely due to additional marketing consulting costs.

General and Administrative Expense

The following table presents the components of general and administrative (“G&A”) expense for the years ended December 31, 2021 and 2020:

(in thousands)	Year Ended December 31,		Variance	Variance %
	2021	2020		
<i>General and Administrative:</i>				
Personnel and related benefits	\$ 3,390	\$ 1,845	\$ 1,545	83.7 %
Stock-based compensation	2,336	1,855	481	25.9 %
Legal services	2,303	2,449	(146)	(6.0)%
Public company expense	2,270	1,179	1,091	92.5 %
Audit, tax and accounting services	982	706	276	39.1 %
Third-party consulting services	859	845	14	1.7 %
Rent and lease expense	282	690	(408)	(59.1)%
Travel, other expenses	197	38	159	418.4 %
Other	4,484	4,780	(296)	(6.2)%
Total	<u>\$ 17,103</u>	<u>\$ 14,387</u>	<u>\$ 2,716</u>	<u>18.9 %</u>

The change in G&A expenses of \$2.7 million for the year ended December 31, 2021 compared to 2020 was due primarily to:

- Personnel and related benefits increased \$1.5 million from \$1.8 million for the year ended December 31, 2020 to \$3.4 million in 2021 due to new hires and increase in bonus.

- Public company expenses increased \$1.1 million from \$1.2 million for the year ended December 31, 2020 to \$2.3 million in 2021 largely attributable to the investor relations and communications consulting expenses, and expenses for the annual shareholder meeting.
- Stock-based compensation expense increased \$481,000 from \$1.9 million for the year ended December 31, 2020 to \$2.3 million in 2021 primarily due to higher expense incurred for options granted with immediate vesting to existing employees.
- Audit, tax and accounting services fees increased \$276,000 from \$706,000 for the year ended December 31, 2020 to \$982,000 in 2021, mostly due to the increased audit fees related to complex debt and equity transactions.
- Travel, other expenses increased \$159,000 from \$38,000 for the year ended December 31, 2020 to \$197,000 in 2021 due to other corporate and investor relations activities.
- Rent and lease expense decreased \$408,000 from \$690,000 for the year ended December 31, 2020 to \$282,000 in 2021 as a result of the transfer to a lower-cost facility and the occupancy of less space.
- Other general and administrative expenses decreased \$296,000 from \$4.8 million for the year ended December 31, 2020 to \$4.5 million in 2021 largely due to decreased consulting expenses in 2021. There was a non-recurring charge of \$1.0 million for the Atlas trial delay penalty incurred in the year ended December 31, 2020.
- Legal services decreased \$146,000 from \$2.4 million for the year ended December 31, 2020 to \$2.3 million in 2021 primarily due to a decrease in fees related to legal proceedings and other regulatory filings.

Series 3 Warrants Inducement Expense

The decrease in the Series 3 Warrants inducement expense of \$2.2 million is due to the following:

- In January 2021, the Company issued 135,416 Series 3 Warrants to a certain investor for the exercise of 135,416 Bridge Note Warrants in accordance with the May 2020 Modification of the 2019 Bridge Note Warrants and Inducement Offer. These Series 3 Warrants were valued at \$1.5 million using the Black-Scholes-Merton option pricing model on the issuance date.
- In May 2020, concurrent with the May 2020 modification of the exercise price of the Series 1, Series 2 and Bridge Warrants and inducement offer, the Company issued unregistered Series 3 warrants to purchase 2,890,284 shares of common stock. These Series 3 warrants were valued at \$3.7 million using the Black-Scholes-Merton option pricing model on the issuance date.

ELOC Warrants Inducement Expense

In April 2021, in consideration for Oasis Capital's entry into the amendment to the March 2020 Equity Line of Credit, the Company issued Oasis Capital a common stock purchase warrant exercisable for 33,333 shares of common stock with an exercise price per share equal to \$5.61 on the date of the amendment. These warrants were valued at \$172,000 on the issuance date.

Series B Convertible Preferred Stock Inducement Expense

On March 24, 2020, the Company entered into a Warrant Exercise and Preferred Stock Amendment Agreement with a holder of its Series 2 warrants previously issued in the Company's registered public offering on July 23, 2019, pursuant to which the holder agreed to exercise in cash its warrants to purchase an aggregate of 416,666

shares of common stock, at a reduced exercise price of \$1.57 per share for gross proceeds to the Company of approximately \$653,000. As a further inducement to enter into the Amendment Agreement, the Company agreed to reduce the conversion price of the Company's Series B Convertible Preferred Stock from \$6.00 to \$1.34. The modification of the conversion price of the Series B Convertible Preferred shares was qualitatively considered an extinguishment and the Company followed the guidance in ASC 260-10-S99-2 and recorded an expense of \$1.6 million and derecognizing the Series B Convertible Preferred shares.

Interest Expense, net

Interest expense increased \$5.6 million from \$2.8 million for the year ended December 31, 2020 to \$8.4 million in 2021 primarily due to additional interest expense incurred on royalty interest agreements.

Loss on Extinguishment of Debt and Exchange of Series D Perpetual Preferred Stock

The loss on extinguishment of debt and conversion of Series D Perpetual Preferred Stock decreased \$1.1 million from \$1.9 million for the year ended December 31, 2020 to \$753,000 in 2021 is due to the following:

- During 2020, the Company recorded a \$560,000 extinguishment loss from exchanges of the outstanding Exchange Note 1 for shares of the Company's common stock; and
- In December 2020, the Company recorded a \$1.3 million loss from exchanges of Series D Perpetual Preferred Stock for shares of the Company's common stock.
- In January 2021, the Company recorded a \$753,000 loss from the exchange of the outstanding balance of Exchange Note 2 for the Company's shares common stock.

Change in Fair Value of Financial Instruments and Hybrid Instrument Designated at FVO

Change in fair value of financial instruments decreased \$743,000 from a loss of \$2.7 million for the year ended December 31, 2020 to a loss of \$2.0 million in 2021 primarily due to fair value adjustments in liability classified warrants and notes payable designated at FVO.

Deemed Dividend Attributable to Series C Perpetual Preferred Stock

The Company recorded a deemed dividend of \$2.5 million for the year ended December 31, 2020 that resulted from the series of exchanges of Series C Perpetual Preferred Stock in October and December 2020.

Deemed Dividend Attributable to Accretion of Series A Redeemable Convertible Preferred Stock

The Company recorded a deemed dividend charge of \$1.3 million for the year ended December 31, 2020 for the accretion of the redemption amount and carrying value of the Series A Convertible Preferred Stock.

Deemed Dividend Attributable to Series 1, Series 2 and Bridge Warrant Holders

The Company recorded a deemed dividend of \$856,000 for the year ended December 31, 2020 that resulted from the modification of the Series 1, Series 2 and Bridge Warrants in May 2020.

Stock Dividend Attributable to Series C Perpetual Preferred Stock

The Company recorded a \$130,000 stock dividend attributable to the Series C Perpetual Preferred Stock for the year ended December 31, 2020. The Series C Perpetual Preferred shares were entitled to receive 10% cumulative stock dividends, to be payable in arrears on a monthly basis for 24 consecutive months. Dividends payable on the

Series C Perpetual Preferred shares shall be payable through the Company's issuance of Series C Perpetual Preferred share by delivering to each record holder the calculated number of payment-in-kind dividend shares.

Liquidity and Capital Resources

Sources of Liquidity

We have incurred net losses since our inception. For the years ended December 31, 2021 and 2020, we had net losses of \$52.6 million and \$33.8 million, respectively, and we expect to incur additional losses in the near-term future. At December 31, 2021, we had an accumulated deficit of \$219.5 million. To date, we have generated only limited revenue, and we may never achieve revenue sufficient to offset our expenses. The Company expects to incur substantial losses and negative cash flows in future periods. Further, the Company's future operations, which include the satisfaction of current obligations, are dependent on the success of the Company's ongoing development and commercialization efforts, as well as securing of additional financing and generating positive cash flows from operations. There is no assurance that the Company will have adequate cash balances to maintain its operations.

We had cash of \$17.1 million as of December 31, 2021 to fund our operating plan through one year from the issuance of these consolidated financial statements.

Although the Company plans to finance its operations and cash flow needs through equity and/or debt financing, collaboration arrangements with other entities, license royalty agreements, as well as revenue from future product sales, the Company does not believe its current cash balances are sufficient to fund its operating plan through one year from the issuance of these consolidated financial statements. The Company has an immediate need to raise cash. There can be no assurance that additional funding will be available to the Company on acceptable terms, or on a timely basis, if at all, or that the Company will generate sufficient cash from operations to adequately fund operating needs. If the Company is unable to obtain an adequate level of financing needed for the long-term development and commercialization of our products, the Company will need to curtail planned activities and reduce costs. Doing so will likely have an adverse effect on our ability to execute our business plan; accordingly, there is substantial doubt about the ability of the Company to continue in existence as a going concern. The accompanying consolidated financial statements do not include any adjustments that might result from the outcome of these uncertainties.

We have funded our operations primarily through the issuance of equity and debt financing, in addition to sales of commercial products. Cash provided by financing activities in 2021 are as follows:

- During January 2021, an aggregate of 416,664 shares of common stock was issued upon the exercise of the December 2019 PIPE Financing Warrants for total proceeds of \$975,000.
- On January 13, 2021, the Company entered into a securities purchase agreement, pursuant to which the Company agreed to issue and sell, in a registered public offering an aggregate of 1,479,290 shares of common stock, at an offering price of \$10.14 per share for net proceeds of approximately \$13.5 million.
- On January 19, 2021, the Company entered into a note purchase agreement with Streeterville Capital, LLC ("Streeterville"), pursuant to which the Company issued a secured promissory note in the aggregate principal amount of \$6.2 million for an aggregate purchase price of \$6.0 million.
- During January and February 2021, the Company issued an aggregate of 669,850 shares under the ATM Agreement for total net proceeds of \$5.4 million.
- On March 8, 2021, the Company entered into a Royalty Purchase Agreement with Streeterville, pursuant to which the Company sold a royalty interest entitling Streeterville to \$10.0 million and any interest, fees, and charges as royalty repayment amount for an aggregate purchase price of \$5.0 million. Interest will accrue on the royalty repayment amount at a rate of 5% per annum, compounding quarterly, and will increase to 10% per annum, compounding quarterly on the 12-month anniversary of the closing date.

- Between January to March 2021, an aggregate of 1,383,524 shares of common stock were issued upon the exercise of Series 1, Series 2 and Bridge Note Warrants for total proceeds of \$2.0 million.
- On April 29, 2021, the Company entered into a securities purchase agreement, pursuant to which the Company agreed to issue and sell, in a registered public offering an aggregate of 2,549,000 shares of common stock at an offering price of \$4.23 per share for gross proceeds of approximately \$10.8 million before deducting placement agent fees and related offering expenses of \$948,000.
- On September 13, 2021, the Company entered into a securities purchase agreement (the “September 2021 PIPE Financing”) with certain investors, pursuant to which the Company agreed to issue and sell to the investors in a private placement an aggregate of 309,242 unregistered shares of the Company’s common stock for an aggregate purchase price of approximately \$776,000 or \$2.51 per share.
- On December 10, 2021, the Company entered into another ATM Agreement (“December 2021 ATM Agreement”) with Ladenburg, pursuant to which the Company may offer and sell, from time to time through Ladenburg, shares of common stock having an aggregate offering price of up to \$15.0 million. As of December 31, 2021, the Company has issued 2,261,596 shares under the December 2021 ATM Agreement for a total net proceeds of \$3.2 million.

We expect our expenditures will continue to increase as we continue our efforts to develop our products and continue development of our pipeline in the near term. We may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. We may also not be successful in entering into partnerships that include payment of upfront licensing fees for our products and product candidates for markets outside the United States, where appropriate. If we do not generate upfront fees from any anticipated arrangements, it would have a negative effect on our operating plan. We still plan to finance our operations and capital funding needs through equity and/or debt financing as well as revenue from future product sales. However, there can be no assurance that additional funding will be available to us on acceptable terms on a timely basis, if at all, or that we will generate sufficient cash from operations to adequately fund operating needs or ultimately achieve profitability. If we are unable to obtain an adequate level of financing needed for the long-term development and commercialization of our products, we will need to curtail planned activities and reduce costs. Doing so will likely have an adverse effect on our ability to execute on our business plan.

Cash Flows for Year Ended December 31, 2021 compared to the Year Ended December 31, 2020

The following table shows a summary of cash flows for the years ended December 31, 2021 and 2020:

<i>(in thousands)</i>	Year Ended December 31,	
	2021	2020
Total cash used in operating activities	\$ (34,970)	\$ (15,278)
Total cash used in investing activities	(6)	(7)
Total cash provided by financing activities	43,937	19,492
Net increase in cash	\$ 8,961	\$ 4,207

Cash Used in Operating Activities

During the year ended December 31, 2021, net cash used in operating activities of \$35.0 million resulted from our net loss of \$52.6 million adjusted by amortization of debt issuance costs, debt discount, and non-cash interest expense of \$5.2 million, stock-based compensation of \$4.0 million, change in fair value of financial instruments and hybrid instruments designated at FVO of \$2.0 million, depreciation and amortization expenses of \$1.7 million, Series 3 and ELOC warrants inducement expenses of \$1.6 million, loss on extinguishment of debt of \$753,000, amortization of operating lease right-of-use assets of \$94,000, derecognition of debt discount on settlement of receivables secured borrowing of \$49,000, shares issued in exchange for services of \$16,000, and net changes in operating assets and liabilities of \$2.3 million.

During the year ended December 31, 2020, net cash used in operating activities of \$15.3 million resulted from our net loss of \$33.8 million adjusted by depreciation and amortization expenses of \$1.7 million, interest paid on the conversion of debt to equity of \$0.6 million, a loss on extinguishment of debt and conversion of Series D Perpetual Preferred Stock of \$1.9 million, a loss on recourse obligation on secured borrowing of \$15,000, amortization of operating lease right-of-use assets of \$553,000, expense on modifications of warrants of \$86,000, inducement charge of \$1.6 million on the modification of Series B Convertible Preferred Stock, stock-based compensation of \$2.8 million, other stock and warrant payments of \$1.1 million, amortization of debt discounts, debt issuance costs, and non-cash interest expense of \$2.7 million, \$2.5 million in shares issued to Atlas Sciences for settlement of the Trial Delay Fee, an increase in fair value of financial instruments of \$2.7 million, and \$3.7 million charge for Series 3 Warrants issued as an inducement to exercise equity-classified Series 1, Series 2 and Bridge warrants, offset by changes in operating assets and liabilities of \$3.5 million.

Cash Used in Investing Activities

During the year ended December 31, 2021, cash used in investing activities was \$6,000 which consisted of cash used to purchase property and equipment.

During the year ended December 31, 2020, cash used in investing activities was \$7,000 which consisted of cash used to purchase property and equipment.

Cash Provided by Financing Activities

During the year ended December 31, 2021, net cash provided by financing activities of \$43.9 million consisted of \$23.2 million in net proceeds received from shares issued in registered public offering, \$11.0 million in net proceeds received from issuance of notes payable, \$8.6 million in net proceeds from shares issued in an At the Market offering, \$2.0 million in net proceeds received from shares issued on conversion of Series 1, Series 2, and 2019 Bridge Note Warrants, \$1.8 million in net proceeds received from shares issued in PIPE financing, \$247 million noncontrolling interest, and \$3,000 in net proceeds from exercise of stock options, offset by \$1.8 million repayment of receivables secured borrowing, \$943,000 repayment of insurance financing, \$100,000 in principal payments of the notes payable and \$35,000 payment of ELOC warrants offering costs.

During the year ended December 31, 2020, net cash provided by financing activities of \$19.5 million consisted of \$12.3 million in net proceeds received from issuances of a notes payable, \$7.1 million received from borrowings secured by the Company's trade receivables, \$668,000 in net proceeds received from shares of common stock issued via a PIPE financing, \$5.8 million in net proceeds received from shares of common stock issued on exercise of Series 1, Series 2, and 2019 Bridge Note warrants, and \$1.3 million in net proceeds received from issuance of other shares of common stock, offset by \$7.3 million in principal payments of the notes payable, secured borrowings and insurance premium borrowings, \$185,000 million in issuance costs from shares issued as part of the underwriter settlement agreement, and \$142,000 other payments of issuance costs.

Off-Balance Sheet Arrangements

Since inception, we have not engaged in the use of any off-balance sheet arrangements, such as structured finance entities, special purpose entities or variable interest entities.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

Not applicable.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

**Jaguar Health, Inc.
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Report of Independent Registered Public Accounting Firm

To the Board of Directors and
Shareholders of Jaguar Health, Inc.:

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheet of Jaguar Health, Inc., (the “Company”) as of December 31, 2021, and the related consolidated statements of operations, changes in stockholders’ equity, and cash flows for the year ended December 31, 2021, and the related notes (collectively referred to as the “consolidated financial statements”). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021, and the results of its operations and its cash flows for the year ended December 31, 2021, in conformity with accounting principles generally accepted in the United States of America.

The Company’s Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, the Company has an accumulated deficit, recurring losses, and expects continuing future losses. These conditions raise substantial doubt about the Company’s ability to continue as a going concern. Management’s evaluation of the events and conditions and management’s plans regarding these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company’s management. Our responsibility is to express an opinion on the Company’s financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit, we are required to obtain an understanding of internal control over financial reporting, but not for the purpose of expressing an opinion on the effectiveness of the Company’s internal control over financial reporting. Accordingly, we express no such opinion.

Our audit included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audit provides a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that:

(1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Impairment of Intangible Assets, Net—Refer to Note 2 and Note 7 to the financial statements

Critical Audit Matter Description

As of December 31, 2021, the Company had intangible assets, net, of \$22.7 million. Intangible assets are evaluated based on the asset group based on product as well as being evaluated between definite-lived and indefinite-lived intangible assets for the purpose of the impairment assessment. The Company assesses potential impairments whenever events or circumstances indicate that the asset may be impaired. For finite-lived intangibles assets the impairment is based on recoverability. Recoverability of an asset group is measured by a comparison of the carrying amount of an asset group to its forecasted cash flows expected to be generated by the asset group. If the carrying amount of the asset group exceeds its estimated forecasted cash flows, an impairment charge is recognized as the amount by which the carrying amount of the asset group exceeds the fair value of the asset group. An indefinite-lived intangible asset is considered impaired if the carrying amount exceeds the fair value of the asset group. The fair value of the asset group was determined using the income approach. The Company did not recognize an impairment loss in the financial statements for the year ended December 31, 2021.

We identified the evaluation of intangible asset impairment as a critical audit matter because the determination of the forecasted individual asset group's cash flows, including revenue, expenses, and other items, requires a high degree of auditor judgment and increased extent of effort.

How the Critical Audit Matter Was Addressed in the Audit

The principal considerations for our determination that performing procedures relating to the valuation of intangible assets as a critical audit matter are (1) there was a high degree of auditor judgment and subjectivity in applying procedures relating to the fair value of intangible assets acquired due to the significant judgment by management when developing the estimates and (2) significant audit effort was required in evaluating the significant assumptions relating to the estimates, including the income projections and discount rates. In addition, the audit effort involved the use of professionals with specialized skill and knowledge to assist in performing these procedures and evaluating the audit evidence obtained.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included the following:

- Inquiry of management regarding the development of the assumptions used in the valuation of the intangible assets.
- Testing management's process included evaluating the appropriateness of the valuation models, testing the completeness, accuracy, and relevance of underlying data used in the models, and testing the reasonableness of significant assumptions, including the income projections and discount rates.
- Professionals with specialized skill and knowledge were used to assist in evaluating the reasonableness of significant assumptions.
- Evaluated the experience, qualifications and objectivity of the Company's specialist, a third-party valuation firm.
- Obtained an understanding of the nature of the work the Company's specialist performed, including the objectives and scope of the specialist's work; the methods or assumptions used; and a comparison of the methods or assumptions used with those used in the preceding period. Identified and evaluated assumptions developed by the specialist considering assumptions generally used in the specialist's field; supporting evidence provided by the specialist; existing market data; historical or recent experience and changes in conditions and events affecting the Company.

- Tested the accuracy and completeness of company-produced data used by the specialist, and evaluated the relevance and reliability of externally obtained data. For assumptions provided to the specialist by the company, evaluated whether there is a reasonable basis for using each assumption considering whether other reasonably likely outcomes could materially affect the relevant financial statement assertions. Identified and evaluated significant assumptions used by the specialist for reasonableness.
- Evaluated the Company's estimates of future revenue projections by completing a retrospective comparison to historical revenue projections. We tested the significant assumptions discussed above, as well as the completeness and accuracy of the underlying data used in the projected cash flows and valuations.
- To reflect the uncertainty inherent in the projections, we performed our own sensitivity analyses by increasing or decreasing the significant assumptions and evaluated the potential impact on the fair value. In addition, we tested the reconciliation of the fair value of the asset group developed by management to the market capitalization of the Company as of the valuation date.

/s/ RBSM, LLP

We have served as the Company's auditor since 2021.
Larkspur, California
March 11, 2022

PCAOB ID Number 587

Report of Independent Registered Public Accounting Firm

To the Board of Directors and
Stockholders of Jaguar Health, Inc.:

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheet of Jaguar Health, Inc. (“Company”) as of December 31, 2020, and the related consolidated statements of operations, changes in stockholders’ equity, and cash flows for the year ended December 31, 2020, and the related notes (collectively referred to as the “financial statements”). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2020, and the results of its operations and its cash flows for the year ended December 31, 2020, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These financial statements are the responsibility of the Company’s management. Our responsibility is to express an opinion on the Company’s financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (“PCAOB”) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company’s internal control over financial reporting. Accordingly, we express no such opinion.

Our audit included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audit provides a reasonable basis for our opinion.

/s/ Mayer Hoffman McCann P.C.

We served as the Company's auditor since 2019, which ended in 2021.

San Diego, California

March 31, 2021 (except for the effects of the reverse stock split described in Note 1, as to which the date is March 11, 2022)

PCAOB ID Number 199

JAGUAR HEALTH, INC.
CONSOLIDATED BALANCE SHEETS

<u>(In thousands, except share and per share data)</u>	<u>December 31,</u> <u>2021</u>	<u>December 31,</u> <u>2020</u>
Assets		
Current assets:		
Cash	\$ 17,051	\$ 8,090
Accounts receivable	1,709	2,098
Accounts receivable - pledged	—	2,434
Other receivable	435	28
Inventory	4,900	2,782
Prepaid expenses and other current assets	4,339	2,360
Total current assets	28,434	17,792
Property and equipment, net	650	677
Operating lease - right-of-use asset	1,084	—
Intangible assets, net	22,651	24,337
Other assets	446	37
Total assets	\$ 53,265	\$ 42,843
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	\$ 4,929	\$ 4,759
Accrued liabilities	7,117	4,493
Warrant liability	1	179
Operating lease liability, current	240	—
Notes payable, current	3,184	3,789
Series D perpetual preferred stock: \$0.0001 par value; 977,300 shares authorized at December 31, 2021 and 2020; zero shares issued and outstanding at December 31, 2021 and 2020	—	—
Total current liabilities	15,471	13,220
Operating lease liability, net of current portion	919	—
Notes payable, net of discount, net of current portion (includes hybrid instrument designated at Fair Value Option amounting to \$7.8 million and zero as of December 31, 2021 and 2020, respectively) ..	25,022	12,421
Total liabilities	41,412	25,641
Commitments and contingencies (See Note 6)		
Stockholders' equity		
Series B-2 convertible preferred stock: \$0.0001 par value, 10,165 shares authorized at December 31, 2021 and 2020; zero shares issued and outstanding at December 31, 2021 and 2020	—	—
Series C perpetual preferred stock: 1,011,000 shares authorized at December 31, 2021 and 2020; zero shares issued and outstanding at December 31, 2021 and 2020	—	—
Common stock - voting: \$0.0001 par value, 150,000,000 shares authorized at December 31, 2021 and 2020; 48,352,527 and 38,007,420 shares issued and outstanding at December 31, 2021 and 2020, respectively	5	4
Common stock - non-voting: \$0.0001 par value, 50,000,000 shares authorized at December 31, 2021 and 2020; 2,120,786 shares issued and outstanding at December 31, 2021 and 2020	—	—
Additional paid-in capital	231,100	184,097
Noncontrolling interest	242	—
Accumulated deficit	(219,494)	(166,899)
Total stockholders' equity	11,853	17,202
Total liabilities and stockholders' equity	\$ 53,265	\$ 42,843

The accompanying notes are an integral part of these consolidated financial statements.

JAGUAR HEALTH, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS

	Year Ended December 31,	
(In thousands, except share and per share data)	2021	2020
Product revenue	\$ 4,335	\$ 9,385
Operating expenses		
Cost of product revenue	2,333	3,280
Research and development	15,079	6,413
Sales and marketing	8,894	6,609
General and administrative	17,103	14,387
Series 3 warrants inducement expense	1,462	3,696
ELOC warrants inducement expense	172	—
Series B convertible preferred stock inducement expense	—	1,647
Total operating expenses	45,043	36,032
Loss from operations	(40,708)	(26,647)
Interest expense	(8,421)	(2,792)
Loss on extinguishment of debt and exchange of Series D perpetual preferred stock	(753)	(1,864)
Change in fair value of financial instruments and hybrid instrument designated at Fair Value Option	(1,953)	(2,696)
Other income (expense), net	(765)	190
Loss before income tax	(52,600)	(33,809)
Income tax expense	—	—
Net loss and comprehensive loss	(52,600)	(33,809)
Deemed dividend attributable to Series C perpetual preferred stock . . .	—	(2,521)
Deemed dividend attributable to accretion of Series A redeemable convertible preferred stock	—	(1,332)
Deemed dividend attributable to Series 1, Series 2 and Bridge warrant holders	—	(856)
Stock dividend attributable to Series C perpetual preferred stock	—	(130)
Adjusted net loss and comprehensive loss	\$ (52,600)	\$ (38,648)
Net loss attributable to noncontrolling interest	\$ (5)	\$ —
Net loss attributable to common shareholders	\$ (52,595)	\$ (38,648)
Net loss per share, basic and diluted	\$ (1.18)	\$ (3.00)
Weighted-average common shares outstanding, basic and diluted	44,711,588	12,880,868

The accompanying notes are an integral part of these consolidated financial statements.

JAGUAR HEALTH, INC.

CONSOLIDATED STATEMENTS OF CHANGES IN STOCKHOLDERS' EQUITY

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Series C Perpetual Preferred Stock		Common Stock - voting		Common Stock - non-voting		Additional paid-in capital		Noncontrolling Interest		Accumulated deficit		Total Stockholders' Equity	
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount
(In thousands, except share data)																		
Balances as of January 1, 2020	5,524,926	\$ 9,895	476	\$ 1,236	—	—	4,757,683	\$ 4	—	—	392	—	—	—	—	—	392	—
Shares issued on exercise of Series 1, Series 2, and Series 3 warrants	—	—	—	—	—	—	182,986	—	—	—	—	—	—	—	—	—	—	—
Shares issued on exercise of Series 2 warrants and conversion of Series B-1 convertible preferred stock	—	—	—	—	—	—	416,666	—	—	—	2,341	—	—	—	—	—	2,341	—
Shares issued on exercise of Series 1, Series 2, and Series 3 warrants, net of issuance costs of \$461, May 2020	—	—	—	—	—	—	2,890,283	—	—	—	3,788	—	—	—	—	—	3,788	—
Shares issued on conversion of Series 1, Series 2, and Series 3 warrants; June 2020	—	—	—	—	—	—	244,104	—	—	—	359	—	—	—	—	—	359	—
Modification of Series 1, Series 2 and Bridge warrants	—	—	—	—	—	—	—	—	—	—	856	—	—	—	—	—	856	—
Deemed dividend attributable to Series 1, Series 2 and Bridge warrant holders	—	—	—	—	—	—	—	—	—	—	(856)	—	—	—	—	—	(856)	—
Shares issued on exercise of Series 3 warrants	—	—	—	—	—	—	2,818,779	—	—	—	6,057	—	—	—	—	—	6,057	—
Shares issued on exercise of Series 1 and Series 2 warrants	—	—	—	—	—	—	426,416	—	—	—	626	—	—	—	—	—	626	—
Shares issued to Atlas Sciences for settlement of Trial Delay Fee	—	—	—	—	—	—	666,666	—	—	—	612	—	—	—	—	—	612	—
Warrants issued and converted to common shares to Atlas Sciences for settlement of Trial Delay Fee	—	—	—	—	—	—	2,072,984	—	—	—	1,904	—	—	—	—	—	1,904	—
Issuance of common stock in PIPE financing, net of issuance costs of \$51	—	—	—	—	—	—	571,427	—	—	—	668	—	—	—	—	—	668	—
Warrants issued in Underwriter settlement agreement	—	—	—	—	—	—	33,333	—	—	—	45	—	—	—	—	—	45	—
Warrants issued in Underwriter settlement agreement	—	—	—	—	—	—	—	—	—	—	31	—	—	—	—	—	31	—
Underwriter settlement offering cost	—	—	—	—	—	—	—	—	—	—	(185)	—	—	—	—	—	(185)	—
Conversion of Series B-2 convertible preferred stock into common stock	—	—	(10,165)	(1,236)	—	—	748,761	—	—	—	1,266	—	—	—	—	—	1,266	—
Conversion of Series B convertible preferred stock into common stock	—	—	(476)	—	—	—	1,474,416	—	—	—	476	—	—	—	—	—	476	—
Shares issued to Onsite as consideration under the March 2020 equity purchase agreement	—	—	—	—	—	—	22,935	—	—	—	33	—	—	—	—	—	33	—
Shares issued to Onsite under the March 2020 equity purchase agreement, net of option exercise, net of Series A convertible preferred stock redeemed and Series C perpetual preferred issued under the exchange transaction	(5,524,926)	(11,227)	—	—	842,500	4,717	—	—	—	—	150	—	—	—	—	—	150	—
Stock dividend attributable to Series C perpetual preferred stock of \$8 per share	—	—	—	—	16,310	130	—	—	—	—	(130)	—	—	—	—	—	—	—
Extinguishment of Series C perpetual preferred stock	—	—	—	—	(2,521)	—	—	—	—	—	2,521	—	—	—	—	—	—	—
Deemed dividend attributable to Series C perpetual preferred stock	—	—	—	—	2,521	—	—	—	—	—	(2,521)	—	—	—	—	—	—	—
Shares issued to third party for services	—	—	—	—	—	—	91,666	—	—	—	105	—	—	—	—	—	105	—
Shares issued to Sagard Capital in exchange of services	—	—	—	—	—	—	763,158	—	—	—	879	—	—	—	—	—	879	—
Shares issued in exchange of CVP Exchange Notes	—	—	—	—	—	—	7,157,239	—	—	—	6,512	—	—	—	—	—	6,512	—
Warrants issued and converted to common shares to Pacific Capital Management in exchange of promissory note	—	—	—	—	—	—	16,666	—	—	—	24	—	—	—	—	—	24	—
Shares issued to PoC Capital in Payment of Contracted Research Fees	—	—	—	—	—	—	444,444	—	—	—	437	—	—	—	—	—	437	—
Shares issued to Iliad in exchange of Royalty Interest	—	—	—	—	—	—	438,324	—	—	—	256	—	—	—	—	—	256	—
Shares issued on conversion of Series C perpetual preferred stock	—	—	—	—	(858,810)	(4,847)	2,817,959	—	—	—	4,847	—	—	—	—	—	—	—
Warrants issued and converted to common stock in exchange for Series C Preferred Stock	—	—	—	—	—	—	2,352,563	1	—	—	(1)	—	—	—	—	—	—	—
Shares issued on conversion of Series D convertible preferred stock	—	—	—	—	—	—	5,296,623	1	—	—	7,876	—	—	—	—	—	7,876	—
Conversion of non-voting common stock to voting common stock	—	—	—	—	—	—	12,120	—	(38,180,451)	(4)	4	—	—	—	—	—	—	—
Shares issued in Registered Direct Offering Priced Above-the-Market, net of \$78 offering costs	—	—	—	—	—	—	1,271,639	—	—	—	1,207	—	—	—	—	—	1,207	—
Accretion to redemption value of redeemable preferred stock	—	—	—	—	—	—	62	—	—	—	(1,332)	—	—	—	—	—	(1,332)	—
Frictional shares	—	—	—	—	—	—	185	—	—	—	—	—	—	—	—	—	—	—
Shares issued upon exercise of stock options	—	—	—	—	—	—	—	—	—	—	2,824	—	—	—	—	—	2,824	—
Stock-based compensation	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Balances as of December 31, 2020	—	\$ —	—	\$ —	—	\$ —	38,007,420	\$ 4	2,120,786	\$ —	184,097	\$ —	—	\$ —	—	\$ (166,890)	—	\$ (33,800)
																		\$ 17,202

The accompanying notes are an integral part of these consolidated financial statements.

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Series B-2 Convertible Preferred Stock		Series C Perpetual Preferred Stock		Common Stock - voting		Common Stock - non-voting		Additional paid-in capital	Noncontrolling interest	Accumulated deficit	Total Stockholders' Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount				
(In thousands, except share data)																
Balances as of January 1, 2021	—	\$ —	—	\$ —	—	\$ —	—	\$ —	38,007,420	\$ 4	2,120,786	\$ —	\$ 184,097	\$ —	\$ (166,899)	\$ 17,202
Shares issued on exercise of Series 1, Series 2, and 2019 Bridge Note Warrants	—	—	—	—	—	—	—	—	1,383,524	—	—	—	2,034	—	—	2,034
Shares issued in PIPE financing	—	—	—	—	—	—	—	—	725,906	—	—	—	1,751	—	—	1,751
Shares issued in At the Market offering, net of issuance and offering costs of \$465	—	—	—	—	—	—	—	—	2,931,446	—	—	—	8,595	—	—	8,595
Shares issued in registered public offering, net of issuance and offering costs of \$2,550	—	—	—	—	—	—	—	—	4,028,290	1	—	—	23,231	—	—	23,232
Shares issued in extinguishment of Exchange Note 2	—	—	—	—	—	—	—	—	471,202	—	—	—	2,516	—	—	2,516
Shares issued on exercise of Series 3 warrants	—	—	—	—	—	—	—	—	206,915	—	—	—	1,776	—	—	1,776
Shares issued to Iliad in exchange of notes payable and accrued interest	—	—	—	—	—	—	—	—	588,235	—	—	—	2,982	—	—	2,982
Warrants issued to Oasis for ELOC amendment, net of offering costs of \$48	—	—	—	—	—	—	—	—	—	—	—	—	124	—	—	124
Shares issued on conversion of Napo merger common shares	—	—	—	—	—	—	—	—	726	—	—	—	—	—	—	—
Shares issued upon exercise of stock options	—	—	—	—	—	—	—	—	3,147	—	—	—	4	—	—	4
Shares issued to third party for services	—	—	—	—	—	—	—	—	5,666	—	—	—	16	—	—	16
Fractional shares	—	—	—	—	—	—	—	—	50	—	—	—	—	—	—	—
Merger of subsidiary	—	—	—	—	—	—	—	—	—	—	—	—	—	247	—	247
Stock-based compensation	—	—	—	—	—	—	—	—	—	—	—	—	3,974	—	—	3,974
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	(5)	(52,595)	(52,600)
Balances as of December 31, 2021	—	\$ —	—	\$ —	—	\$ —	—	\$ —	48,352,527	\$ 5	2,120,786	\$ —	\$ 231,100	\$ 242	\$ (219,494)	\$ 11,853

The accompanying notes are an integral part of these consolidated financial statements.

JAGUAR HEALTH, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year Ended	
	December 31, 2021	December 31, 2020
<i>(in thousands)</i>		
Cash flows from operating activities		
Net loss	\$ (52,600)	\$ (33,809)
Adjustments to reconcile net loss to net cash used in operating activities:		
Amortization of debt issuance costs, debt discount, and non-cash interest expense	5,171	2,670
Stock-based compensation	3,974	2,824
Change in fair value of financial instruments and hybrid instrument designated at Fair Value Option	1,953	2,696
Depreciation and amortization expense	1,719	1,727
Series 3 warrants inducement expense	1,462	3,696
Loss on extinguishment of debt and conversion of Series D perpetual preferred stock	753	1,864
ELOC warrants inducement expense	172	—
Amortization of operating lease - right-of-use-asset	94	553
Derecognition of debt discount on settlement of receivables secured borrowing	49	—
Shares issued in exchange for services	16	984
Series B convertible preferred stock inducement expense	—	1,647
Expense on modification of warrants	—	86
Shares and warrants issued in Underwriter settlement agreement	—	76
Shares issued as consideration paid under the Oasis Capital Equity Purchase Agreement	—	33
Loss on recourse obligation on secured borrowing	—	15
Interest paid on the conversion of debt to equity	—	611
Shares issued to Atlas for settlement of Trial Delay Fee	—	612
Shares issued on conversion of warrants of Atlas for settlement of Trial Delay Fee	—	1,904
Changes in assets and liabilities		
Accounts receivable	2,823	(2,840)
Other receivable	(407)	(26)
Inventory	(2,118)	(653)
Prepaid expenses and other current assets	(796)	(955)
Other assets	(408)	893
Accounts payable	158	(743)
Accrued liabilities	3,034	1,194
Operating lease liability	(19)	(337)
Total cash used in operating activities	<u>(34,970)</u>	<u>(15,278)</u>
Cash flows from investing activities		
Purchase of equipment	(6)	(7)
Total cash used in investing activity	<u>(6)</u>	<u>(7)</u>
Cash flows from financing activities		
Proceeds from issuance of shares in registered public offering, net of issuance and offering costs of \$2,550	23,232	—
Proceeds from issuance of notes payable, net of issuance costs of \$50 in 2021 and 2020	10,975	12,300
Proceeds from issuance of shares in At the Market offering, net of issuance and offering costs of \$465 in 2021 and offering costs of \$78 in 2020	8,595	1,281
Proceeds from issuance of shares on conversion of Series 1, Series 2, and 2019 Bridge Note warrants, net of issuance and offering costs of \$486 in 2020	2,034	5,797
Repayment of receivables secured borrowing	(1,822)	(6,207)
Proceeds from issuance of shares in PIPE financing	1,751	668
Repayment of insurance financing	(943)	(681)
Noncontrolling interest	247	—
Repayment of notes payable	(100)	(406)
Payment of ELOC warrants offering costs	(35)	—
Proceeds from exercise of stock options	3	—
Proceeds from sale of receivables, net of debt discount and issuance costs of \$640	—	7,057
Issuance costs from shares issued on Underwriter settlement agreement	—	(185)
Payments of deferred offering costs	—	(142)
Proceeds from issuance of common stock on conversion of Oasis Capital an Equity Purchase Agreement put options, net of issuance costs of \$13	—	10
Total cash provided by financing activities	<u>43,937</u>	<u>19,492</u>
Net increase in cash	8,961	4,207
Cash at beginning of period	8,090	3,883
Cash at end of period	<u>\$ 17,051</u>	<u>\$ 8,090</u>

JAGUAR HEALTH, INC.
STATEMENTS OF CASH FLOWS (continued)

	Year Ended	
	December 31, 2021	December 31, 2020
Supplemental schedule of cash flow information		
Cash paid for interest	\$ 28	\$ 757
Supplemental schedule of non-cash financing and investing activities		
Shares issued in exchange of partial settlement of royalty interest	\$ 2,982	\$ —
Shares issued on exercise of Series 3 warrants	\$ 1,776	\$ 6,057
Insurance financing	\$ 1,183	\$ 776
Recognition of operating lease - right-of-use asset and operating lease liability	\$ 1,087	\$ —
Lease modification	\$ 91	\$ —
Offering costs included in accounts payable and accrued liabilities	\$ 13	\$ —
Extinguishment of Series A redeemable convertible preferred stock	\$ —	\$ 11,227
Common stock issued as redemption of Series D perpetual preferred stock	\$ —	\$ 6,575
Issuance of Series D perpetual preferred stock	\$ —	\$ 6,404
Common stock issued as redemption of notes payable and related interest	\$ —	\$ 6,165
Issuance of Series C perpetual preferred stock	\$ —	\$ 4,717
Deemed dividend attributable to Series C perpetual preferred stock	\$ —	\$ 2,521
Accretion to redemption value of Series A contingently redeemable convertible preferred stock	\$ —	\$ 1,332
Conversion of Series B-2 convertible preferred stock into common stock	\$ —	\$ 1,236
Deemed dividend attributable to Series 1, Series 2 and Bridge warrant holders	\$ —	\$ 856
Shares issued on exercise of Series B convertible preferred shares	\$ —	\$ 476
Shares issued to PoC Capital in payment of contracted research fees	\$ —	\$ 437
Stock dividend attributable to Series C perpetual preferred stock	\$ —	\$ 130

The accompanying notes are an integral part of these consolidated financial statements.

Jaguar Health, Inc.
Notes to Financial Statements

1. Organization and Business

Jaguar Health, Inc. (“Jaguar” or the “Company”), formerly known as Jaguar Animal Health, Inc., was incorporated on June 6, 2013 (inception) in Delaware. The Company was a majority-owned subsidiary of Napo until the close of the Company's initial public offering on May 18, 2015. The Company was formed to develop and commercialize first-in-class gastrointestinal products for companion and production animals and horses. The Company's first commercial product, Neonorm Calf, was launched in 2014 and Neonorm Foal was launched in the first quarter of 2016. The Company's activities are subject to significant risks and uncertainties, including failing to secure additional funding in order to timely complete the development and commercialization of products.

On July 31, 2017, Jaguar completed a merger with Napo pursuant to the Agreement and Plan of Merger dated March 31, 2017 by and among Jaguar, Napo, Napo Acquisition Corporation (“Merger Sub”), and Napo's representative (the “Merger Agreement”). In accordance with the terms of the Merger Agreement, upon the completion of the merger, Merger Sub merged with and into Napo, with Napo surviving as the wholly-owned subsidiary (the “Merger” or “Napo Merger”). Immediately following the Merger, Jaguar changed its name from “Jaguar Animal Health, Inc.” to “Jaguar Health, Inc.” Napo now operates as a wholly-owned subsidiary of Jaguar focused on human health and the ongoing commercialization of Mytesi, a Napo drug product approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy.

On March 15, 2021, the Company established Napo EU in Italy as a subsidiary of Napo. Napo EU's mission is to develop and commercialize novel, plant-based, sustainably derived prescription medicines in Europe (excluding Russia) for people with gastrointestinal distress to provide relief and treatment from various gut disorders, their symptoms, and interventions. The initial focus of Napo EU is on pursuing the accelerated conditional marketing authorization pathway from the European Medicines Agency for crofelemer for an important orphan-designated disease: Intestinal failure with short bowel syndrome (“SBS-IF”).

On November 3, 2021, Napo EU and Dragon SPAC S.p.A (“Dragon SPAC”) merged. Dragon SPAC is private company limited by shares with registered office in Italy. Upon close, Dragon SPAC became a controlled subsidiary of the Company and will be a consolidated entity. Further, Napo EU was incorporated into Dragon SPAC with Dragon SPAC as the surviving entity which took over by operation of law all the assets, rights, reasons and actions as well as liabilities, obligations and commitments of NAPO EU. The merged entity was named as Napo Therapeutics S.p.A (“Napo Therapeutics”).

The Company manages its operations through two segments – human health and animal health and is headquartered in San Francisco, California.

Nasdaq Communication and Compliance

Minimum Stockholders' Equity Requirement

On February 17, 2022, the Company received a letter from the Staff of Nasdaq indicating that the bid price of the Company's common stock for the last 30 consecutive business days had again closed below the minimum \$1.00 per share required for the continued listing under Nasdaq Listing Rule 5550(a)(2) (see Note 16).

Liquidity and Going Concern

The Company, since its inception, has incurred recurring operating losses and negative cash flows from operations and has an accumulated deficit of \$219.5 million as of December 31, 2021. The Company expects to incur substantial losses and negative cash flows in future periods. Further, the Company's future operations, which include the satisfaction of current obligations, are dependent on the success of the Company's ongoing development and

commercialization efforts, as well as securing of additional financing and generating positive cash flows from operations. There is no assurance that the Company will have adequate cash balances to maintain its operations.

Although the Company plans to finance its operations and cash flow needs through equity and/or debt financing, collaboration arrangements with other entities, license royalty agreements, as well as revenue from future product sales, the Company does not believe its current cash balances are sufficient to fund its operating plan through one year from the issuance of these consolidated financial statements. The Company has an immediate need to raise cash. There can be no assurance that additional funding will be available to the Company on acceptable terms, or on a timely basis, if at all, or that the Company will generate sufficient cash from operations to adequately fund operating needs. If the Company is unable to obtain an adequate level of financing needed for the long-term development and commercialization of our products, the Company will need to curtail planned activities and reduce costs. Doing so will likely have an adverse effect on our ability to execute our business plan; accordingly, there is substantial doubt about the ability of the Company to continue in existence as a going concern. The accompanying consolidated financial statements do not include any adjustments that might result from the outcome of these uncertainties.

Reverse Stock Split

On September 3, 2021, the Company filed the Certificate of Fifth Amendment to its Third Amended and Restated Certificate of Incorporation with the Secretary of State of Delaware to effect a 1-for-3 reverse stock split of the Company's issued and outstanding shares of voting common stock, effective September 8, 2021. The reverse split has been retrospectively reflected in all voting common stock, warrants, and common stock option shares disclosed in these consolidated financial statements. The non-voting common stock and the convertible preferred stock were excluded from the reverse split.

2. Summary of Significant Accounting Policies

Basis of Presentation

The consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP").

Principles of Consolidation

The consolidated financial statements have been prepared in accordance with U.S. GAAP and applicable rules and regulations of the Securities and Exchange Commission ("SEC") and include the accounts of the Company and its subsidiaries. All inter-company transactions and balances have been eliminated in consolidation. The reporting currency of the Company is the U.S. dollar.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires the Company's management to make judgments, assumptions and estimates that affect the amounts reported in its financial statements and the accompanying notes. The accounting policies that reflect the Company's more significant estimates and judgments and that the Company believes are the most critical to aid in fully understanding and evaluating its reported financial results are the valuation of stock options, valuation of Series C Perpetual Preferred Stock and Series D Perpetual Stock, valuation of hybrid instruments designated at fair value option ("FVO"), valuation of warrant liability, acquired in-process research and development ("IPR&D"), useful lives assigned to long-lived assets, impairment assessment of intangible assets, valuation adjustments for excess and obsolete inventory, allowance for doubtful accounts, deferred taxes and valuation allowances on deferred tax assets, evaluation and measurement of contingencies, and recognition of revenue, including estimates for product returns. Those estimates could change, and as a result, actual results could differ materially from those estimates.

In March 2020, the World Health Organization declared the COVID-19 outbreak to be a pandemic. During the year ended December 31, 2021, the Company’s financial results were not significantly affected by the COVID-19 outbreak. The Company has considered all information available as of the date of issuance of these financial statements and the Company is not aware of any specific events or circumstances that would require an update to its estimates or judgments, or a revision to the carrying value of its assets or liabilities. These estimates may change as new events occur and additional information becomes available. The extent to which the COVID-19 outbreak affects the Company’s future financial results and operations will depend on future developments which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity of the outbreak, and current or future domestic and international actions to contain and treat it. For a discussion of risks of COVID-19 relating to the Company’s business, see “Item 1A. - Risk Factors- Risks Related to Our Business- The novel coronavirus global pandemic could adversely impact our business, including our supply chain, clinical trials and commercialization of Mytesi and Canalevia.”

Cash

The Company’s cash on deposit may exceed United States federally insured limits at certain times during the year. The Company maintains cash accounts with certain major financial institutions in the United States. The Company does not have cash equivalents as of December 31, 2021 and 2020.

Accounts Receivable

Accounts receivable is recorded net of allowances for discounts for prompt payment and credit losses. The Company estimates an allowance for credit losses by considering factors such as historical experience, credit quality, the age of the accounts receivable balances, and current economic conditions that may affect a customer’s ability to pay. The corresponding expense for the credit loss allowance is reflected in general and administrative expenses. The credit loss allowance was immaterial as of December 31, 2021 and 2020.

Concentrations

Cash is the financial instrument that potentially subjects the Company to a concentration of credit risk as cash is deposited with banks and cash balances are generally in excess of Federal Deposit Insurance Corporation (“FDIC”) insurance limits.

For the years ended December 31, 2021 and 2020, substantially all of the Company’s revenue was derived from the sale of Mytesi. In looking at sales by the Company to distributors whose net revenue percentage of total net revenue was equal to or greater than 10%, for fiscal years 2021 and 2020, the Company earned Mytesi revenue primarily from three and one major pharmaceutical distributor(s) located in the United States, respectively. Revenue earned from each major customer as a percentage of total revenue is as follows:

	Year Ended December 31,	
	2021	2020
Customer 1	73 %	97 %
Customer 2	11 %	— %
Customer 3	12 %	— %

The Company is subject to credit risk from its accounts receivable related to its sales. The Company generally does not perform evaluations of customers' financial condition and generally does not require collateral. Accounts receivable balance of the significant customers as a percentage of total accounts receivable is as follows:

	<u>December 31,</u>	
	<u>2021</u>	<u>2020</u>
Customer 1	16 %	95 %
Customer 2	37 %	— %
Customer 3	37 %	— %

The Company is subject to concentration risk from its suppliers. The Company sources raw material used to produce the active pharmaceutical ingredient (“API”) in Mytesi from two suppliers and is dependent on a single third-party contract manufacturer for the supply of API in Mytesi and a single third-party contract manufacturer as well for the supply of finished products for commercialization.

Other Risks and Uncertainties

The Company’s future results of operations involve a number of risks and uncertainties. Factors that could affect the Company’s future operating results and cause actual results to vary materially from expectations include, but are not limited to, rapid technological change, obtaining second source suppliers, regulatory approval from the FDA or other regulatory authorities, the results of clinical trials and the achievement of milestones, market acceptance of the Company’s product candidates, competition from other products and larger companies, protection of proprietary technology, strategic relationships and dependence on key individuals.

Fair Value

The Company’s financial instruments include accounts receivable, accounts payable, accrued liabilities, warrant liability, operating lease liability, equity-linked financial instruments, and debt. The recorded carrying amount of accounts receivable, accounts payable and accrued liabilities reflect their fair value due to their short-term nature. Other financial liabilities are initially recorded at fair value, and subsequently measured at either fair value or amortized cost using the effective interest method. See Note 4 for the fair value measurements.

Fair Value Option

ASC 825-10, *Financial Instruments*, provides FVO election that allows companies an irrevocable election to use fair value as the initial and subsequent accounting measurement attribute for certain financial assets and liabilities. ASC 825-10 permits entities to elect to measure eligible financial assets and liabilities at fair value on an ongoing basis. Unrealized gains and losses on items for which the FVO has been elected are reported in earnings. The decision to elect the FVO is determined on an instrument-by-instrument basis, must be applied to an entire instrument and is irrevocable once elected. Assets and liabilities measured at fair value pursuant to ASC 825-10 are required to be reported separately from those instruments measured using another accounting method. In accordance with the options presented in ASC 825-10, the Company elected to present the aggregate of fair value and non-fair-value amounts in the same line item in the consolidated balance sheets and parenthetically disclose the amount measured at fair value in the aggregate amount.

Inventory

Inventory is stated at the lower of cost or net realizable value. Cost is determined using the first-in, first-out method. Cost is initially recorded at the invoiced amount of raw materials or API, including the sum of qualified expenditures and charges in bringing the inventory to its existing condition and location. The Company calculates inventory valuation adjustments when conditions indicate that net realizable value is less than cost due to physical deterioration, usage, obsolescence, reductions in estimated future demand or reduction in selling price. Inventory write-downs are measured as the difference between the cost of inventory and net realizable value.

Property and Equipment

Land is stated at cost, reflecting fair value of the property at July 31, 2017, the date of the Napo merger. Equipment is stated at cost, net of accumulated depreciation. Equipment begins to be depreciated when it is placed into service. Depreciation is calculated using the straight-line method over estimated useful lives ranging between 3 to 10 years.

Expenditures for repairs and maintenance of assets are charged to expense as incurred. Costs of major additions and betterments are capitalized and depreciated on a straight-line basis over their estimated useful lives. Upon retirement or sale, the cost and related accumulated depreciation of assets disposed of are removed from the accounts and any resulting gain or loss is included in the consolidated statements of operations.

Long-Lived Assets

The Company regularly reviews the carrying value and estimated lives of all of its long-lived assets, including property and equipment and definite-lived intangible assets, to determine whether indicators of impairment exist that warrant adjustments to carrying values or estimated useful lives. The determinants used for this evaluation include management's estimate of the asset's ability to generate positive income from operations and positive cash flow in future periods as well as the strategic significance of the assets to the Company's business objectives. If the Company determines that an impairment trigger has been met, the Company evaluates the realizability of its long-lived assets (asset group) based on a comparison of projected undiscounted cash flows from use and eventual disposition with the carrying value of the related asset. Any write-downs (which are measured based on the difference between the fair value and the carrying value of the asset) are treated as permanent reductions in the carrying amount of the assets (asset group). Based on this evaluation, the Company believes that, as of each of the balance sheet dates presented, none of the Company's long-lived assets were impaired. The Company's had no impairment of long-lived assets for the years ended December 31, 2021 and 2020.

Indefinite-lived Intangible Assets

Acquired IPR&D are intangible assets acquired in the July 2017 Napo merger. Under ASC 805, IPR&D are initially recognized at fair value and classified as indefinite-lived assets until the successful completion or abandonment of the associated research and development efforts. During the development period, these assets will not be amortized as charges to earnings; instead, these assets will be tested for impairment on an annual basis or more frequently if impairment indicators are identified. An impairment loss is measured based on the excess of the carrying amount over the asset's fair value. The Company recorded an impairment of zero for the years ended December 31, 2021 and 2020.

Leases

The Company accounts for its leases in accordance with ASC 842, *Leases*.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present. Operating lease liabilities and their corresponding right-of-use assets are recorded based on the present value of lease payments over the expected lease term. Because the interest rate implicit in lease contracts is typically not readily determinable, the Company utilizes its incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term, an amount equal to the lease payments in a similar economic environment. Certain adjustments to the right-of-use asset may be required for items such as initial direct costs paid or incentives received.

Operating Lease

The Company had a non-cancelable operating lease with CA-Mission Street Limited Partnership for its offices in San Francisco, California, through September 30, 2020. The lease agreement called for monthly base rents

between \$38,000 and \$41,000 over the term of the lease. The lease agreement was not renewed during the year ended December 31, 2020.

The Company entered into a sublease agreement with Peacock Construction, Inc., a California corporation, for office space located in San Francisco, California. The term of the sublease began on August 31, 2020 and expired on May 31, 2021. The rent under the sublease was \$15,000 per month beginning October 1, 2020, which includes operating expenses and taxes. On October 1, 2020, the Company transitioned its operations from its existing premises to the sublease premises, which the Company expects will serve as its principal administrative headquarters. The Company elected not to apply the recognition requirements to short-term leases, and instead recognize the lease payments in profit or loss on a straight-line basis over the lease term. As a result, there was no right-of-use asset and lease liability recognized related to the sublease.

In April 2021, the Company entered into an office lease agreement with M & E, LLC, a California Limited Liability Company, to lease approximately 10,526 square feet of office space located in San Francisco, California, inclusive of office space currently covered under the sublease agreement with Peacock. The term of the lease began on September 1, 2021 and will expire on August 31, 2024, unless earlier terminated. The base rent under the lease will be \$42,000 monthly for the first 12 months, \$43,000 monthly for the next 12 months and \$45,000 for the last twelve months.

In December 2021, the Company entered into the first amendment to the lease with M & E, LLC whereby the commencement date of one of the leased premises was modified to March 1, 2022. Accordingly, the expiration of the lease was extended to February 28, 2025. The base rent under the original agreement remained the same but will be due starting March 1, 2022. In addition, the rent for one of the leased premises being occupied by the Company will continue to be \$21,000 until the new commencement date.

Research and Development Expense

Research and development expense consists of expenses incurred in performing research and development activities including related salaries, clinical trial and related drug and non-drug product costs, contract services and other outside service expenses. Research and development expense is charged to operating expense in the period incurred.

Clinical Trial Accruals

Clinical trial costs are a component of research and development expenses. The Company accrues and expenses clinical trial activities performed by third parties based upon actual work completed in accordance with agreements established with clinical research organizations and clinical sites. The Company determines the costs to be recorded based upon validation with the external service providers as to the progress or stage of completion of trials or services and the agreed-upon fee to be paid for such services.

Revenue Recognition

The Company recognizes revenue in accordance with ASC Topic 606, *Revenue from Contracts with Customers* (“ASC 606”).

The Company’s policy typically permits returns if the product is damaged, defective, or otherwise cannot be used when received by the customer if the product has expired. Returns are accepted for product that will expire within six months or that have expired up to one year after their expiration dates. Estimates for expected returns of expired products are based primarily on an ongoing analysis of our historical return patterns.

The Company recognizes revenue in accordance with the core principle of ASC 606 or when there is a transfer of control of promised goods or services to customers in an amount that reflects the consideration that the Company expects to be entitled to in exchange for those goods or services.

The Company recognizes the incremental costs of obtaining a contract as an expense when incurred if the amortization period of the asset that the Company otherwise would have recognized is one year or less.

The Company does not adjust the amount of consideration for the effects of a significant financing component if, at contract inception, the expected period between the transfer of promised goods or services and customer payment is one year or less.

The Company has elected to treat shipping and handling activities as fulfillment costs.

Additionally, the Company elected to record revenue net of sales and other similar taxes.

Contracts – Cardinal Health

Effective January 16, 2019, Napo engaged Cardinal Health SPS as its exclusive third-party logistics distribution agent for commercial sales for the Company's Mytesi product and to perform certain other services which include, without limitation, storage, distribution, returns, customer support, financial support, Electronic Data Interchange and system access support (the "Exclusive Distribution Agreement").

On September 3, 2021, the Company ended its engagement with Cardinal Health as its exclusive title model customer for commercial sales and fully implemented its limited distribution Specialty Pharmacy model. Cardinal Health continues to provide third-party logistics services for Mytesi.

The Company's Neonorm and botanical extract products are primarily sold to distributors, who then sell the products to the end customers. Since 2014, the Company has entered into several distribution agreements with established distributors such as Animart, Vedco, VPI, RJ Matthews, Covetrus, and Stockmen Supply to distribute the Company's products in the United States, Japan, and China. The distribution agreements and the related purchase order together meet the contract existence criteria under ASC 606-10-25-1. The Company sells directly to its customers without the use of an agent.

Performance obligations

For animal products sold by the Company, the single performance obligation identified is the Company's promise to transfer the Company's animal products to distributors based on specified payment and shipping terms in the arrangement. Product warranties are assurance-type warranties that do not represent a performance obligation. For the Company's human product, Mytesi, the single performance obligation identified above is the Company's promise to transfer Mytesi to Cardinal Health, based on specified payment and shipping terms as outlined in the Exclusive Distribution Agreement.

Transaction price

For contracts with Cardinal Health, the transaction price is the amount of consideration to which the Company expects to collect in exchange for transferring promised goods or services. The transaction price of Mytesi and Neonorm is the Wholesaler Acquisition Cost ("WAC"), net of discounts, returns, and price adjustments.

Allocate transaction price

For contracts with Cardinal Health, the entire transaction price is allocated to the single performance obligation contained in each contract.

Revenue recognition

For contracts with Cardinal Health, for the Company, a single performance obligation is satisfied at a point in time, upon the FOB terms of each contract when control, including title and all risks, has transferred to the customer.

Disaggregation of Product Revenue

Human

Sales of Mytesi are recognized as revenue at a point in time when the products are delivered to the wholesaler. Net revenues from the sale of Mytesi were \$3.3 million and \$9.3 million for the years ended December 31, 2021 and 2020, respectively.

Animal

The Company recognized Neonorm revenues of \$62,000 and \$76,000 for the years ended December 31, 2021 and 2020, respectively. Revenues are recognized at a point in time upon shipment, which is when title and control is transferred to the buyer. Sales of Neonorm Calf and Foal to distributors are made under agreements that may provide distributor price adjustments and rights of return under certain circumstances.

Contracts – Atlas Sciences, LLC

Effective April 15, 2020, the Company entered into a patent purchase agreement with Atlas Sciences, LLC (“Atlas”), pursuant to which Atlas agreed to purchase certain patents and patent applications relating to Napo’s NP-500 drug product candidate (the “Patent Rights”) for an upfront cash payment of \$1.5 million.

Concurrent with the Patent Rights sale, the Company entered into a license agreement with Atlas (the “License Agreement”), pursuant to which Atlas granted the Company an exclusive 10-year license to use the Patent Rights and improvements thereon to develop and commercialize NP-500 in all territories worldwide except Greater China (i.e., China, Hong Kong, Taiwan and Macau), inclusive of the right to sublicense NP-500 development and commercialization rights (“The License”).

Included in the arrangement with Atlas, the Company was obligated to initiate a proof of concept Phase 2 study of NP-500 under an investigational new drug (“IND”) application with the U.S. Food and Drug Administration or an IND-equivalent dossier under appropriate regulatory authorities (the “Phase 2 study”) within nine months of April 15, 2020. The Company would incur a trial delay fee if the Company failed to initiate the Phase 2 study by this date, for any reason, including the timely receipt of adequate funding to initiate the Phase 2 study.

In September 2020, the Company made the decision not to initiate the Phase 2 study and negotiated the payment of the trial delay fee of \$2.5 million and terminated this obligation in the contract. Because of this decision, the allocated transaction price for that performance obligation will not be recognized as revenue.

The Company derecognized \$1.5 million in deferred revenue and the excess of the trial delay fee was recognized in general and administrative expenses in the consolidated statements of operations. The payment was deemed not in exchange for a distinct good or service.

The Company evaluated the nature of the consideration payable to the customer and the rights and obligations in the related contract and concluded that the excess payment or loss should be presented as part of the general and administrative expenses due to the following factors:

- No revenue has been recognized from the transaction as the performance obligation was not satisfied.
- The Company settled the trial delay fee in full in October 2020, which constitutes termination of the customer relationship considering that Atlas cannot compel the Company or has no recourse to force the Company to initiate the Phase 2 Study. The Company does not anticipate future revenue contract with Atlas.

- The trial delay fee is a penalty in its economic term, subject to accounting for contingencies and provisions under relevant authoritative guidance.

In October 2020, the Company entered into a fee settlement agreement with Atlas pursuant to which the Company agreed to issue 2,000,000 shares of common stock and pre-funded warrants to purchase 6,218,954 shares of common stock as complete settlement and satisfaction of the trial delay fee of \$2.5 million that the Company incurred pursuant to its license agreement with Atlas dated April 15, 2020. The pre-funded warrants were exercisable immediately and could be exercised at any time until all of the pre-funded warrants were exercised in full. The nominal exercise price of each pre-funded warrant was \$0.0001. The settlement resulted in a loss of \$1.0 million. As of December 31, 2020, the shares of common stock have all been issued and the pre-funded warrants have all been exercised.

Contracts – Specialty Pharmacies

Effective October 1, 2020, the Company engaged a private company as its third-party logistics distribution agent for commercial sales of the Company’s Mytesi product. Under the Specialty Product Distribution Agreement, the Company shall supply the products to the private company’s specialty pharmacies, through a designated wholesaler, in such amounts as may be ordered. There is no minimum purchase or inventory requirement. The specialty pharmacies were authorized distributors of record for all National Drug Codes (“NDCs”) of Mytesi.

Effective April 20, 2021, the Company engaged another private company as an authorized specialty pharmacy provider of Mytesi. Under the Specialty Pharmacy Distribution and Services Agreement, the private company shall sell and dispense the Mytesi directly ordered from the Company at the agreed price to patients within the territories identified in the agreement.

The two contracts with the two specialty pharmacies were combined into one portfolio of contract as they share similar characteristics.

Performance obligations

The single performance obligation is the Company’s promise to transfer Mytesi to specialty pharmacies, based on specified payment and shipping terms outlined in the agreements.

Transaction price

The transaction price is the amount of consideration to which the Company expects to collect in exchange for transferring the promised goods or services. The transaction price of Mytesi is the WAC, net of estimated discounts, returns, and price adjustments.

Allocate transaction price

The entire transaction price is allocated to the single performance obligation contained in each contract.

Revenue recognition

The single performance obligation is satisfied at a point in time, upon the free on board (“FOB”) terms of each contract, when control, including title and all risks, has transferred to the customer.

Product Revenue

Sales of Mytesi are recognized as revenue at a point in time when the products are delivered to the specialty pharmacies. Net revenues from the sale of Mytesi to the specialty pharmacies were \$993,000 and zero for the years ended December 31, 2021 and 2020, respectively.

Collaboration Revenue

Revenue recognition for collaboration agreements requires significant judgment. The Company's assessments and estimates are based on contractual terms, historical experience and general industry practice. Revisions in these values or estimations have the effect of increasing or decreasing collaboration revenue in the period of revision.

On September 24, 2018, the Company entered into a Distribution, License and Supply Agreement ("License Agreement") with Knight Therapeutics ("Knight"). The License Agreement has a term of 15 years (with automatic renewals) and provides Knight with an exclusive right to commercialize current and future Jaguar human health products (including crofelemer, Lechlemer, and any product containing a proanthocyanidin or with an anti-secretory mechanism) in Canada and Israel. Knight forfeited its right of first negotiation for expansion to Latin America. Under the License Agreement, Knight is responsible for applying for and obtaining necessary regulatory approvals in the territory of Canada and Israel, as well as marketing, sales and distribution of the licensed products. Knight will pay a transfer price for all licensed products, and upon achievement of certain regulatory and sales milestones, the Company may receive payments from Knight in an aggregate amount of up to approximately \$18 million payable throughout the initial 15-year term of the agreement. The Company did not have any license revenues for the years ended December 31, 2021 and 2020.

Modifications to Liability-classified Instruments

In accounting for debt modifications and exchange transactions, it is the Company's policy to first determine whether it qualifies as a Troubled Debt Restructuring ("TDR") pursuant to the guidance provided in ASC 470-60. A debt modification or exchange transaction that is not within the scope of the ASC 470-60 is accounted for under ASC 470-50 to determine if the transaction is a mere modification or an extinguishment.

The Company amended the terms of its October 2020 Purchase Agreement and Exchange Note 2 in the year 2021 (see Note 8). The Company also amended the terms of its Exchange Note 1, Exchange Note 2, March 2020 Purchase Agreement, and Series D Perpetual Preferred Stock in the year 2020 (see Note 8).

Modifications to Equity-classified Instruments

In accounting for modifications of equity-classified warrants, it is the Company's policy to determine the impact by analogy to the share-based compensation guidance of ASC 718, *Compensation - Stock Compensation* ("ASC 718"). The model for a modified share-based payment award that is classified as equity and remains classified in equity after the modification is addressed in ASC 718-20-35-3. Pursuant to that guidance, the incremental fair value from the modification is recognized as an expense in the statements of operations to the extent the modified instrument has a higher fair value; however, in certain circumstances, such as when an entire class of warrants are modified, the measured increase in fair value may be more appropriately recorded as a deemed dividend, depending upon the nature of the warrant modification.

The Company modified certain equity-classified warrants in the year 2020 (see Note 9). The Company did not modify any equity-classified warrants in the year 2021.

In accounting for amendments to equity-classified preferred stock, it is the Company's policy to measure the impact by analogy to ASC 470-50 in determining if such an amendment is an extinguishment or a modification. If the amendment results in an extinguishment, the Company follows the SEC staff guidance in ASC 260-10-S99-2 and ASC 470-20. If the amendment results in a modification, the Company follows the model in either ASC 718 or ASC 470-50, depending on the nature of the amendment.

The Company modified the terms of its Series B Convertible Preferred Stock and Series C Perpetual Preferred Stock in the year 2020 (see Note 10). The Company did not modify any equity-classified preferred stock in the year 2021.

Stock-Based Compensation

The Company's Stock Incentive Plan (see Note 12) provides for the grant of stock options, restricted stock and restricted stock unit awards. The Company measures stock awards granted to employees, non-employees and directors at estimated fair value on the date of grant and recognizes the corresponding compensation expense of the awards, net of estimated forfeitures, over the requisite service periods, which correspond to the vesting periods of the awards. Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. The Company issues stock awards with only service-based vesting conditions, and records compensation expense for these awards using the straight-line method.

The Company uses the grant date fair market value of its common stock to determine the grant date fair value of options granted to employees, non-employees and directors. The Company measures and recognizes compensation expense for all stock options and restricted stock units ("RSUs") granted to its employees and directors based on the estimated fair value of the award on the grant date. The Company uses the Black-Scholes valuation model to estimate the fair value of stock option awards. The fair value is recognized as expense, net of estimated forfeitures, over the requisite service period, which is generally the vesting period of the respective award, on a straight-line basis. The Company believes that the fair value of stock options granted to non-employees is more reliably measured than the fair value of the services received. The determination of the grant date fair value of options using an option pricing model is affected by the Company's estimated Common Stock fair value and requires management to make a number of assumptions including the expected life of the option, the volatility of the underlying stock, the risk-free interest rate and expected dividends.

The Company estimates the fair value of stock options using the Black-Scholes option valuation model. The fair value of employee stock options is being amortized on a straight-line basis over the requisite service period of the awards. The fair market value of common stock is based on the closing price of the Company's common stock as reported on the date of the grant.

Income Taxes

The Company uses the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial reporting and the tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is provided when it is more likely than not that some portion or all of a deferred tax asset will not be realized.

The Company has adopted the provisions of ASC 740, *Income Taxes Related to Uncertain Tax Positions*. Under these principals, tax positions are evaluated in a two-step process. The Company first determines whether it is more-likely-than-not that a tax position will be sustained upon examination. If a tax position meets the more-likely-than-not recognition threshold, it is then measured to determine the amount of benefit to be recognized in the financial statements. The tax position is measured as the largest amount of benefit that has a greater than 50 percent likelihood of being realized upon ultimate settlement.

Foreign Currency Remeasurement and Translation

The functional currency of Napo Therapeutics is Euro. The Company follows ASC 830, *Foreign Currency Matters* ("ASC 830"). ASC 830 requires the assets, liabilities, and results of operations of a foreign operation to be measured using the functional currency of that foreign operation. Exchange gains or losses from remeasuring transactions and monetary accounts in a currency other than the functional currency are included in current earnings.

For certain subsidiaries, translation adjustments result from the process of translating the functional currency of subsidiary financial statements into the U.S. Dollar reporting currency. These translation adjustments are reported separately and accumulated in the consolidated balance sheets as a component of accumulated other comprehensive loss.

Comprehensive Loss

The Company follows ASC 220, *Comprehensive Income*, which establishes standards for reporting and displaying comprehensive income and its components (revenue, expenses, gains and losses) in a full set of general-purpose financial statements.

For the year ended December 31, 2020, the comprehensive loss was equal to the net loss; therefore, a separate statement of comprehensive loss was not included in the accompanying consolidated financial statements.

For the year ended December 31, 2021, the amount of other comprehensive loss was only de minimis; hence, a separate statement of comprehensive loss was not also included in the accompanying consolidated financial statements.

Basic and Diluted Net Loss Per Common Share

Basic net loss per common share is computed by dividing net loss attributable to common stockholders for the year by the weighted-average number of common shares outstanding during the year. Diluted net loss per share is computed by dividing the net loss attributable to common stockholders for the year by the weighted-average number of common shares, including potential dilutive shares of common stock assuming the dilutive effect of potential dilutive securities. For years in which the Company reports a net loss, diluted net loss per common share is the same as basic net loss per common share, because their impact would be anti-dilutive to the calculation of net loss per common share. Diluted net loss per common share is the same as basic net loss per common share for the years ended December 31, 2021 and 2020.

Recent Accounting Pronouncements

Recently Adopted Accounting Pronouncements

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*, which is intended to simplify various aspects related to accounting for income taxes. The standard also removes certain exceptions to the general principles in Topic 740 and clarifies and amends existing guidance to improve consistent application. The Company adopted the standard on January 1, 2021. The adoption of this standard did not have a material effect on the Company's consolidated financial statements and related disclosures.

Recently Issued Accounting Pronouncements Not Yet Adopted

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*. The main objective of the standard is to provide financial statement users with more decision-useful information about the expected credit losses on financial instruments and other commitments to extend credit held by a reporting entity at each reporting date. To achieve this objective, the amendments in this standard replace the incurred loss impairment methodology in current GAAP with a methodology that reflects expected credit losses and requires consideration of a broader range of reasonable and supportable information to inform credit loss estimates. The update is effective for the Company beginning January 1, 2023 with early adoption permitted. The Company is still evaluating the impact of the adoption of this standard.

In August 2020, the FASB issued ASU 2020-06, *Debt – Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging – Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity*, which simplifies the accounting for certain financial instruments with characteristics of liabilities and equity, including convertible instruments and contracts on an entity's own equity. The pronouncement is effective for the Company beginning January 1, 2022 with early adoption permitted. The Company is still evaluating the impact of the adoption of this standard.

In May 2021, the FASB issued ASU 2021-04, *Issuer's Accounting for Certain Modification or Exchanges of Freestanding Equity-Classified Written Call Options* – a consensus of the FASB Emerging Issues Task Force. The ASU provides a principles-based framework to determine whether an issue should recognize the modification or exchange as an adjustment to equity or an expense. The amendments in the update are effective for all entities for fiscal years beginning January 1, 2022, including interim periods within those fiscal years with early adoption permitted. The Company is still evaluating the impact of the adoption of this standard.

Reclassification of Prior Year Presentation

Certain prior period amounts of cash flows from financing activities in the consolidated statements of cash flows have been reclassified within the same category of cash flow activity to be consistent with the current period presentation. There were no reclassifications to other categories of cash flow activity and the reclassification did not impact the profit or loss during the prior period.

3. Napo Therapeutics Subsidiary

As discussed in Note 1 – Organization and Business, Napo EU completed a merger with Dragon SPAC on November 3, 2021, with Dragon SPAC as the surviving entity. Dragon SPAC took over by operation of law all the assets, rights, reasons, and actions as well as liabilities, obligations, and commitments of Napo EU. The merged entity was named Napo Therapeutics. Napo Therapeutics now operates as a subsidiary of Napo, with Napo owning 99% of Napo Therapeutics' equity. This transaction was accounted for as a formation of a new subsidiary of the Company.

4. Fair Value Measurements

ASC 820 "Fair Value Measurements," defines fair value, establishes a framework for measuring fair value under U.S. GAAP and enhances disclosures about fair value measurements. Fair value is defined under ASC 820 as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value under ASC 820 must maximize the use of observable inputs and minimize the use of unobservable inputs. The standard describes a fair value hierarchy based on three levels of inputs, of which the first two are considered observable and the last unobservable, that may be used to measure fair value which are the following:

- Level 1 – Observable inputs such as quoted prices (unadjusted) for identical instruments in active markets.
- Level 2 – Observable inputs such as quoted prices for similar instruments in active markets, quoted prices for identical or similar instruments in markets that are not active, or model-derived valuations whose significant inputs are observable.
- Level 3 – Unobservable inputs that reflect the reporting entity's own assumptions.

The following tables set forth the fair value of the Company's consolidated financial instrument that was measured at fair value on a recurring basis as of December 31, 2021 and 2020:

(in thousands)	December 31, 2021			
	Level 1	Level 2	Level 3	Total
Warrant liability	\$ —	\$ —	\$ 1	\$ 1
Streeterville note	—	—	7,818	7,818
Total fair value	\$ —	\$ —	\$ 7,819	\$ 7,819

(in thousands)	December 31, 2020			
	Level 1	Level 2	Level 3	Total
Warrant liability	\$ —	\$ —	\$ 179	\$ 179
Total fair value	\$ —	\$ —	\$ 179	\$ 179

The change in the estimated fair value of the Level 3 liability is summarized below:

(in thousands)	Year Ended December 31, 2021	
	Warrant liability	Streeterville note
Beginning fair value of Level 3 liability	\$ 179	\$ —
Additions	1,462	6,000
Exercises	(1,775)	—
Change in fair value	135	1,818
Ending fair value of Level 3 liability	\$ 1	\$ 7,818

Warrant Liability

The warrants associated with the Level 3 warrant liability were the November 2016 Series A Warrants and the October 2018 Underwriter Warrants, which, at December 31, 2021, were valued at zero and \$1,000, respectively, in the Company's consolidated balance sheet. The warrants associated with the Level 3 warrant liability activity for the year ended December 31, 2020 were the November 2016 Series A Warrants, the October 2018 Underwriter Warrants, and the May 2020 Series 3 Warrants, which at December 31, 2020 were valued at zero, \$4,000, and \$175,000, respectively in the Company's consolidated balance sheet.

The November 2016 Series A Warrants

The Series A warrant valuation of zero at December 31, 2021 was computed using the Black-Scholes-Merton pricing model using a stock price of \$1.04, a strike price of \$2,363 per share, an expected term of 0.41 years, volatility of 89% and a risk-free discount rate of 0.19%. The Series A warrant valuation of zero at December 31, 2020 was computed using the Black-Scholes-Merton pricing model using a stock price of \$2.45, a strike price of \$2,363 per share, an expected term of 1.41 years, volatility of 148% and a risk-free discount rate of 0.13%. The net change in the fair value of the warrants was zero for the year ended December 31, 2021.

The October 2018 Underwriter Warrants

The October 2018 Underwriter Warrants valuation of \$1,000 at December 31, 2021 was computed using the Black-Scholes-Merton pricing model using a stock price of \$1.04, a strike price of \$158 per share, an expected term of 1.75 years, volatility of 180% and a risk-free discount rate of 0.65%. The October 2018 Underwriter Warrants valuation of \$4,000 at December 31, 2020 was computed using the Black-Scholes-Merton pricing model using a stock price of \$2.45, a strike price of \$158 per share, an expected term of 2.76 years, volatility of 156% and a risk-free discount rate of 0.17%. The net decrease in the fair value of the warrants of \$3,000 for the year ended December 31, 2021 was recorded as a gain in the change in fair value of financial instruments and hybrid instrument designated at FVO in the consolidated statements of operations.

The May 2020 Series 3 Warrants

There were no outstanding May 2020 Series 3 Warrants as of December 31, 2021. The May 2020 Series 3 Warrants valuation of \$175,000 at December 31, 2020 was computed using the Black-Scholes-Merton pricing model using a stock price of \$2.45, a strike price of \$0.00 per share, an expected term of 4.89 years, volatility of 142% and a risk-free discount rate of 0.36%. In January 2021, an investor received 135,416 Series 3 Warrants for the exercise of 135,416 2019 Bridge Note Warrants in accordance with the May 2020 Modification of the 2019 Bridge Note Warrants and Inducement Offer. The fair value of these Series 3 Warrants was \$1.5 million on the issuance date. For the year ended December 31, 2021, certain holders of the Series 3 Warrants agreed to exercise total of 206,915 shares for a 1-for-1 exchange of common shares in an Alternate Cashless Exercise. The aggregate fair value of the common stock issued upon the exercise of the Series 3 Warrants as of the exercise date was \$1.8 million. The net increase in the fair value of the warrants of \$138,000 for the year ended December 31, 2021 was recorded as a loss in the change in fair value of financial instruments and hybrid instrument designated at FVO in the consolidated statements of operations.

Streeterville Note

The fair value of the Streeterville Note at January 13, 2021, date of issuance and as of December 31, 2021 amounting to \$6.0 million and \$7.8 million, respectively, were based on the weighted average discounted expected future cash flows representing the terms of the note, discounting them to their present value equivalents. This was classified as Level 3 fair values in the fair value hierarchy due to the use of unobservable inputs, including the Company's own credit risk.

The Company determined and performed the valuations of the Streeterville Note with the assistance of an independent valuation service provider. On a quarterly basis, the Company considers the main Level 3 inputs used as follows:

- Discount rate for the Streeterville note was determined using a comparison of various effective yields on bonds as of the valuation date.
- Market indications for vouchers, which affect the Return Bonus from the sale of Tropical Disease Priority Review Voucher ("TDPRV")
- Weighted probability of cash outflows was estimated based on the entity's knowledge of the business and how the current economic environment is likely to impact the timing of the cash outflows, attributed to the different repayment features of the note.

The following table summarizes the quantitative information about the significant unobservable inputs used in Level 3 fair value measurement:

<u>Unobservable Inputs</u>	<u>Range of Inputs (probability-weighted average)</u>		<u>Relationship of unobservable inputs to fair value</u>
	<u>2021</u>	<u>2020</u>	
Risk Adjusted Discount Rate . . .	6.78% - 21.31% (21.31%)	N/A	If discount rate is adjusted to total of additional 100 basis points (bps), fair value would have decreased by \$367,000.
Sales Proceeds: Amount of comparable TDPRV	\$67.5 million to \$350.0 million (\$100.0 million)	N/A	If discount rate is adjusted to total deduction of 100 bps, fair value would have increased by \$367,000. If expected cash flows by management considered the lowest amount of market indications for vouchers, FV would have decreased by \$1.2 million.

Range of Probability for Timing of Cash Flows: Variations of the terms and conditions of the timing of cash flows, including settlement of the note principal, interest, penalties, and acceleration clause.	0.35% - 46.06%	N/A	<p>If expected cash flows by management considered the highest amount of market indications for vouchers, FV would have increased by \$9.5 million.</p> <p>If expected cash flows by management considered the scenario with the least amount of indicated value, FV would have decreased by \$236,000.</p> <p>If expected cash flows by management considered the scenario with the greatest amount of indicated value, FV would have increased by \$2.3 million.</p>
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Fair Value Option

Beginning January 1, 2021, the Company elected to apply the FVO accounting to selected financial instruments to align the measurement attributes of those instruments under U.S. GAAP and to simplify the accounting model applied to those financial instruments. The Company elected to apply FVO accounting to the entire class of hybrid instruments, including structured notes, of which there are assessed embedded derivatives that would be eligible for bifurcation. Changes in the fair value of FVO assets and liabilities as well as the mark-to-market adjustment on the entire class of hybrid instruments, including derivatives and the net realized gains or losses on these instruments are reported in the change in fair value of financial instruments and hybrid instrument designated at FVO in the consolidated statements of operations.

For the year ended December 31, 2021, the Company did not note any fair value movement on FVO liabilities attributable to any instrument-specific credit risk, which should be recorded in other comprehensive income (loss).

Hybrid Instruments

The Company elected to apply FVO accounting to all of the hybrid instruments issued, including structured notes. The valuation of the hybrid instruments is predominantly driven by the derivative features embedded within the instruments. The Company determined and performed the valuations of the hybrid instruments with the assistance of an independent valuation service provider. The valuation methodology utilized is consistent with the income approach for estimating the fair value of the interest-bearing portion of the instrument and the related derivatives. Cash flows of the hybrid instruments in their entirety, including the embedded derivatives, are discounted at an appropriate rate for the applicable duration of the instrument. Interest on the interest-bearing portion of the instrument that is held to maturity is aggregated as gain (loss) on instruments designated at fair value and related derivatives in the change in fair value of financial instruments and hybrid instruments designated at FVO in the consolidated statements of operations.

The following table summarizes the fair value and unpaid principal balance for items the Company accounts under FVO:

(in thousands)	<u>Fair value</u>	<u>Unpaid Principal Balance</u>	<u>Fair Value Over (Under) Unpaid Principal Balance</u>
At December 31, 2021			
Hybrid Instrument:			
Streeterville note	\$ 7,818	\$ 6,000	\$ 1,818

5. Related Party Transactions

Management Services Agreement

In March 2018, concurrent with the issuance of the Company's Series A Convertible Preferred Stock to Sagard Capital Partners, L.P. ("Sagard Capital"), the Company entered into a Management Services Agreement with Sagard Capital. Under the agreement, Sagard Capital was to provide consulting and management advisory service to the Company from March 2018 through March 2021. These services include assistance with strategic planning regarding the Company's commercial strategy, research and due diligence regarding human resource activities, and strategic advice in financial matters. In consideration for such services, the Company paid Sagard Capital an annual fee of \$450,000, with total fees over the term of the agreement not to exceed \$1.4 million. On September 1, 2020, in concurrence with other transactions by and between the Company, Chicago Venture Partners, L.P. ("CVP" or "Chicago Venture Partners") and its affiliates, and Sagard Capital, the Company and Iliad Research and Trading, L.P. ("Iliad"), a Utah limited partnership affiliated with CVP, agreed to issue 2,289,474 shares of the Company's Common Stock to Sagard Capital pursuant to the Stock Plan Agreement for termination of the Management Services Agreement in lieu of payment of \$1.1 million in accrued consulting and management fees. For the years ended December 31, 2021 and 2020, total fees incurred were zero and \$338,000, respectively. As of December 31, 2021 and 2020, the Company had a balance of zero due to Sagard Capital.

Letter of Credit

On March 24, 2020, the Company entered into a letter of credit agreement with Dr. Charles Conte, the brother of Lisa Conte, the Company's President, CEO and member of the Company's board of directors ("BOD"), pursuant to which the Company replaced then existing letter of credit in the amount of \$475,000 entered into on August 28, 2018 by the Company with CA-Mission Street Partnership to satisfy the letter of credit requirement in the Company's office lease agreement with a new letter of credit in the amount of \$475,000. In consideration of the new letter of credit, the Company paid Dr. Conte an amount equal to \$10,000 per month and agreed to reimburse up to \$7,500 for reasonable out-of-pocket expenses incurred. For the years ended December 31, 2021 and 2020, total fees incurred were zero and \$65,000, respectively. In October 2020, CA Mission Street Partnership released the letter of credit agreement with Dr. Conte pursuant to the expiration and termination of the office lease agreement between the Company and CA-Mission Street Partnership on September 30, 2020. In October 2020, the Company paid Dr. Conte a prorated amount due through the effective date of the release of the letter of credit of \$7,000. As of December 31, 2021 and 2020, the Company had a balance of zero due to Dr. Conte.

BOD Cash Compensation

Effective May 2021, the Company will pay the BOD cash compensation on a quarterly basis based on the Director Compensation Program for 2021. For the year ended December 31, 2021, the Company paid approximately \$124,000 cash compensation to its directors.

6. Commitments and Contingencies

Commitments

Leases

On August 28, 2018, the Company entered into an office lease extension agreement for approximately 6,311 square feet of office space in San Francisco, CA. The term of the lease began on September 1, 2018 and expired on September 30, 2020. An existing shareholder provided a standby letter of credit in the amount of \$475,000 to the lessor as collateral for the full performance by the Company of all of its obligations under the lease. In consideration of the Letter of Credit, the Company issued the shareholder a five-year warrant (see Note 9) to purchase 9,580 shares of the Company's voting common stock.

On August 31, 2020, the Company entered into an office sublease of approximately 5,263 square feet of office space in San Francisco. The term of the sublease expired on May 31, 2021. The rent sublease is \$15,000 per month beginning on October 1, 2020, which includes operating expenses and taxes. The Company recognizes rent expense on a straight-line basis over the non-cancellable lease period. Rent expense, included in general and administrative expenses in the consolidated statements of operations, was \$75,000 and \$45,000 for the year ended December 31, 2021 and 2020, respectively. As of December 31, 2021, there were no remaining commitments under the lease.

On April 6, 2021, the Company entered into an office lease agreement of approximately 10,526 square feet of office space in San Francisco, inclusive of office space covered under the previous sublease agreement. The term of the lease began on September 1, 2021 and will expire on August 31, 2024, unless terminated earlier. The lease has an early occupancy provision which entitled the Company to use a portion of the leased premises on June 1, 2021, free of rent obligation. In addition, the Company has the option to extend the lease for one three-year period after the expiration date. This option was not included as part of the lease term as the Company was not reasonably certain to exercise it, hence the lease term only includes the noncancellable period of three years plus the period of early occupancy.

The base rent under the lease were \$42,000 monthly for the first 12 months, \$43,000 monthly for the next 12 months and \$45,000 for the last twelve months. The lease agreement only contained one lease component, that is, the lease of the office space. Non-lease components such as payment of building operating costs and share in real property taxes were accounted for separately and were not considered as part of the total lease payments. The lease was classified as an operating lease.

On December 24, 2021, the Company entered into the first amendment of the lease of office space in San Francisco. The expiration of the lease was extended to February 28, 2025 due to the change in the commencement date of one of the leased premises to March 1, 2022. The base rent under the lease amendment remained the same but will only be due starting March 1, 2022. The rent in one of the leased premises currently being occupied by the Company was and will still be \$21,000 until the new commencement date. The lease amendment constituted a lease modification where the Company remeasured the original lease liability using a discount rate determined at the effective date of the modification and the amount of remeasurement of the lease liability was recognized as an adjustment to the corresponding right-of-use asset without affecting profit or loss.

The table below provided additional details of the office space lease presented in the consolidated balance sheet:

(in thousands)	December 31,	
	2021	2020
Operating lease - right-of-use asset	\$ 1,084	\$ —
Operating lease liability, current	240	—
Operating lease liability, net of current portion	919	—
Total	\$ 1,159	\$ —
Weighted-average remaining life (years)	3.21	—
Weighted-average discount rate	21.10%	—

Lease cost included in general and administrative expenses in the consolidated statements of operations for the year ended December 31, 2021 was approximately \$144,000.

For the year ended December 31, 2021 and 2020, cash paid for operating lease liabilities recognized under operating cash flows amounted to \$105,260 and \$357,079, respectively. Non-cash investing and financing activities for the year ended December 31, 2021 and 2020 include addition to right-of-use asset obtained from new operating

liabilities amounting to \$1.1 million and zero, respectively, and lease modification amounting to \$91,243 and zero, respectively.

The following table summarizes the undiscounted cash payment obligations for the operating lease liability:

<u>(in thousands)</u>	December 31,	
	2021	2020
2021.....	\$ —	\$ —
2022.....	463	—
2023.....	518	—
2024.....	534	—
2025.....	89	—
Total undiscounted operating lease payments	1,604	—
Imputed interest expenses	(445)	—
Total operating lease liability	1,159	—
Less: Operating lease liability, current.....	240	—
Operating lease liability, net of current portion	<u>\$ 919</u>	<u>\$ —</u>

On October 10, 2021, the Company also entered into a short-term office lease in Milan, Italy. The term of the lease began on November 1, 2021 and will expire on April 30, 2022, subject to automatic renewal equal to the present term until terminated by mutual agreement. The Company recognizes rent expense on a straight-line basis over the non-cancellable lease period. Rent expense, included in general and administrative expenses in the consolidated statements of operations, was \$23,000 and zero for the years ended December 31, 2021 and 2020, respectively.

Purchase Commitment

On September 3, 2020, the Company entered into a manufacturing and supply agreement (the “Agreement”) with Glenmark Life Sciences Limited (“Glenmark”), pursuant to which Glenmark will continue to serve as the Company’s manufacturer of crofelemer for use in Mytesi, the Company’s human prescription drug product approved by the U.S. Food and Drug Administration, and for other crofelemer-based products manufactured by the Company or its affiliates for human or animal use. The term of the Agreement is approximately 2.5 years (i.e., until March 31, 2023) and may be extended for successive two-year renewal terms upon mutual agreement between the parties thereto. Pursuant to the terms of the Agreement, Glenmark will supply crofelemer to the Company. The Agreement contains provisions regarding the rights and responsibilities of the parties with respect to manufacturing specifications, forecasting and ordering, delivery arrangements, payment terms, confidentiality and indemnification, as well as other customary provisions. The Agreement includes a commitment for the purchase from Glenmark of a minimum quantity of 300 kilograms of crofelemer per year, pro-rated for partial years, where the Company may be obligated to pay any shortfall. Either party may terminate the Agreement for any reason with 12 months prior written notice to the other party. In addition, either party may terminate the Agreement upon written notice as a result of a material breach of the Agreement that remains uncured for a period of 90 days. If the Company terminates the Agreement as a result of a material breach caused by Glenmark, the Company will not be obligated to pay for any minimum quantity shortfall.

Master Services Agreement (“MSA”)

On June 24, 2019, the Company entered into an MSA for clinical research organization services (the “2019 MSA”) and a service order under such 2019 MSA with Integrium, LLC (“Integrium”). The service order supports the Company’s study to evaluate the effect of Mytesi on gastrointestinal microbiome in people living with HIV. The 2019 MSA will terminate upon the satisfactory performance of all services to be provided thereunder unless earlier terminated by the parties.

On October 5, 2020, the Company entered into another MSA for clinical research organization services (the “2020 MSA”) and a service order under such 2020 MSA with Integrium. The service order covers the Company’s planned upcoming pivotal Phase 3 clinical trial for cancer-therapy related diarrhea. As consideration for its services,

the Company will pay Integrium a total amount of up to approximately \$12.4 million that will be paid over the term of the engagement and based on the achievement of certain milestones. The 2020 MSA will terminate upon the satisfactory performance of all services to be provided thereunder unless earlier terminated by the parties. For the year ended December 31, 2021 and 2020, the Company paid Integrium \$1.7 million and \$529,000, respectively.

Asset Transfer and Transition Commitment

On September 25, 2017, Napo entered into the Termination, Asset Transfer and Transition Agreement dated September 22, 2017 with Glenmark. As a result of the agreement, Napo now controls commercial rights for Mytesi for all indications, territories and patient populations globally, and also holds commercial rights to the existing regulatory approvals for crofelemer in Brazil, Ecuador, Zimbabwe and Botswana. In exchange, Napo agrees to pay Glenmark 25% of any payment it receives from a third party to whom Napo grants a license or sublicense or with whom Napo partners in respect of, or sells or otherwise transfers any of the transferred assets, subject to certain exclusions, until Glenmark has received a total of \$7.0 million. For the year ended December 31, 2021 and 2020, the Company paid Glenmark \$2.0 million and zero, respectively.

Revenue Sharing Commitment Update

On December 14, 2017, the Company announced its entry into a collaboration agreement with Seed Mena Businessmen Services LLC (“SEED”) for Equilevia™, the Company's non-prescription, personalized, premium product for total gut health in equine athletes. According to the terms of the Agreement, the Company will pay SEED 15% of total revenue generated from any clients or partners introduced to the Company by SEED in the form of fees, commissions, payments or revenue received by the Company or its business associates or partners, and the agreed-upon revenue percentage increases to 20% after the first million dollars of revenue. In return, SEED will provide the Company access to its existing United Arab Emirates (“UAE”) network and contacts and assist the Company with any legal or financial requirements. The agreement became effective on December 13, 2017 and will continue indefinitely until terminated by either party pursuant to the terms of the Agreement. No payments have been made to date.

Legal Proceedings

On July 20, 2017, a putative class action complaint was filed in the United States District Court, Northern District of California, Civil Action No. 3:17-cv-04102, by Tony Plant (the “Plaintiff”).

The Company answered the complaint on August 2, 2019; the answer denied the material allegations of the second amended complaint. Following the completion of document discovery, the parties engaged in a mediation that resulted in an agreement in principle to settle the litigation on a class-wide basis for \$2.6 million.

On May 27, 2021, the court gave the final approval to the proposed settlement and the entire settlement consideration will be provided by the Company’s director and officer liability insurance carrier. Under the loss recovery model in ASC 450 and in reference to ASC 410, the ultimate net income effect of the recognized loss and the insurance proceeds directly related to the recognized loss is zero.

As of December 31, 2021 and 2020, the Company concluded not to record any loss contingency and insurance recovery.

Settlement of Underwriter Fee

In August 2018, the Company entered into an agreement with an underwriter pursuant to which the underwriter would aid the Company in identifying certain financing transactions, in exchange for a percentage fee of any such financing and warrants. In the first quarter of 2020, the Company and the underwriter agreed on a final settlement for the underwriter services comprised of a cash payment, warrants and common stock. The cash payment amount totalled \$387,000, of which \$202,000 had been paid in 2019, and \$185,000 was paid in 2020. The total warrant issuance payment consisted of the Company issuing 365 equity-classified warrants to the underwriter in 2018

and, in 2020, issuing an additional 33,593 equity-classified warrants (see Note 9) to the underwriter to purchase shares of common stock at an exercise price of \$7.50 per share. The common stock issuance payment consisted of the Company issuing 33,333 shares of the Company's common stock to the underwriter with a value of \$45,000 in 2020. The Company classified the cash payments, warrant and commons stock issuance payments as issuance costs in the consolidated statements of stockholders' equity.

Severance Agreements

In June 2020, the Company entered into certain agreements relating to the payment of severance and other benefits to executive officers of the Company, the severance agreements provide for compensation and benefits if the executive officer is subject to (a) a termination of employment by the Company without cause or (b) a good reason termination, within three months following a change in control.

Contingencies

From time to time, the Company maybe a party to various legal actions, both inside and outside the U.S., arising in the ordinary course of its business or otherwise. The Company accrues amounts, to the extent they can be reasonably estimated, that the Company believes will result in a probable loss (including, among other things, probable settlement value), to adequately address any liabilities related to legal proceedings and other loss contingencies. A loss or a range of loss is disclosed when it is reasonably possible that a material loss will incur and can be estimated, or when it is reasonably possible that the amount of a loss, when material, will exceed the recorded provision. The Company did not have any material accruals for any currently active legal action in its consolidated balance sheets as of December 31, 2021, as the Company could not predict the ultimate outcome of these matters, or reasonably estimate the potential exposure.

7. Balance Sheet Components

Inventory

Inventory at December 31, 2021 and 2020 consisted of the following:

<i>(in thousands)</i>	December 31,	
	2021	2020
Raw Material	\$ 1,248	\$ 1,321
Work in Process	2,760	1,026
Finished Goods	892	435
Inventory	<u>\$ 4,900</u>	<u>\$ 2,782</u>

Property and Equipment, net

Property and equipment at December 31, 2021 and 2020 consisted of the following:

<i>(in thousands)</i>	December 31,	
	2021	2020
Land	\$ 396	\$ 396
Lab equipment	424	418
Clinical equipment	65	65
Software	63	63
Total property and equipment at cost	<u>948</u>	<u>942</u>
Accumulated depreciation	<u>(298)</u>	<u>(265)</u>
Property and equipment, net	<u>\$ 650</u>	<u>\$ 677</u>

Depreciation and amortization expense was \$33,000 and \$40,000 for the years ended December 31, 2021 and 2020, respectively.

Intangible assets, net

Intangible assets, net of amortization, at December 31, 2021 and 2020 consisted of the following:

<u>(in thousands)</u>	December 31,	
	2021	2020
Developed technology	\$ 25,000	\$ 25,000
Accumulated developed technology amortization	(7,361)	(5,694)
Developed technology, net	17,639	19,306
In-process research and development	4,800	4,800
In process research and development, net	4,800	4,800
Trademarks	300	300
Accumulated trademark amortization	(88)	(69)
Trademarks, net	212	231
Total intangible assets, net	<u>\$ 22,651</u>	<u>\$ 24,337</u>

Amortization expense of finite-lived intangible assets was \$1.7 million for the years ended December 31, 2021 and 2020.

The following table summarizes the Company’s estimated future amortization expense of intangible assets with finite lives as of December 31, 2021:

<u>(in thousands)</u>	Amounts
2022	\$ 1,687
2023	1,687
2024	1,687
2025	1,687
2026	1,687
Thereafter	9,416
	<u>\$ 17,851</u>

Accrued Liabilities

Accrued liabilities at December 31, 2021 and 2020 consisted of the following:

<u>(in thousands)</u>	December 31,	
	2021	2020
Accrued interest	\$ 3,456	\$ 696
Accrued legal costs	414	291
Accrued chargebacks and discounts	335	736
Accrued local tax	285	—
Accrued vacation	281	277
Accrued distributor services fees	250	1,314
Accrued audit and tax services	167	70
Accrued payroll and commission	120	43
Accrued payroll tax	58	57
Accrued consulting	47	31
Accrued other	1,704	978
Total	<u>\$ 7,117</u>	<u>\$ 4,493</u>

Other accrued liabilities as of December 31, 2021 largely consist of other accrued interests, contract fees and scientific advisory board fees while other accrued liabilities as of December 31, 2020 significantly comprise of contract fees and scientific advisory board fees.

8. Debt

Notes payable at December 31, 2021 and 2020 consisted of the following:

<u>(in thousands)</u>	<u>December 31,</u>	
	<u>2021</u>	<u>2020</u>
Royalty Interest	\$ 37,000	\$ 30,000
Streeterville Note	7,818	—
Insurance Financing	335	95
Tempesta Note	350	450
Oasis Secured Borrowing	—	1,822
Exchange Note 2	—	1,525
	<u>45,503</u>	<u>33,892</u>
Less: unamortized discount and debt issuance costs	<u>(17,297)</u>	<u>(17,682)</u>
Note payable, net of discount	<u>\$ 28,206</u>	<u>\$ 16,210</u>
Notes payable - non-current, net	<u>\$ 25,022</u>	<u>\$ 12,421</u>
Notes payable - current, net	<u>\$ 3,184</u>	<u>\$ 3,789</u>

Future maturities of the notes payable as of December 31, 2021 are as follows:

<u>(in thousands)</u>	<u>Amounts</u>
Years ended December 31,	
2022	\$ 3,183
2023	13,493
2024	10,959
2025	6,187
2026	3,863
	<u>37,685</u>
Less: unamortized discount and debt issuance costs	<u>(17,297)</u>
Total	<u>\$ 20,388</u>

Future maturities are based on contractual minimum payments. Timing of maturities may fluctuate based on future revenue.

Sale of Future Royalty Interest

March 2020 Purchase Agreement

In March 2020, the Company entered into a royalty interest purchase agreement (the “March 2020 Purchase Agreement”) with Iliad, pursuant to which the Company sold to Iliad a royalty interest entitling Iliad to receive \$500,000 of future royalties on sales of Mytesi and certain up-front license fees and milestone payments from licensees and/or distributors (the “Royalty Repayment Amount”) for an aggregate purchase price of \$350,000.

Until such time as the Royalty Repayment Amount has been paid in full, the Company will pay Iliad ten percent (10%) of the Company’s Net Sales on Included Products and ten percent (10%) of worldwide revenues related to upfront licensing fees and milestone payments from licensees and/or distributors, but specifically excluding licensing fees and/or milestone payments that are reimbursements of clinical trial expenses (the “Royalty Payments”). Beginning on the six-month anniversary of the Purchase Price Date and continuing until the 12-month anniversary of

the Purchase Price Date, the monthly Royalty Payment shall be the greater of (a) \$25,000, and (b) the actual Royalty Payment amount Iliad is entitled to for such month. Beginning on the 12-month anniversary of the Purchase Price Date and continuing until the Revenue Repayment Amount has been paid in full, the monthly Royalty Payment shall be the greater of (a) \$44,000 and (b) the actual Royalty Payment amount Iliad is entitled to for such month.

The Royalty Interest amount of \$500,000 is classified as debt, net of a \$150,000 discount. Under ASC 470-10-35-3, royalty payments to Iliad will be amortized under the interest method per ASC 835-30. Because there is no set interest rate, and because the royalty payments are variable, the discount rate is variable. After each royalty payment, the Company will use a prospective method to determine a new discount rate based on the revised estimate of remaining cash flows. The new rate is the discount rate that equates the present value of the revised estimate of remaining cash flows with the carrying amount of the debt, and it will be used to recognize interest expense for the remaining periods. At issuance, based on projected cash outflows from future revenue streams, the discount rate was 105%.

On July 10, 2020, the Company and Iliad entered into an amendment to the March 2020 Purchase Agreement to which the parties agreed that no royalty payments or other payment will be due prior to December 10, 2020. The Royalty Payments shall resume as of December 10, 2020, which Royalty Payment will cover Net Sales on Included Products and licensing fees and milestone payments for the month of November. In consideration of the amendment, the balance of the Royalty Repayment Amount as of July 10, 2020 was increased by 10%. All other terms remain unchanged. This amendment resulted in the Company accounting for the transaction as a TDR, under which the carrying amount of the debt remained unchanged but interest expense is computed using a new effective rate that equates the present value of future cash payments specified by the new terms with the carrying amount of the debt. Subsequent to March 2020, the Company had paid \$283,000 of the \$500,000 Royalty Interest Amount.

In November 2020, the Company and Iliad entered into an exchange agreement pursuant to which the Company issued 1,314,974 shares of common stock in exchange for the outstanding balance of the debt as of November 16, 2020. The exchange agreement was accounted for as a TDR.

As of December 31, 2020, the carrying amount of the debt was zero.

October 2020 Purchase Agreement

On October 8, 2020, the Company entered into another royalty interest purchase agreement (the "October 2020 Purchase Agreement") with Iliad, pursuant to which the Company sold to Iliad a royalty interest entitling Iliad to receive \$12.0 million of future royalties on sales of Mytesi and certain up-front license fees and milestone payments from licensees and/or distributors (the "Royalty Repayment Amount") for an aggregate purchase price of \$6.0 million.

Until such time as the Royalty Repayment Amount has been paid in full, the Company will pay Iliad 10% of the Company's net sales on included products and 10% of worldwide revenues related to upfront licensing fees and milestone payments from licensees and/or distributors, but specifically excluding licensing fees and/or milestone payments that are reimbursements of clinical trial expenses (the "Royalty Payments"). Beginning on the six-month anniversary of the delivery of the October 2020 Purchase Agreement to the Company (the "Purchase Price Date") and continuing until the 12-month anniversary of the Purchase Price Date, the monthly Royalty Payment shall be the greater of (a) \$250,000, and (b) the actual Royalty Payment amount Iliad is entitled to for such month. Beginning on the 12-month anniversary of the Purchase Price Date and continuing until 18-month anniversary of the Purchase Price Date, the monthly Royalty Payment shall be the greater of (a) \$400,000 and (b) the actual Royalty Payment amount Iliad is entitled to for such month. Beginning on the 18-month anniversary of the Purchase Price Date and continuing until 24-month anniversary of the Purchase Price Date, the monthly Royalty Payment shall be the greater of (a) \$600,000 and (b) the actual Royalty Payment amount Iliad is entitled to for such month. Beginning on the 24-month anniversary of the Purchase Price Date and continuing until the Royalty Repayment Amount has been paid in full, the monthly Royalty Payment shall be the greater of (a) \$750,000, and (b) the actual Royalty Payment amount Iliad is entitled to for such month.

The Royalty Interest amount of \$12.0 million is classified as debt, net of a \$6.0 million discount. Under ASC 470-10-35-3, royalty payments to Iliad will be amortized under the interest method per ASC 835-30. Because there is no set interest rate, and because the royalty payments are variable, the discount rate is variable. After each royalty payment, the Company will use a prospective method to determine a new discount rate based on the revised estimate of remaining cash flows. The new rate is the discount rate that equates the present value of the revised estimate of remaining cash flows with the carrying amount of the debt, and it will be used to recognize interest expense for the remaining periods. At issuance, based on projected cash outflows from future revenue streams, the discount rate was 34.51%.

Pursuant to the October 2020 Purchase Agreement, if the weekly volume weighted average price (“VWAP”) of the Company’s common stock is not equal or greater than the minimum VWAP of \$0.9105 at least twice during each calendar month during the six-month period beginning on November 1, 2020, then the Royalty Repayment Amount will be automatically be increased by \$6.0 million at the end of such six-month period. During the observation period starting November 1, 2020, the Company’s weekly VWAP failed to reach the minimum VWAP of \$0.9105 and on November 13, 2020, the Company concluded that the contingent clause has been met, warranting an additional \$6.0 million Royalty Repayment Amount, to be added to the outstanding balance commencing on May 10, 2021 for the purpose of cash interest calculation. The change in the Royalty Repayment Amount was accounted for as a debt modification and resulted in a new discount rate of 45.42%.

On April 13, 2021, the Company entered into an exchange agreement with Iliad, pursuant to which the parties agreed to partition \$3.0 million from the original outstanding balance of the royalty interest. The parties further agreed to exchange the partitioned royalty for 588,235 shares of the Company’s common stock. The exchange consisted of Iliad surrendering the partitioned royalty in exchange for the exchange shares. The exchange agreement was accounted for as a modification and resulted in a new discount rate of 77.09%. As of December 31, 2021, the forecasted future revenues changed which resulted to a new discount rate of 74.59%.

Interest expense for the years ended December 31, 2021 and 2020 was \$4.2 million and \$543,000, respectively. As of December 31, 2021 and 2020, the carrying value of the debt was \$6.3 million and \$6.6 million, respectively.

December 2020 Purchase Agreement

On December 22, 2020, the Company entered into a royalty interest purchase agreement (the “December 2020 Purchase Agreement”) with Irving Park Capital, LLC (“Irving”), pursuant to which the Company sold to Irving a royalty interest entitling Irving to receive \$12.0 million of future royalties on sales of Mytesi and certain up-front license fees and milestone payments from licensees and/or distributors (the “Royalty Repayment Amount”) for an aggregate purchase price of \$6.0 million.

Until such time as the Royalty Repayment Amount has been paid in full, the Company will pay Irving 10% of the Company’s Net Sales on Included Products and 10% of worldwide revenues related to upfront licensing fees and milestone payments from licensees and/or distributors, but specifically excluding licensing fees and/or milestone payments that are reimbursements of clinical trial expenses (the “Royalty Payments”). Beginning on the payment start date and continuing until the 12-month anniversary of the Purchase Price Date, the monthly Royalty Payment shall be the greater of (a) \$750,000, and (b) the actual Royalty Payment amount Irving is entitled to for such month.

The Royalty Interest amount of \$12.0 million is classified as debt, net of a \$6.0 million discount. Under ASC 470-10-35-3, royalty payments to Irving will be amortized under the interest method per ASC 835-30. Because there is no set interest rate, and because the royalty payments are variable, the discount rate is variable. After each royalty payment, the Company will use a prospective method to determine a new discount rate based on the revised estimate of remaining cash flows. The new rate is the discount rate that equates the present value of the revised estimate of remaining cash flows with the carrying amount of the debt, and it will be used to recognize interest expense for the remaining periods. At issuance, based on projected cash outflows from future revenue streams, the discount rate was 23.70%. As of December 31, 2021, the forecasted future revenues changed which resulted to a new discount rate of 23.28%.

Interest expense for the years ended December 31, 2021 and 2020 was \$2.9 million and \$14,000, respectively. As of December 31, 2021 and 2020, the carrying value of the debt was \$7.6 million and \$6.0 million, respectively.

March 2021 Purchase Agreement

On March 8, 2021, the Company entered into a purchase agreement (the “March 2021 Purchase Agreement”) with Streeterville Capital, LLC (“Streeterville”), a company affiliated with CVP, pursuant to which the Company sold a royalty interest entitling Streeterville to \$10.0 million and any interest, fees, and charges as royalty repayment amount for an aggregate purchase price of \$5.0 million. Interest will accrue on the royalty repayment amount at a rate of 5% per annum, compounding quarterly, and will increase to 10% per annum, compounding quarterly on the 12-month anniversary of the closing date.

The Company will be obligated to make minimum royalty payments on a monthly basis beginning at the earlier of (a) 36 months following the closing date or (b) 30 days following the satisfaction of all existing royalties to Streeterville, and its affiliates namely Iliad and Irving, but not earlier than 18 months following the closing date in an amount equal to the greater of (i) \$250,000 beginning on the royalty payment start date and continuing until either the royalty repayment amount has been paid in full or the 6-month anniversary of the royalty payment start date, \$400,000 beginning on the 6-month anniversary of the royalty payment start date and continuing until either the royalty repayment amount has been paid in full or the 12-month anniversary of the royalty payment start date, \$600,000 beginning on the 12-month anniversary of the royalty payment start date and continuing until either the royalty repayment amount has been paid in full or the 18-month anniversary of the royalty payment start date, \$750,000 beginning on the 18-month anniversary of the royalty payment start date and continuing until the royalty repayment amount has been paid in full, and (ii) 10% of the Company’s net sales on included products, 10% of worldwide revenues related to upfront licensing fees and milestone payments from licensees and/or distributors but specifically excluding licensing fees and/or milestone payments that are reimbursements of clinical trial expenses or associated with the license of Included Products from the Company to Napo Therapeutics, including but not limited to the upfront fee payable by Napo Therapeutics to Napo for included products and Crofelemer for other indications; and 50% of royalties collected from licenses of the included products to third parties.

The Royalty Interest amount of \$10.0 million is classified as debt, net of a \$5.0 million discount, at initial recognition. Under ASC 470-10-35-3, royalty payments to Streeterville will be amortized under the interest method per ASC 835-30. Because there is no set interest rate, and because the royalty payments are variable, the discount rate is variable. After each royalty payment, the Company will use a prospective method to determine a new discount rate based on the revised estimate of remaining cash flows. The new rate is the discount rate that equates the present value of the revised estimate of remaining cash flows with the carrying amount of the debt, and it will be used to recognize interest expense for the remaining periods. At issuance, based on projected cash outflows from future revenue streams, the discount rate was 19.36%. As of December 31, 2021, the forecasted future revenues changed which resulted to a new discount of 19.14%.

Interest expense for the year ended December 31, 2021 was \$1.2 million. As of December 31, 2021, the carrying value of the debt was \$5.8 million.

Streeterville Note

On January 13, 2021, the Company issued a secured promissory note to Streeterville in the original principal amount of \$6.2 million for an aggregate purchase price of \$6.0 million. The Company will use the proceeds to fund development of the Company’s NP-300 (lechlemer) drug product candidate for the indication of the symptomatic relief of diarrhea from cholera and general corporate purposes, including the Company’s product pipeline activities. The note is due after four years and bears interest at 3.25% per annum. Interest on the note is payable annually in advance by adding the interest charge for each upcoming year to the outstanding balance on the date each such interest charge is accrued. The Company also paid \$25,000 to cover legal fees, accounting costs, due diligence, monitoring and other transaction costs incurred in connection with the issuance of the note. The first year of prepaid interest and the transaction expenses are included in the original principal amount.

At any time following the occurrence of a trial failure which refers to any of the following: (i) the Company abandons the clinical trial with lechlemer for an indication for the symptomatic relief of infectious diarrhea for cholera; (ii) the Company fails to start the Phase 1 clinical trial of lechlemer for the symptomatic relief of infectious diarrhea for cholera by July 1, 2022; or (iii) the Company fails to meet all primary endpoints in the pivotal trials of Lechlemer for the symptomatic relief of infectious diarrhea for cholera with statistical significance, Streeterville may elect to increase the outstanding balance as of the date of the trial failure by 25% without acceleration (the "Trial Failure Effect"). If Streeterville elects to apply the Trial Failure Effect, it reserves the right to declare the outstanding balance immediately due and payable at any time. As of December 31, 2021, no trial failure occurred.

Streeterville is entitled to a maximum of 18% and a minimum of 1% of the gross proceeds received by the Company from the sale of TDPRV (the "Return Bonus"). The Return Bonus percentage is reduced pro rata based on the percentage of the original principal balance of the note that has been repaid as of the date of the sale of the TDPRV. Even if the note has been paid in full at the time of the sale of the TDPRV, the Company is still obliged to pay Streeterville a Return Bonus of 1%. If Streeterville applies the Trial Failure Effect, the Return Bonus will automatically be reduced to 1%. If the TDPRV has not been sold as of the day immediately preceding the maturity date of the note, the Return Bonus percentage will be fixed as of such date. As of December 31, 2021, the Company has not sold any TDPRV.

Beginning on the earlier of (a) 6 months after January 2021, and (b) initiation of human trials with lechlemer for symptomatic relief of infectious diarrhea for cholera, the Company may pay all or any portion of the outstanding balance earlier than it is due. In the event the Company elects to prepay all or any portion of the outstanding balance, it shall pay to Streeterville 112.5% of the portion of the outstanding balance the Company elects to prepay. The Company may not prepay the note without the Streeterville's consent on the date the last patient is enrolled in a pivotal trial.

After Streeterville becomes aware of the occurrence of any default, Streeterville may accelerate the note, with the outstanding balance becoming immediately due and payable in cash at the Mandatory Default Amount (i.e., the outstanding balance following the application of the Default Effect). Streeterville reserves the right to declare the outstanding balance immediately due and payable at any time following the default. Default Effect means multiplying the outstanding balance as of the date of default by 5% or 15% for each occurrence of default, capped at an aggregate of 25%, and then adding the resulting product to the outstanding balance. The percentage to be used depends on whether the default is viewed as minor or major as defined in the agreement. Furthermore, interest accrues on the outstanding balance beginning on the date of default at an interest rate equal to the lesser of 18% per annum or the maximum rate permitted under applicable law. As of December 31, 2021, no default has occurred.

In connection with the note issuance, the Company has entered into a security agreement with Streeterville, pursuant to which Streeterville will receive a first priority security interest in all existing and future lechlemer technology, and any TDPRV and the sale proceeds therefrom that may be granted to the Company by the FDA in connection with the development of lechlemer for the cholera indication. The Company also agreed, with certain exceptions, not to grant any lien on any of the collateral securing the note and not to grant any license under any of the intellectual property relating to such collateral. The grant of security interest has become effective upon the receipt of the Salix Waiver on April 6, 2021 in observance to the requirement of the settlement agreement previously entered by the Company with Salix Pharmaceuticals, Inc.

The Company irrevocably elected to initially and subsequently apply the FVO accounting to the entire note. The fair value at transaction date was equal to the cash proceeds received of \$6.0 million. The transaction expense of \$25,000 was recognized in profit and loss as incurred. The Company used the valuation report from an independent valuation service provided to measure the reporting date fair value of the note. At December 31, 2021, the fair value was determined to be \$7.8 million. For the year ended December 31, 2021, the net increase in the fair value of \$1.8 million was recorded as loss included in the change in fair value of financial instruments and hybrid instrument designated at FVO in the consolidated statements of operations.

Insurance Financing

Insurance Premium Financing

In May 2020, the Company entered into a financing agreement for \$873,000 for a portion of the Company's annual insurance premiums. The balance is due in monthly installments over nine months with an annual interest rate of 4.15%. The financing balance was zero and \$95,000 as of December 31, 2021 and 2020, respectively.

March 2021 First Insurance Financing

In March 2021, the Company entered into a premium finance agreement for \$98,000 with First Insurance Funding ("First Insurance") representing the unpaid balance of the total premiums, taxes, and fees of \$115,000 with an annual interest rate of 4.6%. The total finance charge was \$2,000. Payment of principal and interest is due in equal monthly installments over ten months. The Company granted and assigned First Insurance a first priority lien on and security interest in the financed policies and any additional premium required under the financed policies. Interest expense for the year ended December 31, 2021 was \$2,000. The financing balance was \$10,000 at December 31, 2021.

May 2021 First Insurance Financing

In May 2021, the Company entered into another premium finance agreement for \$1.1 million with First Insurance representing the unpaid balance of the total premiums, taxes, and fees of \$1.4 million with an annual interest rate of 4.15%. The total finance charge was \$21,000. Payment of principal and interest is due in equal monthly installments over ten months. Interest expense for the year ended December 31, 2021 was \$13,000. The financing balance was \$326,000 at December 31, 2021.

2019 Tempesta Note

In October 2019, the Company entered into a License Termination and Settlement Agreement with Dr. Michael Tempesta, pursuant to which certain royalty payment disputes between Napo and Tempesta were settled. Per the terms of the Agreement, Tempesta received \$50,000 in cash, an unsecured promissory note issued by the Company in the aggregate principal amount of \$550,000 and 13,333 shares of the Company's common stock in exchange for the cessation of all royalty payments by Napo to Dr. Tempesta under the License Agreements. The \$550,000 promissory note bears interest at the rate of 2.5% per annum and matures on March 1, 2025. The promissory note provides for the Company to make semiannual payments equal to \$50,000 plus accrued interest beginning on March 1, 2020 until the Note is paid in full. Interest expense for the year ended December 31, 2021 was \$10,000. At December 31, 2021 and 2020, the net carrying value of the Tempesta note was \$350,000 and \$450,000 respectively.

Oasis Secured Borrowing

The Purchase Agreement

In May 2020, the Company, entered into a one-year Accounts Receivable Purchase Agreement (the "Purchase Agreement") with Oasis Capital ("Oasis"), pursuant to which Oasis may from time to time at its discretion purchase accounts receivable of the Company on a recourse basis, at a purchase price equal to 37.5% of the face amount of the first purchase, and at a purchase price equal to 42.5% for subsequent purchased accounts ("Purchase Price"). With respect to purchased accounts, in the event that Oasis receives more than an amount equal to the sum of (i) the face amount of such purchased account multiplied by 0.0545 and (ii) the Purchase Price (such amount, the "Threshold Price") from collection on such purchased accounts, then Oasis will return any such excess overage amount (the "Overage") to the Company, as applicable, within five days after Oasis's receipt thereof.

In the event Oasis does not receive at least the Threshold Price for a purchased account on or before such account becomes due and payable, the Company will, at Oasis's election, be obligated to either (i) pay the difference

between the Threshold Price and the amount received by Oasis for such account (the “Shortfall”) within 30 days thereof, or (ii) assign or transfer to Oasis additional accounts receivable with a Purchase Price equal to (A) the Shortfall plus (B) an amount equal to 25% of the Shortfall (the “Additional Amount”).

The initial term of the Purchase Agreement is one year, which will automatically renew for successive one-year periods unless notice of non-renewal is provided by the Company at least 30 days prior to the expiration of a term. Notwithstanding the foregoing, either Oasis or the Company may terminate the Purchase Agreement on 60 days prior written notice. Under the Purchase Agreement, Oasis is entitled to a transaction fee of \$25,000 and may be entitled to additional transaction fees to the extent Oasis acquires additional accounts receivable under the Purchase Agreement, which fees will not exceed \$5,000 per transaction.

Per the Purchase Agreement, the Company will service and administer the purchased accounts receivable for Oasis. Oasis appointed the Company to be its agent and servicer for monitoring and collecting the accounts receivable subject to the terms of the Purchase Agreement. The Company will perform its duties in a commercially reasonable manner and agrees that Company will not commence any legal action with respect to such servicing and collection efforts and shall not terminate, discharge, discount or write off any accounts receivable without Oasis's prior written consent.

The Company, having determined that it did not meet the criteria per ASC 860-10-40-5 to account for the transactions under the Purchase Agreement as sales, accounts for such transactions as secured borrowings in accordance with ASC 860-30, “Transfers – Secured Borrowings and Collateral.”

During 2020, the Company made the required payments to Oasis for the first five purchases with total payments equalling to \$8.0 million and the related notes payable were extinguished.

In December 2020, for its sixth purchase under the terms of the Purchase Agreement, the Company received cash proceeds of \$1.6 million from Oasis (the “Tranche #6 Secured Note”). Oasis purchased accounts receivable with a carrying value of \$2.2 million, or gross accounts receivable of \$3.8 million net of chargebacks and discounts of \$1.6 million. The purchase was effectuated pursuant to an amended Assignment Agreement, effective December 3, 2020, between the Company and Oasis. The Maturity Date, by which date Oasis must collect the \$1.8 million Threshold Price, was February 10, 2021.

The Company recorded the sale to Oasis as a short-term secured borrowing with a principal amount of \$1.6 million, or \$1.8 million net of a \$213,000 discount. Though there was no stated interest rate, the effective interest rate at issuance was 128.4%. The Tranche #6 Secured Note had a maturity date of February 10, 2021, or earlier if the Threshold amount was received by Oasis prior to that date (payment of the Threshold amount is the maturity date). Accordingly, during the term of the Tranche #6 Secured Note, the effective interest rate is variable, dependent on the amount of any principal payment and payment dates. The secured borrowing gross balance remaining to be paid is \$1.8 million as of December 31, 2020.

In February 2021, the Company made its final required payment to Oasis under Tranche #6 Secured Note, with total payments equalling the \$1.8 million Threshold amount plus the transaction fee, and the Tranche #6 Secured Note was extinguished.

Exchange Note 2

In May 2019, CVP and the Company agreed to exchange two Napo convertible notes for a single CVP Note (“Exchange Note 1”). Per agreement, in consideration of the extension of the maturity date of Exchange Note 1 from December 31, 2019 to December 31, 2020, the Company issued a note (“Exchange Note 2”) with a principal balance of \$2.3 million. The maturity date of Exchange Note 2 is December 31, 2020, with an interest rate of 10%. Between September 2020 and November 2020, the Company and CVP entered into a series of note exchange agreements pursuant to which the Company made prepayments of principal and related accrued interest of an aggregate amount of \$5.0 million, in lieu of making cash payments to CVP on Exchange Note 1, by issuing a total of 6,740,573 shares of

the Company's common stock to CVP. The series of exchanges was accounted for as an extinguishment which resulted in a loss of \$560,000. As of December 31, 2020, the carrying value of Exchange Note 1 was zero.

In September 2020, the Company and CVP also entered into a global amendment agreement, pursuant to which the maturity date of Exchange Note 2 is extended to December 31, 2021. In consideration of CVP's grant of extension, together with the related fees and other accommodation set forth, principal debt was increased by 5% of the outstanding balance of Exchange Note 2, which was \$2.6 million as of the global amendment date. The global amendment requires redemption of Series D Perpetual Preferred Stock prior to payment of principal of Exchange Note 2. The Company determined the incremental value of cash flows amounting to \$228,000 with the assistance of an independent valuation service provider, based on weighted probability assumptions of various settlement conditions and penalties stipulated in the contract therein. The global amendment agreement was accounted for as a modification; hence a new effective rate was determined at the date of modification that equated the revised cash flows to the carrying amount of the note.

Pursuant to the global amendment agreement, the Company issued 842,500 shares of Series D Perpetual Preferred Stock. The Series D Perpetual Preferred shares were redeemable upon the option or discretion of the Company. The Series D Perpetual Preferred stockholders were entitled to receive 8% cumulative stock dividends, to be payable in arrears on a monthly basis for 24 consecutive months. Dividends payable on the Series D perpetual preferred shares shall be payable through the Company's issuance of Series D Perpetual Preferred share by delivering to each record holder the calculated number of payment-in-kind ("PIK") dividend shares. The Series D Perpetual Preferred shares were classified as liability and were measured at fair value using the income approach, which considered the weighted probability of discounted cash flows at various scenarios of redemption and perpetual holding of the shares. The Company determined the fair value of \$6.4 million at contract inception date with the assistance of an independent valuation service provider to be based on discounted cash flows representing the settlement value of the shares and cumulative dividends issued using an effective borrowing rate of 12% to 15% adjusted for counterparty and a maturity date of September 30, 2021. In consideration of the global amendment agreement, no principal payment shall be made to the Exchange Note 2 until the redemption of Series D Perpetual Preferred shares. Due to the restrictive nature of the timing of cash outflows in response to the settlement of the Exchange Note 2, Series D Perpetual Preferred shares were implicitly deemed to be mandatorily redeemable upon the ultimate settlement of the outstanding balance of Exchange Note 2. The shares were redeemable at \$8.00 per share on or before December 31, 2024, the date in which contractual cash outflows of the Exchange Note 2 require the entire settlement or redemption of the Series D Perpetual Preferred shares. In December 2020, the Company entered into a series of exchange agreements with a stockholder pursuant to which the Company agreed to issue a total of 5,296,623 shares of common stock in exchange for redeeming 859,348 shares of Series D Perpetual Preferred Stock. The series of exchanges was accounted for as an extinguishment which resulted to a loss amounting to \$1.3 million. This is included in loss on extinguishment of debt and conversion of Series D Perpetual Preferred Stock on the statement of operations as of December 31, 2020. As of December 31, 2021 and 2020, there were no Series D Perpetual Preferred shares outstanding.

In December 2020, the Company and CVP entered into a note exchange agreement to which the Company made a prepayment of principal amounting to \$1.0 million, in lieu of making cash payments to CVP on Exchange Note 2, by issuing 416,666 shares of the Company's common stock to CVP on December 31, 2020. The exchange agreement was accounted for as a modification.

In January 2021, the Company and CVP entered into another note exchange agreement to which the Company made a prepayment of the remaining outstanding balance of Exchange Note 2 amounting to \$1.8 million, in lieu of making cash payments to CVP by issuing 471,202 shares of the Company's common stock to CVP on January 4, 2021. The exchange was accounted for as debt extinguishment which resulted in a loss of \$753,000.

As of December 31, 2021 and 2020, the carrying value of Exchange Note 2, net of discount, was zero and \$1.4 million, respectively.

9. Warrants

The following table summarizes information about warrants outstanding and exercisable into shares of the Company's common stock for the years ended December 31, 2021 and 2020:

	December 31,	
	2021	2020
Warrants outstanding, beginning balance . .	2,401,818	6,473,964
Issuances	168,750	7,349,426
Exercises	(2,007,117)	(11,421,464)
Expirations and cancelations	—	(108)
Warrants outstanding, ending balance . . .	<u>563,451</u>	<u>2,401,818</u>

May 2020 Series 3 Warrants

In May 2020, concurrent with the May 2020 modification of the exercise price of the Series 1, Series 2 and Bridge Note Warrants and inducement offer, the Company issued unregistered Series 3 Warrants to purchase 2,890,284 shares of common stock. The Series 3 Warrants had an exercise price of \$1.59 per share and are exercisable beginning the earlier of (i) six months from their May 22, 2020 issuance date and (ii) receipt of the requisite Stockholder Approval (defined below), and expire five years thereafter. In addition to the fixed settlement method at \$1.59 per warrant share, the Series 3 Warrants had two contingent settlement methods: (i) if at the time of exercise there is no effective registration statement, then the holders of the 2,890,284 warrants may exercise the warrants in a "cashless exercise," under which the holders will receive the aggregate warrants less the number of warrants equal to the exercise price; or (ii) a cashless exercise feature wherein, regardless if there is an effective registration agreement, following the requisite Stockholder Approval, each such Series 3 Warrant will be exercisable into one share of common stock for no consideration (the "Alternate Cashless Exercise").

The Series 3 Warrants were initially valued at \$3.7 million using the Black-Scholes-Merton option pricing model as follows: probability-weighted exercise price of \$0.15 per share, stock price of \$1.32 per share, expected life of 5.50 years, volatility of 141%, and a risk-free rate of 0.34%. The Series 3 Warrants were classified as liabilities on the Company's consolidated balance sheets.

A Special Meeting of Stockholders was held on July 21, 2020, whereupon a proposal to approve the "Alternate Cashless Exercise" settlement method for the Series 3 Warrants was approved. In 2020, certain holders of the Series 3 Warrants agreed to exercise a total of 2,818,784 shares for a 1-for-1 exchange of common shares in an Alternate Cashless Exercise. The aggregate fair value of the common stock issued upon the exercise of the Series 3 Warrants as of the exercise date was \$6.1 million.

On January 8, 2021, in accordance with the May 2020 Modification of the 2019 Bridge Note Warrants and Inducement Offer, an investor received 135,416 Series 3 Warrants for the exercise of 135,416 2019 Bridge Note Warrants on the same date.

During the year ended December 31, 2021, certain holders of the Series 3 Warrants agreed to exercise a total of 206,915 shares for a 1-for-1 exchange of common shares in an Alternate Cashless Exercise. The aggregate fair value of the common stock issued upon the exercise of the Series 3 Warrants as of the exercise date was \$1.8 million.

A total of zero and 71,500 Series 3 Warrants were outstanding as of December 31, 2021 and 2020, respectively.

October 2018 Underwriter Warrants

In October 2018, in consideration of services provided leading up to the Company's October 2018 public offering, the Company issued warrants to various service providers to purchase an aggregate of 5,713 shares

of common stock at an exercise price of \$157.50 per common share. The warrants were classified as liabilities pursuant to ASC 815-40 as there was potential cash settlement.

April 2020 Underwriter Warrants

In April 2020, in consideration of the settlement of a dispute regarding underwriting fees (see Note 6), the Company issued warrants to purchase 33,592 shares of common stock at an exercise price of \$7.50 per common share. The warrants were valued at \$32,000 using the Black-Scholes-Merton option pricing model as follows: exercise price of \$7.50 per share, stock price of \$1.35 per share, expected life of 4.25 years, volatility of 141%, and a risk-free rate of 0.29%. The warrants were equity classified in the consolidated statements of stockholders' equity.

March 2019 Ladenburg Warrants

In March 2019, in consideration of services provided in the Company's March 2019 public offering of 6,339 common shares, the Company issued to Ladenburg Thalmann & Co. warrants to purchase an aggregate of 253 shares of common stock at an exercise price of \$52.50 per common share. The warrants were valued at \$13,000 using the Black-Scholes-Merton option pricing model as follows: exercise price of \$52.50 per share, stock price of \$56.70 per share, expected life of 5 years, volatility of 146%, and a risk-free rate of 2.21%. The warrants were equity classified in the consolidated statements of stockholders' equity.

March 2019 LOC Warrant

In March 2019, in consideration of a letter of credit cancellation related to the Company's office lease, the Company issued a warrant to purchase warrant shares equal to a fixed principal amount divided by a variable exercise price. The warrants were initially classified as liabilities pursuant to ASC 480-10 due to their debt-like nature. On July 23, 2019, upon the exercise price of the warrants becoming fixed, the warrants became exercisable into 15,250 shares of the Company's common stock and were reclassified to additional paid-in-capital with a fair value of \$71,000.

2019 Bridge Note Warrants

Between March 18, 2019 and June 26, 2019, concurrent to the Company entering into Promissory Notes of \$5.1 million, the Company issued twenty-one warrants to purchase warrant shares equal to a fixed principal amount divided by a variable exercise price. The warrants for all twenty-one Bridge Notes were initially liability classified pursuant to ASC 480-10 due to their debt-like nature. On July 23, 2019, upon the exercise price of the warrants becoming fixed, the warrants became exercisable into 927,083 shares of the Company's common stock and were reclassified to additional paid-in-capital with a fair value of \$4.3 million, calculated using the Black-Scholes-Merton pricing model using a stock price of \$5.19, a strike price of \$6.00 per share, an average expected term of 4.80 years, volatility of 146% and a risk-free discount rate of 1.76%.

February 2020 Modification of Certain 2019 Bridge Note Warrants

In February 2020, the Company entered into a warrant exercise agreement with a holder of its Bridge warrants, pursuant to which the holder agreed to exercise 83,333 Bridge warrants in consideration of the Company lowering the exercise price of the 83,333 warrants from \$6.00 to \$2.08. Upon exercise of the warrants, the Company received cash proceeds of \$173,000 and, in turn, issued 83,333 common shares. It is the Company's policy to determine the impact of modifications to equity-classified warrants by analogy to the share-based compensation guidance per ASC 718, Compensation – Stock Compensation. Pursuant to that guidance, and due to the modification being applicable only to a single holder of the Bridge warrants, the incremental increase of \$9,000 in fair value of the modified warrants was recorded as an expense in the consolidated statement of operations for the year ended December 31, 2020.

May 2020 Modification of the 2019 Bridge Note Warrants and Inducement Offer

In May 2020, the Company reduced the exercise price of all outstanding 2019 Bridge Note Warrants from \$6.00 per share to \$1.47 per share. The Company determined the impact of this modification to be an increase in the fair value of the warrants of \$166,000. Because the modification applied to the entire class of Bridge Note Warrant holders, the increase in fair value represented a deemed dividend to the entire class of Bridge Note Warrant holders. The modification did not result in the reclassification of the equity-classified Bridge Note Warrants from additional paid-in-capital to liability classification.

In May 2020, concurrent with the reduction of the exercise price of the Bridge Note Warrants, the Company entered into a warrant exercise inducement offer with certain holders of the Bridge Note Warrants, pursuant to which such holders agreed to exercise for cash Bridge Note Warrants to purchase 31,250 shares of common stock, in exchange for the Company's issuing to the exercising holders new unregistered Series 3 Warrants to purchase 31,250 shares of common stock.

During the year ended December 31, 2021, an aggregate of 443,748 shares of common stock were issued upon the exercise of the Bridge Note Warrants for total proceeds of \$652,000.

A total of 190,622 and 634,370 Bridge Notes Warrants were outstanding as of December 31, 2021 and 2020, respectively.

July 2019 Series 1 Warrants

In July 2019, the Company entered into an underwriting agreement, relating to a public offering, which was comprised of (1) 962,166 Class A Units, priced at \$6.00 per unit, with each unit consisting of (i) one share of the Company's common stock, (ii) one Series 1 warrant to purchase one share of common stock, and (iii) one Series 2 warrant to purchase one share of common stock, and (2) 10,787 Class B Units, priced at a price of \$1,000 per unit, with each unit consisting of (i) one share of Series B Convertible Preferred Stock, convertible into 166 shares of common stock, (ii) 166 Series 1 Warrants and (iii) 166 Series 2 Warrants.

The Series 1 Warrants had an exercise price of \$6.00 and expire on the earlier of (a) 5 years from the date of issuance and (b) 30 calendar days following the public announcement of Positive Interim Results related to the diarrhea results from the HALT-D investigator-initiated trial, if and only if certain trading benchmarks are achieved during such 30 calendar day period.

In the offering, the Company sold (i) 962,166 Class A Units, which included Series 1 warrants to purchase 962,166 shares of the Company's common stock and (ii) 10,787 Class B Units, which included Series 1 warrants to purchase 1,797,833 shares of the Company's common stock. In total, 2,760,000 Series 1 warrants were issued, with an initial valuation of \$5.0 million computed using the Black-Scholes-Merton pricing model using a stock price of \$5.19, a strike price of \$6.00, an expected term of 5.0 years, volatility of 109% and a risk-free discount rate of 1.83%. Upon issuance, the Series 1 warrants were classified in additional paid-in-capital.

September 2019 Modification of the July 2019 Series 1 Warrants

In September 2019, the Company reduced the exercise price of all 2,760,000 Series 1 Warrants from \$6.00 to \$4.20. The Company determined the impact of this modification to be an increase in the fair value of the warrants of \$522,000. Because the modification applied to the entire class of Series 1 Warrant holders, the increase in fair value represented a deemed dividend to the entire class of Series 1 Warrant holders. The modification did not result in the reclassification of the equity-classified Series 1 warrants from additional paid-in-capital to liability classification.

February 2020 Modification of the July 2019 Series 1 Warrants

In February 2020, the Company entered into a warrant exercise agreement with a holder of its Series 1

Warrants, pursuant to which the holder agreed to exercise 69,340 Series 1 Warrants in consideration of the Company lowering the exercise price of the 69,340 warrants from \$6.00 to \$2.08. Upon exercise of the warrants, the Company received cash proceeds of \$144,000 and, in turn, issued 69,340 common shares. It is the Company's policy to determine the impact of modifications to equity-classified warrants by analogy to share-based compensation guidance per ASC 718, Compensation – Stock Compensation. Pursuant to that guidance, and due to the modification being applicable only to a single holder of the Series 1 Warrants, the incremental increase of \$6,000 in fair value of the modified warrants was recorded as an expense in the consolidated statement of operations for the year ended December 31, 2020.

May 2020 Modification of the July 2019 Series 1 Warrants and Inducement Offer

In May 2020, the Company reduced the exercise price of all outstanding Series 1 Warrants from \$4.20 per share to \$1.47 per share. The Company determined the impact of this modification to be an increase in the fair value of the warrants of \$284,000. Because the modification applied to the entire class of Series 1 Warrant holders, the increase in fair value represented a deemed dividend to the entire class of Series 1 Warrant holders. The modification did not result in the reclassification of the equity-classified Series 1 Warrants from additional paid-in-capital to liability classification.

In May 2020, concurrent with the reduction of the exercise price of the Series 1 Warrants, the Company entered into a warrant exercise inducement offer with certain holders of the Series 1 Warrants, pursuant to which such holders agreed to exercise for cash Series 1 Warrants to purchase 1,524,013 shares of common stock, in exchange for the Company's issuing to the exercising holders new unregistered Series 3 Warrants to purchase 1,524,013 shares of common stock.

During the year ended December 31, 2021, an aggregate of 464,058 shares of common stock were issued upon the exercise of the Series 1 Warrants for total proceeds of \$682,000.

A total of 145,396 and 609,450 Series 1 Warrants were outstanding as of December 30, 2021 and 2020, respectively.

July 2019 Series 2 Warrants

The Series 2 Warrants had an exercise price of \$6.00 and expire on the first date on the earlier of (a) 5 years from the date of issuance and (b) 30 calendar days following the public announcement by the Company that a pivotal phase 3 clinical trial using crofelemer (Mytesi, or the same or similar product with a different name) for the treatment of cancer therapy-related diarrhea in humans has met its primary endpoint in accordance with the protocol, if and only if certain trading benchmarks are achieved during such 30 calendar day period. In addition, each Series 2 Warrant has an embedded call option that allows the Company to redeem any unexercised warrants if certain contingencies are met.

In the July 2019 offering, the Company sold (i) 962,166 Class A Units, which included Series 2 warrants to purchase 962,166 shares of the Company's common stock and (ii) 10,787 Class B Units, which included Series 2 warrants to purchase 1,797,833. In total, 2,760,000 Series 2 warrants were issued, with an initial valuation of \$5.0 million computed using the Black-Scholes-Merton pricing model using a stock price of \$5.19, a strike price of \$6.00, an expected term of 5.0 years, volatility of 109% and a risk-free discount rate of 1.83%. Upon issuance, the Series 2 Warrants were classified in additional paid-in-capital.

March 5, 2020 Modification of the July 2019 Series 2 Warrants

On March 5, 2020, the Company entered into a warrant exercise agreement with a holder of its Series 2 Warrants, pursuant to which the holder agreed to exercise 30,313 Series 2 Warrants in consideration of the Company lowering the exercise price of the 30,313 warrants from \$6.00 to \$1.82. Upon exercise of the warrants, the Company received cash proceeds of \$55,000 and, in turn, issued 30,313 common shares. It is the Company's policy to determine

the impact of modifications to equity-classified warrants by analogy to share-based compensation guidance per ASC 718, Compensation – Stock Compensation. Pursuant to that guidance, and due to the modification being applicable only to a single holder of the Series 2 Warrants, the incremental increase of \$6,000 in fair value of the modified warrants was recorded as an expense in the consolidated statement of operations for the year ended December 31, 2020.

March 23, 2020 Modification of the July 2019 Series 2 Warrants

On March 23, 2020, the Company entered into a Warrant Exercise and Preferred Stock Amendment Agreement (see Note 10) with Ionic Ventures of its Series 2 Warrants, pursuant to which the holder agreed to exercise in cash its Series 2 Warrants to purchase an aggregate of 416,666 shares of common stock, in consideration of the Company reducing the Series 2 Warrant exercise price from \$6.00 to \$1.57 per share, for gross proceeds to the Company of approximately \$653,000, or \$628,000 net of \$25,000 of issuance costs. The Company determined the impact of this modification to be an increase in the fair value of the warrants of \$65,000. Because the modification applied to a sole holder of Series 2 Warrants, the \$65,000 increase in fair value was recorded as an expense in the consolidated statement of operations for the year ended December 31, 2020. The modification did not result in the reclassification of the equity-classified Series 2 Warrants from additional paid-in-capital to liability classification, and as of December 31, 2020, all 2,760,000 Series 2 Warrants have been exercised.

May 2020 Modification of the July 2019 Series 2 Warrants and Inducement Offer

In May 2020, the Company reduced the exercise price of all outstanding Series 2 Warrants from \$6.00 per share to \$1.47 per share. The Company determined the impact of this modification to be an increase in the fair value of the warrants of \$406,000. Because the modification applied to the entire class of Series 2 Warrant holders, the increase in fair value represented a deemed dividend to the entire class of Series 2 Warrant holders. The modification did not result in the reclassification of the equity-classified Series 2 Warrants from additional paid-in-capital to liability classification.

In May 2020, concurrent with the reduction of the exercise price of the Series 2 Warrants, the Company entered into a warrant exercise inducement offer with certain holders of the Series 2 Warrants, pursuant to which such holders agreed to exercise for cash Series 2 Warrants to purchase 1,344,520 shares of common stock, in exchange for the Company's issuing to the exercising holders new unregistered Series 3 Warrants to purchase 1,335,020 shares of common stock.

During the year ended December 31, 2021, an aggregate of 475,725 shares of common stock were issued upon the exercise of the Series 2 Warrants for total proceeds of \$700,000.

A total of 133,730 and 609,450 Series 2 Warrants were outstanding as of December 31, 2021 and 2020, respectively.

December 2019 PIPE Financing Warrants

In December 2019, the Company entered into a securities purchase agreement with certain investors pursuant to which the Company, in a Private Placement, sold (i) an aggregate of 833,333 unregistered shares of the Company's common stock, and (ii) Warrants to purchase up to an aggregate of 416,664 shares of common stock, for an aggregate purchase price of \$1.5 million (see Note 11). The warrants have an exercise price of \$2.34 per share and become exercisable on June 24, 2020 (6 months after their issuance date) and have a five-year term.

The warrants were valued at \$686,000 using the Black-Scholes-Merton option pricing model as follows: exercise price of \$2.34 per share, stock price of \$1.86 per share, expected life of five years, volatility of 143%, and a risk-free rate of 2.42%. As the common stock and warrants were issued in a unit structure, the aggregate proceeds of \$1.5 million were allocated to the two securities using the relative fair value method, resulting with the common stock

and warrants being allocated \$1.0 million and \$465,000, respectively. The warrants were classified in stockholders' equity

During January 2021, an aggregate of 416,664 shares of common stock was issued upon the exercise of the December 2019 PIPE Financing Warrants for total proceeds of \$975,000. As of December 31, 2021, all December 2019 PIPE Financing Warrants have been exercised.

April 2021 ELOC Warrants

On April 7, 2021, in consideration for Oasis Capital's entry into the March 2020 ELOC amendment, the Company issued Oasis Capital a common stock purchase warrant ("ELOC Warrants") exercisable for 33,333 shares of common stock with an exercise price per share equal to \$5.61 on the date of the amendment. The warrants were valued at \$172,000 using the Black-Scholes option pricing model as follows: exercise price of \$5.61 per share, stock price of \$5.61 per share, expected life of five years, volatility of 156%, and a risk-free rate of 0.87%. The warrants were classified in additional paid-in-capital.

10. Preferred Stock

At December 31, 2021 and 2020, preferred stock consisted of the following:

<u>(in thousands, except share and per share data)</u>	<u>Shares</u>	<u>Issued and</u>	<u>Carrying</u>	<u>Liquidation</u>
<u>Series</u>	<u>Authorized</u>	<u>Outstanding</u>	<u>Value</u>	<u>Preference</u>
				<u>per Share</u>
B-2	10,165	—	\$ —	\$ —
C	1,011,000	—	—	8.00
Total	<u>1,021,165</u>	<u>—</u>	<u>\$ —</u>	

Series A Convertible Preferred Stock

In March 2018, the Company entered into a stock purchase agreement with Sagard Capital pursuant to which the Company, in a private placement, agreed to issue and sell to Sagard Capital 5,524,926 shares of the Company's Series A Convertible Preferred Stock, \$0.0001 par value per share, for gross proceeds of \$9.2 million, or \$9.0 million net of issuance costs. The preferred stock was convertible into approximately 157,855 shares of common stock at the option of the holder at an effective conversion price of \$582.75 per share. Subject to certain limited exceptions, the shares of preferred stock could not be offered, pledged or sold by Sagard Capital for one year from the date of issuance. The conversion price was subject to certain adjustments in the event of any stock dividend, stock split, reverse stock split, combination or other similar recapitalization.

Holders of the Series A Convertible Preferred shares were entitled to participate equally and ratably with the holders of shares of common stock in all dividends paid and distributions made to the holders of the common stock as if, immediately prior to each record date of the common stock, the shares of Series A Convertible Preferred Stock then outstanding were converted into shares of common stock.

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or deemed liquidation event, the holders of Series A Convertible Preferred shares then outstanding were entitled to be paid in cash out of the assets of the Company before any payment shall be made to the holders of common stock or shares of any series or class of preferred or other capital stock then outstanding that by its terms is junior to the Series A Convertible Preferred Stock in respect of the preferences as to distributions and payments upon such liquidation event by reason of their ownership, an amount per share of Series A Convertible Preferred Stock equal to one times the Series A Convertible Preferred Stock original issue price.

The Series A Convertible Preferred shares were redeemable by Sagard Capital upon a Redemption Event that is not solely within the control of the Company. Were a Redemption Event to occur as of the Measurement Date (the later of April 30, 2021 and the date on which the Company files its Form 10-Q for the three months ending March 31, 2021, but in no event later than September 30, 2021), the holders of at least a majority of the shares of Series A Convertible Preferred Stock then outstanding may require the Company to redeem all Series A shares for cash at a per share purchase price equal to \$2.3057. Any one of the following conditions can result in a Redemption Event: (i) revenue attributable to the Mytesi product for the six-month period ended March 31, 2021 is less than \$22.0 million; (ii) the daily VWAP of the Company's common stock on Nasdaq for the 30 days prior to a Measurement Date is less than \$315.00; (iii) the Company fails to file with the Securities and Exchange Commission ("SEC") on or before June 30, 2021, its Form 10-Q for the three months ending March 31, 2021.

The preferred stock was classified outside of stockholders' equity in accordance with authoritative guidance for the classification and measurement of potentially redeemable securities.

In September 2020, the Company and Sagard Capital entered into an exchange agreement, by which the remaining Series A Convertible Preferred shares were exchanged for (i) 842,500 shares of the Company's Series C Perpetual Preferred shares, and (ii) 842,500 shares of the Company's Series D Perpetual Preferred shares, all issued to Iliad. The exchange agreement was entered into to effect a share-for-share exchange transaction. The Series A Convertible Preferred shares were cancelled upon surrender, and the Company issued Iliad the Series C and Series D Perpetual Preferred shares. The exchange agreement was treated as an extinguishment of the Series A Convertible Preferred shares. As of the exchange date, the related extinguishment required recording derecognition of the Series A accreted value and recording Series C and Series D at fair value. The related excess of the carrying value over the fair value of the new instruments of \$150,000 was recorded to additional paid-in-capital and increased earnings available to common stockholders.

During the year ended December 31, 2020, the Company determined that a Redemption Event was probable. The Company recorded a deemed dividend charge of \$1.3 million for the accretion of the redemption amount and carrying value of the Series A Convertible Preferred Stock.

In September 2020, the Company filed a certificate with the Secretary of State of Delaware effecting the retirement and cancellation of the Series A Convertible Preferred Stock. As of December 31, 2020, there were no Series A Convertible Preferred shares authorized or outstanding.

Series B Convertible Preferred Stock

In July 2019, the Company entered into an underwriting agreement relating to the public offering comprised of (1) 962,166 Class A Units, priced at a public offering price of \$6.00 per unit, with each unit consisting of (i) one share of the Company's voting common stock, (ii) one Series 1 warrant to purchase one share of common stock and (2) 10,787 Class B Units, priced at a public offering price of \$1,000 per unit, with each Class B unit consisting of (i) one share of Series B Convertible Preferred Stock with a stated value of \$1,000 and convertible into 166 shares of common stock, (ii) 166 Series 1 Warrants and (iii) 166 Series 2 Warrants, at a public offering price of \$1,000 per Class B Unit.

The Company sold 10,787 Class B Units, comprised of 10,787 shares of Series B Convertible Preferred Stock, Series 1 warrants to purchase 1,797,833 shares of common stock and Series 2 warrants to purchase 1,797,833 shares of common stock. The total gross proceeds to the Company from the offering of the Class B Units were \$10.8 million of which \$4.2 million was allocated to the Series B Convertible Preferred Stock, \$3.3 million to the Series 1 Warrants and \$3.3 million to the Series 2 Warrants. Issuance costs of \$1.6 million were allocated to the Class B Units.

Holder of the Series B shares are entitled to participate equally and ratably with the holders of shares of common stock in all dividends paid and distributions made to the holders of the common stock as if, immediately prior to each record date of the common stock, the shares of Series B then outstanding were converted into shares of common stock. With certain exceptions, the shares of Series B Convertible Preferred Stock have no voting rights.

However, as long as any shares of Series B Convertible Preferred Stock remain outstanding, the Company shall not, without the affirmative vote of holders of a majority of the then outstanding shares of Series B Convertible Preferred Stock, (a) alter or change adversely the powers, preferences or rights given to the Series B Convertible Preferred Stock or alter or amend the Series B Certificate of Designation or (b) enter into any agreement with respect to any of the foregoing. Each share of Series B Convertible Preferred Stock is convertible at any time at the holder's option into 500 shares of Common Stock, which conversion ratio will be subject to adjustment for stock splits, stock dividends, distributions, subdivisions and combinations and other similar transactions.

In March 2020, the Company entered into a Warrant Exercise and Preferred Stock Amendment Agreement ("Amendment Agreement") with a Ionic Ventures of its Series 2 Warrants, pursuant to which the holder agreed to exercise in cash its Series 2 Warrants to purchase an aggregate of 416,666 shares of common stock, in consideration of the Company reducing the warrant exercise price from \$6.00 to \$1.57 per share, for gross proceeds to the Company of approximately \$653,000 (see Note 9). As a further inducement to enter into the Amendment Agreement, the Company agreed to reduce the conversion price of the Company's Series B Convertible Preferred Stock from \$6.00 to \$1.34, resulting in the application of accounting for modification of preferred stock instruments under ASC 260-10-S99-2 where the difference between the fair value of the consideration transferred and the net carrying amount of the convertible preferred stock is treated as a dividend and must be deducted from net income in arriving at income available to common stockholders. Because the reduction to the conversion price was an inducement, the Company applied the guidance in ASC 470-20, resulting in the recording of an inducement charge of \$1.6 million in the consolidated statement of operations for the year ended December 31, 2020.

In September 2020, the Company filed a certificate with the Secretary of State of Delaware effecting the retirement and cancellation of the Series B Convertible Preferred Stock. As of December 31, 2020, there were no Series B Convertible Preferred shares authorized or outstanding.

Series B-2 Convertible Preferred Stock

In December 2019, the Company entered into an exchange agreement with Oasis Capital, pursuant to which Oasis Capital gave up (i) its remaining unexercised Prepaid Forward contracts exercisable for 412,074 shares of the Company's common stock and (ii) 231,709 common shares held as an investment by Oasis Capital, in exchange for 10,165 shares of the Company's newly authorized Series B-2 Convertible Preferred Stock.

Holders of the Series B-2 Convertible Preferred Stock are entitled to receive dividends on shares of Series B-2 Convertible Preferred Stock equal (on an as-if-converted-to-common-stock basis) to and in the same form as dividends actually paid on shares of the common stock when, as and if such dividends are paid on shares of the common stock. No other dividends shall be paid on shares of the Series B-2 Convertible Preferred Stock.

The shares of Series B-2 Convertible Preferred Stock have no voting rights. However, as long as any shares of Series B-2 Convertible Preferred Stock remain outstanding, the Company shall not, without the affirmative vote of holders of a majority of the then outstanding shares of Series B-2 Convertible Preferred Stock, (a) alter or change adversely the powers, preferences or rights given to the Series B-2 Convertible Preferred Stock or alter or amend the Series B-2 Certificate of Designation or (b) enter into any agreement with respect to any of the foregoing.

Upon any liquidation, dissolution or winding-up of the Company, whether voluntary or involuntary, the Holders of the Series B-2 Convertible Preferred Stock are entitled to receive out of the assets, whether capital or surplus, of the Company the same amount that a holder of common stock would receive if the Series B-2 Convertible Preferred Stock were fully converted to common stock which amounts shall be paid *pari passu* with all holders of common stock.

Each share of Series B-2 Convertible Preferred Stock is convertible at any time at the holder's option into 63 shares of common stock, as determined by dividing the \$153.90 stated value of each Series B-2 Convertible Preferred Share by the \$2.43 conversion price ($\$153.90 \div \$2.43 = 63$ conversion ratio), and which conversion ratio is subject to adjustment for stock splits, stock dividends, distributions, subdivisions and combinations and other similar

transactions as specified in the Series B-2 Certificate of Designation. The Series B-2 Convertible Preferred Stock was classified in stockholders' equity in accordance with authoritative guidance.

In January 2020, a holder of the Series B-2 Convertible Preferred Stock converted 2,631 preferred shares into 166,630 shares of common stock. In October 2020, the Company entered into an exchange agreement with Oasis Capital pursuant to which the Company agreed to issue 166,728 shares of common stock in exchange for 975 shares of the Series B-2 Convertible Preferred Stock. The exchange agreement was accounted for as a modification. In December 2020, an investor converted the remaining 6,559 Series B-2 Convertible Preferred Stock into a total of 415,403 shares of the Company's common stock.

As of December 31, 2020, there were no Series B-2 Convertible Preferred shares outstanding.

Series C Perpetual Preferred Stock

In September 2020, the Company entered into an exchange agreement with Iliad to issue 842,500 shares of the Company's Series C Perpetual Preferred Stock at \$0.0001 par value per share, for a non-cash exchange of equity instruments. The exchange agreement was contemporaneously entered with the issuance of Series D Perpetual Preferred shares, in exchange of remaining Series A Convertible Preferred shares totaling 5,524,926 shares, and accreted value of \$11.2 million as of the exchange date. An amendment agreement of the Exchange Note 2 was also entered into, with issuance value of \$2.3 million and carrying value of \$2.6 million as of the exchange date, to extend maturity from December 31, 2020 to December 31, 2021, in consideration of 5% increase in the outstanding balance.

Holders of the Series C Perpetual Preferred Stock were not entitled to voting rights. However, as long as any Series C Perpetual Preferred share is outstanding, the Company is restricted to alter, change, or enter into an agreement to alter or change adversely the powers, preferences, or rights given to the shareholders.

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or deemed liquidation event, the holders of Series C Perpetual Preferred shares then outstanding would be entitled to be paid in cash out of the assets of the Company before any payment shall be made to the holders of common stock or shares of any series or class of preferred or other capital stock then outstanding that by its terms is junior to the Series C Perpetual Preferred shares in respect of the preferences as to distributions and payments upon such liquidation event by reason of their ownership, an amount per share of Series C equal to one times the Series C original issue price.

The Series C Perpetual Preferred shares were redeemable upon the option or discretion of the Company.

The Series C Perpetual Preferred shares were entitled to receive 10% cumulative stock dividends, to be payable in arrears on a monthly basis for 24 consecutive months. Dividends payable on the Series C Perpetual Preferred shares shall be payable through the Company's issuance of Series C Perpetual Preferred share by delivering to each record holder the calculated number of PIK dividend shares.

The Series C Perpetual Preferred shares were initially measured at fair value using the income approach, which considered the weighted probability of discounted cash flows at various scenarios of redemption by the Company or liquidation event and perpetual holding of the shares. As of the date of exchange, total fair value of the Series C Perpetual Preferred shares amounted to \$4.7 million. Subsequently, the carrying amount of Series C Perpetual Preferred shares increased as the PIK dividend shares were recognized.

The preferred stock has been classified as permanent stockholders' equity in accordance with authoritative guidance for the classification and measurement of perpetual shares without mandatory redemption period because the redemption option was ultimately in the control of the Company.

In October 2020, the Company entered into an exchange agreement with Iliad pursuant to which the Company agreed to issue a total of 83,333 shares of common stock and pre-funded warrants to purchase 2,352,563 shares of common stock in exchange for 285,000 shares of Series C Perpetual Preferred Stock. The pre-funded warrants were exercisable immediately and could be exercised at any time until all of the pre-funded warrants were

exercised in full. The nominal exercise price of each pre-funded warrant was \$0.0001. In December 2020, the Company also entered into a series of exchange agreements with Iliad pursuant to which the Company agreed to issue a total of 2,734,626 shares of common stock in exchange for 573,810 shares of Series C Perpetual Preferred Stock. The series of exchanges were viewed as singular transaction, hence combined for purposes of accounting for the subsequent amendments. The series of exchanges was accounted for as an extinguishment which resulted in a \$2.5 million deemed dividend, recorded against additional paid-in capital, for the difference between the fair value of the shares of common stock and pre-funded warrants transferred and the carrying amount of the Series C Perpetual Preferred Stock. As of December 31, 2020, Iliad had exercised all pre-funded warrants for \$1,000.

As of December 31, 2020, there were no Series C Perpetual Preferred shares outstanding.

11. Stockholders' Equity

As of December 31, 2021 and 2020, the Company had reserved shares of common stock, on an as-if converted basis, for issuance as follows:

	<u>December 31,</u>	
	<u>2021</u>	<u>2020</u>
Options issued and outstanding	2,348,199	1,485,518
Inducement options issued and outstanding	154,893	38,289
Options available for grant under stock option plans	631,270	198,866
Restricted stock unit awards issued and outstanding	487,456	1,871
Warrants issued and outstanding	<u>563,451</u>	<u>2,401,818</u>
Total	<u>4,185,269</u>	<u>4,126,362</u>

Common Stock

The holders of common stock are entitled to one vote for each share of common stock held. The common stockholders are also entitled to receive dividends whenever funds and assets are legally available and when declared by the Board of Directors.

The holders of non-voting common stock are not entitled to vote, except on an as converted basis with respect to any change of control of the Company that is submitted to the stockholders of the Company for approval. Shares of the Company's non-voting common stock have the same rights to dividends and other distributions and are convertible into shares of the Company's common stock on a one-for-one basis.

The Company is authorized to issue a total number of 204,475,074 shares, of which 150,000,000 shares are common stock, 50,000,000 are non-voting common stock and 4,475,074 are preferred stock.

Reverse Stock-Split

On December 22, 2020, the Company obtained approval through a special shareholders meeting held on December 9, 2020 to effect a reverse split of the Company's issued and outstanding voting common stock at a ratio not less than 1-for-2 and not greater than 1-for-20.

On September 3, 2021, the reverse stock split became effective. Upon effectivity, every three shares of the Company's issued and outstanding common stock immediately prior to the effective time shall automatically be reclassified into one share of common stock without any change in the par value. The reverse stock split reduces the number of shares of common stock issuable upon the conversion of the Company's outstanding non-voting common stock and the exercise or vesting of its outstanding stock options and warrants in proportion to the ratio of the reverse stock split and causes a proportionate increase in the conversion and exercise prices of such non-voting common

stock, stock options and warrants. In addition, the number of shares reserved for issuance under the Company's equity compensation plans immediately prior to the effective time will be reduced proportionately. The reverse stock split did not change the total number of authorized shares of common stock or preferred stock.

March 2020 ELOC (Equity Line of Credit)

In March 2020, the Company entered into an equity purchase agreement (the "March 2020 ELOC") with Oasis Capital, which provides that Oasis Capital is committed to purchase up to an aggregate of \$2.0 million shares of the Company's common stock over the 36-month term of the March 2020 ELOC.

Pursuant to the terms and conditions of the March 2020 ELOC, on any trading day selected by the Company (such date the "Put Date"), after the SEC has declared effective the registration statement registering the sale of the shares of common stock that may be issued to Oasis Capital under the March 2020 ELOC, the Company has the right, in its sole discretion, to present to Oasis Capital with a purchase notice (each a "Put Notice"), directing Oasis Capital to purchase up to the lesser of (i) 66,666 shares of common stock or (ii) 20% of the average trading volume of common stock in the 10 trading days immediately preceding the date of such Put Notice, at a per share price equal to \$1.31 (each an "Option 1 Put"), provided that the aggregate of all Option 1 Puts and Option 2 Puts (described below) does not exceed \$2.0 million.

In addition, on any date on which Oasis Capital receives shares of common stock in connection with a Put Notice (the "Clearing Date"), the Company also has the right, in its sole discretion, to present to Oasis Capital with a Put Notice (each an "Option 2 Put") directing Oasis Capital to purchase an amount of common stock equal to the lesser of (i) such amount that equals 10% of the daily trading volume of the common stock on the date of such Put Notice and (ii) \$200,000, provided that the aggregate amount of the Option 1 Put and Option 2 Put on any Put Date or Clearing Date does not exceed \$500,000 and the aggregate amount of all Option 1 Puts and Option 2 Puts does not exceed \$2.0 million. The purchase price per share pursuant to such Option 2 Put is equal to \$1.31. The threshold price and the purchase price will be adjusted for any reorganization, recapitalization, non-cash dividend, stock split, reverse stock split or other similar transaction occurring during the period used to compute the threshold price or the purchase price.

On April 15, 2020, the SEC declared effective the registration statement registering the sale of the shares of common stock issued to Oasis Capital under the March 2020 ELOC. The Company will control the timing and amount of sales of common stock to Oasis Capital. Oasis Capital has no right to require any sales by the Company but is obligated to make purchases from the Company as directed by the Company in accordance with the March 2020 ELOC.

In connection with the equity line, the Company agreed to pay Oasis Capital a commitment fee and in April 2020, in settlement of the commitment fee, the Company issued to Oasis Capital 22,935 shares of common stock. At issuance, the 22,935 shares of common stock had a fair value of \$33,000 and were expensed as an issuance cost in the Company's consolidated statements of operations.

Per the terms of the equity purchase agreement, the Option Put 1 and Option Put 2 may be exercised only at a price that is always above the trading price of the underlying common stock at the exercise date, thereby rendering any exercise by the Company being out-of-the-money. At inception of the equity line on March 24, 2020, the Put Options were classified as derivative assets with a fair value of zero, and upon an effective registration statement on April 15, 2020, were reclassified to stockholders' equity with a fair value of zero.

In April 2020, the Company sold 17,333 common shares to Oasis for gross proceeds of \$23,000. As of December 31, 2021 and 2020, the Company had not exercised any further put options to require Oasis Capital to purchase common stock under the equity purchase agreement.

On April 7, 2021, the Company entered into an amendment to the March 2020 ELOC with Oasis Capital, pursuant to which the parties agreed to increase (i) the purchase price from \$1.31 to \$9.00 and (ii) the threshold price

from \$1.50 to \$10.35. In consideration for Oasis Capital's entry into the amendment, the Company issued Oasis Capital a common stock purchase warrant ("ELOC Warrants") exercisable for 33,333 shares of common stock with an exercise price per share equal to \$5.61 on the date of the amendment.

March 2020 PIPE Financing

In March 2020, Company entered into a securities purchase agreement (the "PIPE Purchase Agreement") with certain investors, pursuant to which the Company agreed to issue and sell to the Investors in a private placement an aggregate of 571,427 shares of the Company's common stock, for an aggregate purchase price of approximately \$720,000, or \$668,000 net of \$52,000 of issuance costs.

At The Market Offering ("ATM")

October 2020 ATM Agreement

On October 5, 2020, the Company entered into an ATM Agreement ("October 2020 ATM Agreement") with Ladenburg, pursuant to which the Company may offer and sell, from time to time through Ladenburg, shares of common stock, subject to the terms and conditions of the October 2020 ATM Agreement. The October 2020 ATM Agreement will terminate upon the earlier of (i) October 5, 2022 and (ii) termination of the October 2020 ATM Agreement as permitted therein. In 2020, the Company sold 1,271,639 shares of common stock under the October 2020 ATM Agreement resulting in net proceeds of approximately \$1.3 million after commissions and expenses of approximately \$40,000.

During January and February 2021, the Company issued an aggregate of 669,850 shares under the October 2020 ATM Agreement for total net proceeds of \$5.4 million after commissions and expenses of approximately \$311,000. As of December 31, 2021, all shares under the October 2020 ATM Agreement have been issued.

December 2021 ATM Agreement

On December 10, 2021, the Company entered into another ATM Agreement ("December 2021 ATM Agreement") with Ladenburg, pursuant to which the Company may offer and sell, from time to time through Ladenburg, shares of common stock having an aggregate offering price of up to \$15.0 million, subject to the terms and conditions of the December 2021 ATM Agreement. The offering will terminate upon the earlier of (i) December 10, 2024 and (ii) termination of the December 2021 ATM Agreement as permitted therein.

As of December 31, 2021, the Company has issued 2,261,596 shares under the December 2021 ATM Agreement for a total net proceeds of \$3.2 million.

PoC Capital Registered Direct Offering

On October 6, 2020, the Company entered into a Stock Plan Agreement for payment of contracted research fees (the "SPA") with PoC Capital, LLC ("PoC"), pursuant to which the Company issued to PoC an aggregate of 444,444 shares of the Company's common stock as consideration for PoC's assumption of \$400,000 in payment obligations of Napo under the service order with Integrium for Napo's planned upcoming pivotal Phase 3 clinical trial for cancer-therapy related diarrhea, for an effective offering price of \$0.90 per share.

Securities Purchase Agreement

On January 13, 2021, the Company entered into a securities purchase agreement, pursuant to which the Company agreed to issue and sell, in a registered public offering an aggregate of 1,479,290 shares of common stock at an offering price of \$10.14 per share for gross proceeds of approximately \$15.0 million before deducting \$1.6 million placement agent fee and related offering expenses. The offering closed on January 15, 2021.

On April 29, 2021, the Company entered into another securities purchase agreement, pursuant to which the Company agreed to issue and sell, in a registered public offering through Ladenburg as the placement agent, an aggregate of 2,549,000 shares of common stock at an offering price of \$4.23 per share for gross proceeds of approximately \$10.8 million before deducting placement agent fees and related offering expenses of \$948,000.

Subscription Agreement

On June 1, 2021, the Company entered into a subscription agreement with the SPAC and its sponsor, pursuant to which Dragon SPAC agreed to issue and sell, in a private placement by Dragon SPAC directly to the Company, units of Dragon SPAC, with each unit consisting of one ordinary share of Dragon SPAC and a warrant to purchase a share, for gross proceeds of approximately €8.8 million (corresponding, as at June 1, 2021, to \$10.8 million). Dragon SPAC is an Italy special purpose acquisition company formed for the purpose of entering into a business combination with Napo Therapeutics, with the aim of developing the pharmaceutical activities of Dragon SPAC/Napo Therapeutics combined entity in Europe. Each warrant will entitle the holder thereof to purchase one share at an exercise price of €10 per share at any time prior to the earlier of (i) the 10-year anniversary of the consummation of the business combination and (ii) the five-year anniversary of the listing of the combined entity on a public exchange.

On November 3, 2021, Dragon SPAC issued 883,000 ordinary shares, each reserved to the exercise of warrants pursuant to the warrant agreement approved by Dragon SPAC. As a result, Dragon SPAC became a substantially owned subsidiary, at the same time, the related advances will be converted to investment at a stand-alone level, and will be eliminated at the consolidated level.

September 2021 PIPE Financing

On September 13, 2021, the Company entered into a securities purchase agreement (the “September 2021 PIPE Financing”) with certain investors, pursuant to which the Company agreed to issue and sell to the investors in a private placement an aggregate of 309,242 unregistered shares of the Company’s common stock for an aggregate purchase price of approximately \$776,197 or \$2.51 per share.

Noncontrolling Interest

As a result of the merger last November 3, 2021 between Napo EU and Dragon SPAC, the Company assumed a non-controlling interest amounting to \$242,000 as of December 31, 2021 which represents minority interest held by an investor in Napo Therapeutics.

12. Stock-Based Compensation

2013 Equity Incentive Plan

In November 2013, the Company's board of directors and sole stockholder adopted the Jaguar Health, Inc. 2013 Equity Incentive Plan (the “2013 Plan”). The 2013 Plan allows the Company's board of directors to grant stock options, restricted stock awards and restricted stock unit awards to employees, officers, directors and consultants of the Company. Following the effective date of the IPO and after effectiveness of any grants under the 2013 Plan that were contingent on the IPO, no additional stock awards will be granted under the 2013 Plan. Outstanding grants continue to be exercisable, however, any unissued shares under the plan and any forfeitures of outstanding options do not rollover to the 2014 Stock Incentive Plan. There were 123 option shares outstanding at December 31, 2021 and 2020.

2014 Stock Incentive Plan

Effective May 12, 2015, the Company adopted the Jaguar Health, Inc. 2014 Stock Incentive Plan (“2014 Plan”). The 2014 Plan provides for the grant of options, restricted stock and restricted stock units to eligible employees, directors and consultants to purchase the Company's common stock. The term of an incentive stock option may not exceed 10 years, except that with respect to any participant who owns more than 10% of the voting power of all classes or our outstanding stock, the term must not exceed 5 years. The 2014 Plan provides for automatic share increases on the first day of each fiscal year in the amount of 2% of the outstanding number of shares of the Company's common stock on last day of the preceding calendar year. The 2014 Plan replaced the 2013 Plan except that all outstanding options under the 2013 Plan remain outstanding until exercised, cancelled or expired.

As of December 31, 2021, there were 2,348,076 options outstanding and 619,480 options available for grant. As of December 31, 2020, there were 1,485,395 options outstanding and 70,472 options available for grant.

2020 New Employee Inducement Award Plan

Effective June 16, 2020, the Company adopted the Jaguar Health, Inc. New Employee Inducement Award Plan (“2020 Inducement Award Plan”) and, subject to the adjustment provisions of the Inducement Award Plan, reserved 166,666 shares of the Company’s common stock for issuance pursuant to equity awards granted under the Inducement Award Plan. The term of an incentive stock option may not exceed 10 years, except that with respect to any participant who owns more than 10% of the voting power of all classes or our outstanding stock, the term must not exceed 5 years. The 2020 Inducement Award Plan provides for the grant of non-statutory stock options, restricted stock units, restricted stock, and performance shares. The 2020 Inducement Award Plan was adopted without stockholder approval pursuant to Rule 5635(c)(4) of the Nasdaq Listing Rules. The terms and conditions of the 2020 Inducement Award Plan are substantially similar to the Company’s 2014 Stock Incentive Plan, but with such other terms and conditions intended to comply with the Nasdaq inducement award rules. In accordance with Rule 5635(c)(4) of the Nasdaq Listing Rules, the only persons eligible to receive grants of equity awards under the Inducement Award Plan are individuals who were not previously an employee or director of the Company, or following a bona fide period of non-employment, as an inducement material to such persons entering into employment with the Company.

As of December 31, 2021, there were 154,876 options outstanding and 11,790 options available for grant. As of December 31, 2020, there were 38,272 options outstanding and 128,394 options available for grant.

Stock Options and Restricted Stock Units (“RSUs”)

The following table summarized the incentive plan activity for the year ended December 31, 2021:

(in thousands, except share and per share data)	Shares Available for Grant	Stock Options Outstanding	RSUs Outstanding	Weighted Average Stock Option Exercise Price	Weighted Average Remaining Contractual Life (Years)	Aggregate Intrinsic Value*
Outstanding at December 31, 2020	198,866	1,523,790	1,871	\$ 12.68	8.71	\$ 364
Additional shares authorized	1,900,421	—	—	—	—	—
Options granted	(1,016,044)	1,016,044	—	5.41	—	—
Options exercised	—	(3,147)	—	1.34	—	—
Options canceled	33,612	(33,612)	—	30.47	—	—
RSUs granted	(485,585)	—	485,585	—	—	—
Outstanding at December 31, 2021	<u>631,270</u>	<u>2,503,075</u>	<u>487,456</u>	<u>\$ 9.44</u>	<u>8.35</u>	<u>\$ 3</u>
Exercisable at December 31, 2021		<u>1,431,658</u>		<u>\$ 12.92</u>	<u>7.84</u>	<u>\$ 2</u>
Vested and expected to vest at December 31, 2021		<u>2,362,310</u>		<u>\$ 9.70</u>	<u>8.30</u>	<u>\$ 3</u>

*Fair market value of Jaguar stock on December 31, 2021 was \$1.04 per share.

The intrinsic value is calculated as the difference between the exercise price of the underlying options and the fair market value of the Company's common stock for options that were in-the-money.

The number of options exercised during the year ended December 31, 2021 and 2020 were 3,147 and 185, respectively.

The weighted average grant date fair value of stock options granted was \$5.06 and \$1.20 per share during the years ended December 31, 2021 and 2020, respectively.

The number of options that vested in the years ended December 31, 2021 and 2020 was 695,995 and 483,021, respectively. The grant date weighted average fair value of options that vested in the years ended December 31, 2021 and 2020 was \$4.49 and \$5.97, respectively.

Stock-Based Compensation

The following table summarizes stock-based compensation expense related to stock options, inducement stock options and RSUs for the years ended December 31, 2021 and 2020, and are included in the consolidated statements of operations as follows:

(in thousands)	Year Ended December 31,	
	2021	2020
Research and development expense	\$ 1,319	\$ 749
Sales and marketing expense	319	220
General and administrative expense	2,336	1,855
Total	<u>\$ 3,974</u>	<u>\$ 2,824</u>

As of December 31, 2021, the Company had \$3.9 million of unrecognized stock-based compensation expense for options and RSU's, which is expected to be recognized over a weighted-average period of 1.87 years.

The fair value of options granted during the years ended December 31, 2021 and 2020, respectively, were calculated using the range of assumptions set forth below:

	Year Ended December 31,	
	2021	2020
Volatility	163.8 - 164.0 %	150.1 - 167.9 %
Expected term (years)	5.0	5.0
Risk-free interest rate	0.5 - 1.2 %	0.3 - 0.5 %
Expected dividend yield	—	—

401(k) Plan

The Company sponsors a 401(k) defined contribution plan covering all employees. There were no employer contributions to the plan from plan inception through December 31, 2021.

13. Net Loss Per Share Attributable to Common Stockholders

The following table presents the calculation of basic and diluted net loss per common share for the years ended December 31, 2021 and 2020:

(In thousands, except share and per share data)	Year Ended December 31,	
	2021	2020
Net loss attributable to common shareholders (basic and diluted)	\$ (52,595)	\$ (38,648)
Shares used to compute net loss per common share, basic and diluted	44,711,588	12,880,868
Net loss per share attributable to common shareholders, basic and diluted	\$ (1.18)	\$ (3.00)

Basic net loss per share is calculated by dividing net loss by the weighted-average number of common shares outstanding during the period. Diluted net loss per share is computed by dividing net loss by the weighted-average number of common shares and common share equivalents outstanding for the period. Common stock equivalents are only included when their effect is dilutive. The Company's potentially dilutive securities which include stock options, convertible preferred stock, RSUs and common stock warrants have been excluded from the computation of diluted net loss per share as they would be anti-dilutive. For all periods presented, there is no difference in the number of shares used to compute basic and diluted shares outstanding due to the Company's net loss position.

The following outstanding common stock equivalents have been excluded from diluted net loss per common share for the years ended December 31, 2021 and 2020 because their inclusion would be anti-dilutive:

	December 31,	
	2021	2020
Options issued and outstanding	2,348,199	1,485,518
Inducement options issued and outstanding	154,893	38,289
Restricted stock units issued and outstanding	487,456	1,871
Warrants issued and outstanding	563,451	2,401,818
Total	3,553,999	3,927,496

As of March 10, 2022 there were 28,701,463 shares of common stock issued after the balance sheet date. Including these shares will have a material effect on the diluted net loss per common share in future periods.

14. Income Taxes

The Company's loss before provision for income taxes during the years ended December 31, 2021 and 2020, was a domestic loss of \$48.0 million and \$33.8 million, and a foreign loss of \$4.6 million and zero, respectively.

The effective tax rate for 2021 and 2020 was 0%. As a result of the Company's history of net operating losses ("NOL") and a full valuation allowance against its deferred tax assets, there was minimal current income tax and no deferred income tax provision for the years ended December 31, 2021 and 2020.

The Company's effective tax during the years ended December 31, 2021 and 2020, differed from the federal statutory rate as follows:

	December 31,	
	2021	2020
Statutory rate	(21.0)%	(21.0)%
Intercompany transactions	15.5 %	— %
Valuation allowance	3.0 %	13.4 %
Nondeductible warrant expense	0.7 %	— %
Book loss on debt extinguishment	0.3 %	4.2 %
Foreign rate differential	(0.3)%	— %
Other	1.8 %	3.4 %
Effective tax rate	<u>(0.0)%</u>	<u>— %</u>

Net deferred tax assets as of December 31, 2021 and 2020 consisted of the following:

<i>(In thousands)</i>	December 31,	
	2021	2020
Non-current deferred tax assets:		
Net operating losses	\$ 21,153	\$ 19,863
Tax credits	241	241
Stock compensation	2,161	1,711
Other	450	156
	<u>24,005</u>	<u>21,971</u>
Valuation allowance	(19,865)	(18,437)
Net non-current deferred tax assets	<u>4,140</u>	<u>3,534</u>
Non-current deferred tax liabilities:		
Other	(678)	—
Property and equipment	(3,462)	(3,534)
Net non-current deferred tax liability	<u>(4,140)</u>	<u>(3,534)</u>
Net non-current deferred tax asset (liability)	<u>\$ —</u>	<u>\$ —</u>

A valuation allowance is provided when it is more likely than not that the deferred tax assets will not be realized. The Company has established a valuation allowance to offset net deferred tax assets as of December 31, 2021 and 2020, due to the uncertainty of realizing future tax benefits from its NOL carryforwards and other deferred tax assets.

The valuation allowance increased by \$1.4 million during the year ended December 31, 2021.

As of December 31, 2021, the Company had federal and California NOL carryovers of approximately \$88.3 million and \$23.8 million, respectively. Of the federal NOL, \$20.7 million will begin to expire in 2034 and \$106.3 million will carryforward indefinitely. The California NOL will begin to expire in 2033.

As of December 31, 2021, the Company had California research credit carryovers of approximately \$382,000. The California research credits carry forward indefinitely. The Company had no Federal research credit carryovers.

Utilization of the domestic NOL and tax credit forwards may be subject to a substantial annual limitation due to ownership change limitations that may have occurred or that could occur in the future, as required by the Internal Revenue Code Section 382, as well as similar state provisions. In general, an "ownership change," as defined by the code, results from a transaction or series of transactions over a three-year period resulting in an ownership change of more than 50 percentage points of the outstanding stock of a company by certain stockholders or public groups. Any

limitation may result in expiration of all or a portion of the NOL or tax credit carryforwards before utilization. The Company has previously reduced its federal and California R&D credit carryforwards by \$1.4 million and \$697,000, respectively.

Enacted on March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act (“the CARES Act”) authorizes more than \$2.0 trillion to battle COVID-19 and its economic effects, including immediate cash relief for individual citizens, loan programs for small business, support for hospitals and other medical providers, and various types of economic relief for impacted businesses and industries. The CARES Act does not have a material impact on the Company’s financial results for the year ended December 31, 2021.

The Consolidated Appropriations Act, 2021 (the "Act") was enacted in the United States on December 27, 2020. The Act enhances and expands certain provisions of the CARES Act. The Act does not have a material impact on the Company’s financial results for the year ended December 31, 2021.

Uncertain Tax Positions

The Company has adopted the provisions of ASC 740, “Income Taxes Related to Uncertain Tax Positions.” Under these principals, tax positions are evaluated in a two-step process. The Company first determines whether it is more-likely-than-not that a tax position will be sustained upon examination. If a tax position meets the more-likely-than-not recognition threshold it is then measured to determine the amount of benefit to be recognized in the financial statements. The tax position is measured as the largest amount of benefit that has a greater than 50 percent likelihood of being realized upon ultimate settlement.

As of December 31, 2021, all unrecognized tax benefits were offset against deferred tax assets which are subject to a full valuation allowance, and if recognized, will not affect the Company's tax rate.

The Company does not anticipate that the total amounts of unrecognized tax benefits will significantly increase or decrease in the next 12 months.

The Company's policy is to include interest and penalties related to unrecognized tax benefits within its provision for income taxes. Due to the Company's net operating loss position, the Company has not recorded an accrual for interest or penalties related to uncertain tax positions for the years ended December 31, 2021 or 2020.

The following is a reconciliation of the beginning and ending amount of the Company’s total gross unrecognized tax benefit liabilities:

(In thousands)	<u>December 31,</u>	
	<u>2021</u>	<u>2020</u>
Gross Unrecognized Tax Benefit--Beginning Balance	\$ 77	\$ 77
Increases Related to Tax Positions from Prior Years	—	—
Increases Related to Tax Positions Taken During the Current Year . .	—	—
Gross Unrecognized Tax Benefit--Ending Balance	<u>\$ 77</u>	<u>\$ 77</u>

15. Segment Data

The Company has two reportable segments-human health and animal health. The animal health segment is focused on developing and commercializing prescription and non-prescription products for companion and production animals. The human health segment is focused on developing and commercializing of human products and the ongoing commercialization of Mytesi, which is approved by the U.S. FDA for the symptomatic relief of non-infectious diarrhea in adults with HIV/AIDS on antiretroviral therapy.

The Company's reportable segments sales and net income consisted of:

<i>(in thousands)</i>	Year Ended December 31,	
	2021	2020
Revenue from external customers		
Human Health	\$ 4,273	\$ 9,309
Animal Health	62	76
Consolidated Totals	\$ 4,335	\$ 9,385
Segment net loss		
Human Health	\$ (24,276)	\$ (9,779)
Animal Health	(28,324)	(24,030)
Consolidated Totals	\$ (52,600)	\$ (33,809)

The Company's reportable segments assets consisted of the following:

<i>(in thousands)</i>	December 31,	
	2021	2020
Segment assets		
Human Health	\$ 42,250	\$ 34,201
Animal Health	115,580	79,760
Total	\$ 157,830	\$ 113,961

The reconciliation of segments assets to the consolidated assets is as follows:

<i>(in thousands)</i>	December 31,	
	2021	2020
Total assets for reportable segments	\$ 157,830	\$ 113,961
Less: Investment in subsidiary	(29,232)	(29,241)
Less: Intercompany loan	(75,333)	(41,877)
Consolidated Totals	\$ 53,265	\$ 42,843

16. Subsequent Events

Issuances under the December 2021 ATM Agreement

During January to March 2022, the Company issued an aggregate of 20,046,463 shares under the December 2021 ATM Agreement for total net proceeds of \$9.2 million.

Amendment to December 2021 ATM Agreement

On February 2, 2022, the Company entered into an amendment to the December 2021 ATM Agreement, pursuant to which, the aggregate offering amount of the shares of the Company's common stock which the Company may sell and issue through Ladenburg, as the sales agent, was increased from \$15.0 million to \$75.0 million (the "ATM Upsize").

3a9 Exchange Agreements

On February 11, 2022, the Company entered into a privately-negotiated exchange agreement with Iliad, pursuant to which, the Company issued 2,375,000 shares ("Exchange Shares") of common stock in exchange for a \$1.7 million reduction ("Partitioned Royalty") in the outstanding balance of the royalty interest held by Iliad in relation to the October 2020 Purchase Agreement. The exchange will consist of Iliad surrendering the Partitioned

Royalty in exchange for the Exchange Shares, which will be free of any restrictive securities legend. Other than the surrender of the Partitioned Royalty, no consideration of any kind whatsoever will be given by Iliad to the Company in connection with the exchange agreement.

On March 2, 2022, the Company entered into another exchange agreement with Iliad, pursuant to which, the Company issued 2,425,000 shares of common stock in exchange for a \$1.1 million reduction in the outstanding balance of the royalty interest held by Iliad in relation to the October 2020 Purchase Agreement. The exchange will consist of Iliad surrendering the Partitioned Royalty in exchange for the Exchange Shares, which will be free of any restrictive securities legend. Other than the surrender of the Partitioned Royalty, no consideration of any kind whatsoever will be given by Iliad to the Company in connection with the exchange agreement.

On March 4, 2022, the Company entered into another exchange agreement with Iliad, pursuant to which, the Company issued 2,000,000 shares of common stock in exchange for a \$828,000 reduction in the outstanding balance of the royalty interest held by Iliad in relation to the October 2020 Purchase Agreement. The exchange will consist of Iliad surrendering the Partitioned Royalty in exchange for the Exchange Shares, which will be free of any restrictive securities legend. Other than the surrender of the Partitioned Royalty, no consideration of any kind whatsoever will be given by Iliad to the Company in connection with the exchange agreement.

On March 9, 2022, the Company entered into another exchange agreement with Iliad, pursuant to which, the Company issued 1,850,000 shares of common stock in exchange for a \$747,000 reduction in the outstanding balance of the royalty interest held by Iliad in relation to the October 2020 Purchase Agreement. The exchange will consist of Iliad surrendering the Partitioned Royalty in exchange for the Exchange Shares, which will be free of any restrictive securities legend. Other than the surrender of the Partitioned Royalty, no consideration of any kind whatsoever will be given by Iliad to the Company in connection with the exchange agreement.

Notice of Delisting

On February 17, 2022, the Company received a letter from the Staff of Nasdaq indicating that the bid price of the Company's common stock for the last 30 consecutive business days had closed below the minimum \$1.00 per share required for the continued listing under Nasdaq Listing Rule 5550(a)(2).

Under Nasdaq Listing Rule 5810(c)(3)(A), the Company has been granted a 180 calendar day grace period, or until August 16, 2022, to regain compliance with the minimum bid price requirement. The continued listing standard will be met if the Company evidences a closing bid price of at least \$1.00 per share for a minimum of 10 consecutive business days during the 180 calendar day grace period. In order for Nasdaq to consider granting the Company additional time beyond August 16, 2022, the Company would be required, among other things, to meet the continued listing requirement for market value of publicly held shares as well as all other standards for initial listing on Nasdaq, with the exception of the minimum bid price requirement. If measured today, the Company would qualify for Nasdaq's consideration of an extension because the Company currently has stockholders' equity of at least \$5.0 million. In the event the Company does not regain compliance with the \$1.00 bid price requirement by August 16, 2022, eligibility for Nasdaq's consideration of a second 180 day grace period would be determined on the Company's compliance with the above referenced criteria on August 16, 2022.

The Company is diligently working to evidence compliance with the minimum bid price requirement for continued listing on Nasdaq; however, there can be no assurance that the Company will be able to regain compliance or that Nasdaq will grant the Company a further extension of time to regain compliance, if necessary. If the Company fails to regain compliance with the Nasdaq continued listing standards, its common stock will be subject to delisting from Nasdaq.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Disclosure Controls and Procedures

Our management, Chief Executive Officer and Principal Financial and Accounting Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2021. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms.

Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is accumulated and communicated to our management, including our Chief Executive Officer and Principal Financial and Accounting Officer, as appropriate, to allow timely decisions regarding required disclosure. Based on this evaluation, our Chief Executive Officer and Principal Financial and Accounting Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2021.

Material Weaknesses

A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim consolidated financial statements will not be prevented or detected and corrected on a timely basis. As previously reported in our annual report on Form 10-K for the year ended December 31, 2020, management concluded that, as of such date, our disclosure controls and procedures were not effective due to the existence of a material weakness in the design and operating effectiveness of internal controls related to staff turnover in our accounting department and inadequate internal technical staffing levels.

In connection with our preparation of our annual financial statements for the year ended December 31, 2019, we identified a material weakness in our internal control over financial reporting related to staff turnover in our accounting department. We did not maintain a sufficient complement of internal personnel with appropriate knowledge, experience and/or training commensurate with our financial reporting requirements. We relied on outside consulting technical experts and did not maintain adequate internal qualified personnel to properly supervise and review the information provided by the outside consulting technical experts to ensure certain significant complex transactions and technical matters were properly accounted for. In addition, we identified inadequate internal technical staffing levels and expertise to properly supervise and review the information of the outside consulting technical experts to properly apply ASC 815-40 for liability classification of certain warrants and ASC 470-50 and ASC 470-60 to properly reflect the accounting impact to multiple modifications of the Company's debt instruments. In connection with the preparation of our annual financial statements for the year ended December 31, 2020, we did not have adequate policies and procedures in place to ensure the timely, effective review of assumptions used in measuring the fair value of certain financial instruments. In addition, we did not have adequate policies and procedures in place to ensure the timely, effective review of compliance with contractual covenants in certain financial instruments. As discussed below in *Remediation Efforts to Address Material Weaknesses*, we believe these material weaknesses have been remediated as of December 31, 2021.

Remediation Efforts to Address Material Weaknesses

To remediate the material weaknesses described above, management added controls to further enhance and revise the design of the existing controls including:

- Established policies and procedures to ensure timely review, by qualified personnel, of assumptions used in measuring fair value of certain financial instruments.
- Reassessed the design and operation of internal controls over financial reporting and review procedures over the preparation of our financial statements.
- Hired permanent accounting personnel and used consultants to provide support during our quarterly and annual preparation, review, and reporting of our financial statements.
- Maintained adequate internal qualified personnel to properly supervise and review the information provided by the outside consulting technical experts to ensure certain significant complex transactions and technical matters were properly accounted for.

Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rule 13a-15(f) and 15d-15(c) under the Exchange Act. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of the effectiveness of internal control to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with policies or procedures may deteriorate. Under the supervision and with the participation of our management, including our Chief Executive Officer and Principal Financial and Accounting Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2021 using the criteria established in Internal Control-Integrated Framework (“2013 Framework”) issued by the Committee of Sponsoring Organization of the Treadway Commission (“COSO”). Based on our evaluation using those criteria, our management has concluded that, as of December 31, 2021, our internal control over financial reporting was effective to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles for the reasons discussed above.

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm on our internal control over financial reporting because we are an SRC and are not subject to auditor attestation requirements under applicable SEC rules.

Changes in Internal Control over Financial Reporting

Other than the changes disclosed above regarding the remediation efforts to address the material weaknesses, there were no changes in our internal control over financial reporting that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting during the year ended December 31, 2021.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated by reference from the Proxy Statement for the 2022 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the fiscal year ended December 31, 2021.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item is incorporated by reference from the information under the captions “Compensation of Directors and Executive Officers” contained in the Proxy Statement for the 2022 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the fiscal year ended December 31, 2021.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this item is incorporated by reference from the information under the captions “Security Ownership of Certain Beneficial Owners and Management” and “Compensation of Directors and Executive Officers—Equity Compensation” contained in the Proxy Statement for the 2022 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the fiscal year ended December 31, 2021.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this item is incorporated by reference from the information under the caption “Proposal 1—Election of Directors—Director Independence” and “Certain Relationships and Related Transactions” contained in the Proxy Statement for the 2022 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the fiscal year ended December 31, 2021.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this item is incorporated by reference from the information under the caption “Proposal 2—Ratification of the Appointment of Independent Registered Public Accounting Firm—Principal Accountant Fees and Services” contained in the Proxy Statement for the 2022 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the fiscal year ended December 31, 2021.

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

Exhibit No.	Description
2.1	Agreement and Plan of Merger, dated as of March 31, 2017, by and among Jaguar Health, Inc. (f/k/a Jaguar Animal Health, Inc.), Napo Acquisition Corporation, Napo Pharmaceuticals, Inc. and Gregory Stock (incorporated by reference to Exhibit 2.1 to the Current Report on Form 8-K of Jaguar Health, Inc. filed March 31, 2017, File No. 001-36714).
3.1	Third Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K (No. 001-36714) filed with the Securities and Exchange Commission on August 1, 2017).
3.2	Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.2 to the Annual Report on Form 10-K filed with the Securities and Exchange Commission on April 9, 2018).
3.3	Certificate of Second Amendment of the Third Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K filed with the Securities and Exchange Commission on June 1, 2018).
3.4	Certificate of Third Amendment of the Third Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.2 to the Current Report on Form 8-K filed with the Securities and Exchange Commission on June 1, 2018).
3.5	Certificate of Fifth Amendment of the Third Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K filed with the Securities and Exchange Commission on June 6, 2019).
3.6	Amended and Restated Bylaws (incorporated by reference to Exhibit 3.2 to the Current Report on Form 8-K (No. 001-36714) filed with the Securities and Exchange Commission on May 18, 2015).
3.7	Certificate of Designation of Series C Perpetual Preferred Stock (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K (No. 001-036714) filed with the Securities and Exchange Commission on September 2, 2020).
3.8	Certificate of Designation of Series D Perpetual Preferred Stock (incorporated by reference to Exhibit 3.2 to the Current Report on Form 8-K (No. 001-036714) filed with the Securities and Exchange Commission on September 2, 2020).
3.9	Certificate of Retirement of Series A Convertible Participating Preferred Stock, Series B Convertible Preferred Stock and Series B-1 Convertible Preferred Stock of Jaguar Health, Inc. (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K (No. 001-036714) filed with the Securities and Exchange Commission on September 9, 2020)
3.10	Corrected Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to the Form 8-K of Jaguar Health, Inc. filed December 10, 2020, File No. 001-36714).
3.11	Certificate of Fifth Amendment of the Third Amended and Restated Certificate of Incorporation of Jaguar Health, Inc. (incorporated by reference to Exhibit 3.1 to the Form 8-K of Jaguar Health, Inc. filed September 3, 2021, File No. 001-36714).
4.1	Specimen Non-Voting Common Stock Certificate of Jaguar Health, Inc. (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed August 1, 2017, File No. 001-36714).
4.2	Common Stock Warrant, dated August 28, 2018, by and between Jaguar Health, Inc. and the holder named therein (incorporated by reference to Ex. 4.1 to the Current Report on Form 8-K filed on September 4, 2018).
4.3	Common Stock Warrant, dated September 11, 2018, by and between Jaguar Health, Inc. and L2 Capital, LLC (incorporated by reference to Ex. 4.3 to the Current Report on Form 8-K filed on September 12, 2018).
4.4	Common Stock Warrant, dated September 11, 2018, by and between Jaguar Health, Inc. and Charles Conte (incorporated by reference to Ex. 4.4 to the Current Report on Form 8-K filed on September 12, 2018).
4.5	Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.6 to the Registration Statement on Form S-1 (No. 333-227292) filed with the Securities and Exchange Commission on October 1, 2018).

Exhibit No.	Description
4.6	Form of Common Stock Warrant (incorporated by reference to Exhibit 4.3 to the Form 8-K of Jaguar Health, Inc. filed March 22, 2019).
4.7	Form of Placement Agent Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K/A of Jaguar Health, Inc. filed March 26, 2019).
4.8	Form of LOC Common Stock Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed April 4, 2019, File No. 001-36714).
4.9	Specimen Common Stock Certificate of Jaguar Health, Inc. (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed June 1, 2018, File No. 001-36714).
4.10	Form of Series 1 Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed July 23, 2019, File No. 001-36714).
4.11	Form of Series 2 Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed July 23, 2019, File No. 001-36714).
4.12	Promissory Note, dated October 1, 2019, between Napo Pharmaceuticals, Inc. and Michael Tempesta (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed October 7, 2019, File No. 001-36714).
4.13	Form of Pre-Funded Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed November 14, 2019, File No. 001-36714).
4.14	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed December 26, 2019, File No. 001-36714).
4.15	Royalty Interest, dated March 4, 2020, by and between the Company and Iliad Research and Trading L.P. (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed March 6, 2020, File No. 001-36714).
4.16	Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1945, as amended (incorporated herein by reference to Exhibit 4.26 to the Annual Report on Form 10-K filed on April 3, 2020).
4.17	Form of Series 3 Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar health, Inc. filed May 22, 2020).
4.18	Global Amendment, dated September 1, 2020, by and among Jaguar Health, Inc., Napo Pharmaceuticals, Inc. and Chicago Ventures, L.P. (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar health, Inc. filed September 2, 2020).
4.19	Royalty Interest, dated October 8, 2020, by and between Jaguar Health, Inc. and Iliad Research and Trading, L.P. (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed October 9, 2020).
4.20	Form of Pre-Funded Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar health, Inc. filed October 9, 2020).
4.21	Royalty Interest, dated December 22, 2020, by and between Jaguar Health, Inc. and Irving Park Capital, LLC (incorporated by reference to Exhibit 4.1 to the Form 8-K filed December 29, 2020, File No. 001-36714).
4.22	Secured Promissory Note, dated January 19, 2021, by and among Jaguar Health, Inc., Napo Pharmaceuticals, Inc. and Streeterville Capital, LLC (incorporated by reference to Exhibit 4.1 to the Form 8-K filed January 22, 2021, File No. 001-36714).
4.23	Common Stock Purchase Warrant, dated April 7, 2021, by and between Jaguar Health, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 4.1 to the Form 8-K of Jaguar Health, Inc. filed April 8, 2021, File No. 001-36714).
10.1‡	Form of Indemnification Agreement by and between Jaguar Health, Inc. and its directors and officers (incorporated by reference to Exhibit 10.1 to the Registration Statement on Form S-1 (No. 333-198383) filed with the Securities and Exchange Commission on August 27, 2014).

Exhibit No.	Description
10.2‡	Form of Notice of Grant of Stock Option and Stock Option Agreement under the 2014 Stock Incentive Plan (incorporated by reference to Exhibit 10.6 to the Registration Statement on Form S-1 (No. 333-198383) filed with the Securities and Exchange Commission on August 27, 2014).
10.3‡	Form of Notice of Grant of Restricted Stock and Restricted Stock Agreement under the 2014 Stock Incentive Plan (incorporated by reference to Exhibit 10.7 to the Registration Statement on Form S-1 (No. 333-198383) filed with the Securities and Exchange Commission on August 27, 2014).
10.4‡	Form of Notice of Grant of Restricted Stock Units and Restricted Stock Unit Agreement under the 2014 Stock Incentive Plan (incorporated by reference to Exhibit 10.8 to the Registration Statement on Form S-1 (No. 333-198383) filed with the Securities and Exchange Commission on August 27, 2014).
10.5‡	Offer Letter by and between Jaguar Health, Inc. and Lisa A. Conte, dated March 1, 2014 (incorporated by reference to Exhibit 10.9 to the Registration Statement on Form S-1 (No. 333-198383) filed with the Securities and Exchange Commission on August 27, 2014).
10.6‡	Offer Letter by and between Jaguar Health, Inc. and Steven R. King, Ph.D., dated February 28, 2014 (incorporated by reference to Exhibit 10.11 to the Registration Statement on Form S-1 (No. 333-198383) filed with the Securities and Exchange Commission on August 27, 2014).
10.7†	Formulation Development and Manufacturing Agreement between Jaguar Health, Inc. and Patheon Pharmaceuticals Inc., dated October 8, 2015 (incorporated by reference to Exhibit 10.30 to the Registration Statement on Form S-1 (No. 333-208905) filed with the Securities and Exchange Commission on January 7, 2016).
10.8	Common Stock Warrant issued pursuant to the Letter Agreement, dated November 8, 2016, between Jaguar Health, Inc. and Serious Change II LP, which expires July 28, 2022 (incorporated herein by reference to Exhibit 10.2 to the Quarterly Report on Form 10-Q (No. 001-36714) filed on November 14, 2016).
10.9	Distribution Agreement, dated December 9, 2016, by and between Jaguar Health, Inc. and Henry Schein, Inc. (incorporated herein by reference to Exhibit 10.41 to the Annual Report on Form 10-K filed on February 15, 2017).
10.10	Alliance Agreement, dated May 23, 2005, by and among AsiaPharm Investment Limited and its Affiliates, including Shandong Luye Pharmaceuticals Co. Ltd., and Napo Pharmaceuticals, Inc. (incorporated herein by reference to Exhibit 10.61 to the Registration Statement on Form S-4/A filed May 26, 2017 (No. 333-217364)).
10.11†	Finder's Agreement, dated April 9, 2010, by and among Luye Pharma Group Limited and its Affiliates, including Shandong Luye Pharmaceuticals Co. Ltd., and Napo Pharmaceuticals, Inc. (incorporated herein by reference to Exhibit 10.62 to the Registration Statement on Form S-4/A filed May 26, 2017 (No. 333-217364)).
10.12‡	License Agreement, dated February 28, 2007, by and between Insmed Incorporated and Napo Pharmaceuticals, Inc. (incorporated herein by reference to Exhibit 10.77 to the Registration Statement on Form S-4/A filed May 26, 2017 (No. 333-217364)).
10.13‡	Amendment, Waiver & Consent, dated June 27, 2017, by and among Jaguar Health, Inc., Nantucket Investments Limited, and Napo Pharmaceuticals, Inc. (incorporated by reference to Ex. 10.83 of the Company's Registration Statement on Form S-4 (Registration No. 333-217364) filed on July 5, 2017).
10.14†	Termination, Asset Transfer and Transition Agreement, dated September 22, 2017, by and between Napo Pharmaceuticals, Inc. and Glenmark Pharmaceuticals, Ltd. (incorporated by reference to Ex. 10.8 to the Quarterly Report on Form 10-Q filed on November 20, 2017)
10.15	Registration Rights Agreement, dated March 23, 2018, by and between Jaguar Health, Inc. and Sagar Capital Partners, L.P. (incorporated by reference to Ex. 10.2 to the Current Report on Form 8-K filed on March 27, 2018).
10.16	Registration Rights Agreement, dated September 11, 2018, by and between Jaguar Health, Inc. and L2 Capital, LLC (incorporated by reference to Ex. 10.3 to the Current Report on Form 8-K filed on September 12, 2018).

Exhibit No.	Description
10.17	Registration Rights Agreement, dated September 11, 2018, by and between Jaguar Health, Inc. and Charles Conte (incorporated by reference to Ex. 10.4 to the Current Report on Form 8-K filed on September 12, 2018).
10.18	Form of Registration Rights Agreement (incorporated by reference to Exhibit 10.2 to the Form 8-K of Jaguar Health, Inc. filed March 22, 2019).
10.19	Letter of Credit Cancellation & Warrant Issuance Agreement, dated March 29, 2019, by and between Jaguar Health, Inc. and the letter of credit beneficiary named therein (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed April 4, 2019).
10.20	Amendment No. 1 to Registration Rights Agreement, dated May 30, 2019, by and between Jaguar Health, Inc. and Sagard Capital Partners, L.P. (incorporated by reference to Exhibit 10.120 to the Registration Statement on Form S-1 (No. 333-233989) filed with the Securities and Exchange Commission on September 27, 2019).
10.21	Form of Amendment Agreement (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed July 5, 2019, File No. 001-36714).
10.22#	Master Services Agreement, dated June 24, 2019, by and among Napo Pharmaceuticals, Inc., Integrium, LLC, and POC Capital, LLC (incorporated by reference to Exhibit 10.24 to the Form 10-K of Jaguar Health, Inc. filed on March 31, 2021, File No. 001-36714).
10.23	Form of Exchange Agreement, between Jaguar Health, Inc. and Chicago Venture Partners, L.P. (incorporated by reference to Exhibit 10.6 to the Form 10-Q of Jaguar Health, Inc. filed on August 14, 2019, File No. 001-36714).
10.24	Form of Warrant Agency Agreement between Jaguar Health, Inc. and American Stock Transfer & Trust Company, LLC (incorporated by reference to Exhibit 10.117 to the Form S-1/A of Jaguar Health, Inc. filed on July 15, 2019, File No. 333-231399).
10.25	License Termination and Settlement Termination Agreement, dated October 1, 2019, by and among Jaguar Health, Inc., Napo Pharmaceuticals, Inc. and Michael Tempesta (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed October 7, 2019, File No. 001-36714).
10.26#	Securities Purchase Agreement, dated November 13, 2019, by and between Jaguar Health, Inc. and the purchasers named therein (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed November 14, 2019, File No. 001-36714).
10.27	Securities Purchase Agreement, dated December 20, 2019, by and between Jaguar Health, Inc. and the investors named therein (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed December 26, 2019, File No. 001-36714).
10.28	Form of Warrant Exercise Agreement by and between Jaguar Health, Inc. and the Holder named therein (incorporated by reference to Exhibit 10.1 to the Form 8-K filed February 28, 2020, File No. 001-36714).
10.29	Securities Purchase Agreement, dated March 23, 2020, by and between Jaguar Health, Inc. and the investors named therein (incorporated by reference to Exhibit 10.1 to the Form 8-K filed March 26, 2020, File No. 001-36714).
10.30	Equity Purchase Agreement, dated March 24, 2020, by and between Jaguar Health, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.4 to the Form 8-K filed March 26, 2020, File No. 001-36714).
10.31	Registration Rights Agreement, dated March 24, 2020, by and between Jaguar Health, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.5 to the Form 8-K filed March 26, 2020, File No. 001-36714).
10.32‡	Jaguar Health, Inc. 2014 Stock Incentive Plan as amended and restated effective October 1, 2019 (incorporated by reference to Exhibit 10.101 to the Form 10-K of Jaguar Health, Inc. filed April 3, 2020, File No. 001 36714).

Exhibit No.	Description
10.33	Purchase Agreement, dated April 15, 2020, by and between Napo Pharmaceuticals, Inc. and Atlas Sciences, LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K filed April 16, 2020, File No. 001-36714).
10.34	License Agreement, dated April 15, 2020, by and between Jaguar Health, Inc. and Atlas Sciences, LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K filed April 16, 2020, File No. 001-36714).
10.35	Purchase Agreement, dated May 12, 2020, by and among Jaguar Health, Inc., Napo Pharmaceuticals, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K filed May 21, 2020, File No. 001-36714).
10.36	Assignment Agreement, dated May 12, 2020, by and between Napo Pharmaceuticals, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.2 to the Form 8-K filed May 21, 2020, File No. 001-36714).
10.37‡	Jaguar Health, Inc. New Employee Inducement Award Plan (incorporated by reference to Exhibit 10.1 to the Form 8-K filed June 19, 2020, File No. 001-36714).
10.38‡	Form of Notice of Grant of Stock Option and Stock Option Agreement under Jaguar Health, Inc. New Employee Inducement Award Plan (incorporated by reference to Exhibit 10.2 to the Form 8-K filed June 19, 2020, File No. 001-36714).
10.39‡	Form of Notice of Grant of Restricted Stock Units and Restricted Stock Unit Agreement under the Jaguar Health, Inc. New Employee Inducement Award Plan (incorporated by reference to Exhibit 10.3 to the Form 8-K filed June 19, 2020, File No. 001-36714).
10.40	Securities Purchase Agreement, dated March 4, 2020, by and between Jaguar Health, Inc. and Iliad Research and Trading, L.P. (incorporated by reference to Exhibit 10.1 to the Form 8-K filed March 6, 2020, File No. 001-36714).
10.41	First Amendment to Royalty Interest Purchase Agreement and Related Documents, dated July 10, 2020, between Jaguar Health, Inc. and Iliad Research and Trading, L.P. (incorporated by reference to Exhibit 10.1 to the Form 8-K filed July 14, 2020, File No. 001-36714).
10.42‡	Form of Severance and Change of Control Agreement (incorporated by reference to Exhibit 10.11 to the Form 10-Q filed August 13, 2020 File No. 001-36714).
10.43	First Amendment to Purchase Agreement, dated June 26, 2020, by and among Jaguar Health, Inc., Napo Pharmaceuticals, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.12 to the Form 10-Q filed August 13, 2020 File No. 001-36714).
10.44	First Amendment to Assignment Agreement, dated June 26, 2020, by and between Napo Pharmaceuticals, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.13 to the Form 10-Q filed August 13, 2020 File No. 001-36714).
10.45	Exchange Agreement, dated September 1, 2020, by and between Jaguar Health, Inc. and Iliad Research and Trading, L.P. (incorporated by reference to Exhibit 10.1 to the Form 8-K filed September 2, 2020, File No. 001-36714).
10.46	Stock Plan Agreement for Payment of Consulting Services, dated September 1, 2020, by and among Jaguar Health, Inc., Sagard Capital Partners Management Corp. and Sagard Capital Partners, L.P. (incorporated by reference to Exhibit 10.2 to the Form 8-K filed September 2, 2020, File No. 001-36714).
10.47	Stock Plan Agreement, dated October 6, 2020, by and between Jaguar Health, Inc. and PoC Capital, LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K filed October 7, 2020, File No. 001-36714).
10.48	Fee Settlement Agreement dated October 7, 2020, by and between Jaguar Health, Inc. and Atlas Sciences, LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K filed October 9, 2020, File No. 001-36714).
10.49	Royalty Interest Purchase Agreement, dated October 8, 2020, by and between Jaguar Health, Inc. and Iliad Research and Trading, L.P. (incorporated by reference to Exhibit 10.1 to the Form 8-K filed October 9, 2020, File No. 001-36714).

Exhibit No.	Description
10.50	Exchange Agreement, dated October 8, 2020, by and between Jaguar Health, Inc. and Iliad Research and Trading, L.P. (incorporated by reference to Exhibit 10.2 to the Form 8-K filed October 9, 2020, File No. 001-36714).
10.51#	Office Sublease Agreement, dated August 31, 2020, by and between Jaguar Health, Inc. and Peacock Construction, Inc. (incorporated by reference to Exhibit 10.4 to the Form 10-Q filed November 16, 2020, File No. 001-36714).
10.52	Consent to Sublease Agreement, dated August 31, 2020, by and among M&E, LLC, Jaguar Health, Inc. and Peacock Construction, Inc. (incorporated by reference to Exhibit 10.5 to the Form 10-Q filed November 16, 2020, File No. 001-36714).
10.53#	Manufacturing and Supply Agreement, dated September 3, 2020, by and between Glenmark Life Sciences Limited and Napo Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.6 to the Form 10-Q filed November 16, 2020, File No. 001-36714).
10.54	Securities Purchase Agreement, dated December 22, 2020, by and between Jaguar Health, Inc. and Irving Park Capital, LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K filed December 29, 2020, File No. 001-36714).
10.55	Note Purchase Agreement, dated January 19, 2021, by and among Jaguar Health, Inc., Napo Pharmaceuticals, Inc. and Streeterville Capital, LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K filed January 22, 2021, File No. 001-36714).
10.56	Security Agreement, dated January 19, 2021, by and between Napo Pharmaceuticals, Inc. and Streeterville Capital, LLC (incorporated by reference to Exhibit 10.2 to the Form 8-K filed January 22, 2021, File No. 001-36714).
10.57#	Master Services Agreement, dated October 5, 2020, by and between Napo Pharmaceuticals, Inc. and Integrium, LLC (incorporated by reference to Exhibit 10.67 to the Form 10-K filed March 31, 2021, File No. 001-36714).
10.58	Form of Securities Purchase Agreement (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed January 14, 2021, File No. 001-36714).
10.59#	Office Lease Agreement, dated March 25, 2021, by and between Jaguar Health, Inc. and M & E LLC (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed April 8, 2021, File No. 001-36714).
10.60	First Amendment to the Equity Purchase Agreement, dated April 7, 2021, by and between Jaguar Health, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.2 to the Form 8-K of Jaguar Health, Inc. filed April 8, 2021, File No. 001-36714).
10.61	Registration Rights Agreement, dated April 7, 2021, by and between Jaguar Health, Inc. and Oasis Capital, LLC (incorporated by reference to Exhibit 10.3 to the Form 8-K of Jaguar Health, Inc. filed April 8, 2021, File No. 001-36714).
10.62	Form of Securities Purchase Agreement, dated April 29, 2021 (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed April 30, 2021, File No. 001-36714).
10.63#	Subscription Agreement, dated June 1, 2021, by and among Dragon SPAC S.p.A., Napo Pharmaceuticals, Inc. and Joshua Mailman (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed June 4, 2021, File No. 001-36714).
10.64#	License Agreement, dated August 18, 2021, by and between Napo Pharmaceuticals, Inc. and Napo EU S.p.A. (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed August 24, 2021, File No. 001-36714).
10.65	Securities Purchase Agreement, dated September 13, 2021, by and between Jaguar Health, Inc. and the investors named therein (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed September 17, 2021, File No. 001-36714).
10.66	At The Market Offering Agreement, dated December 10, 2021, by and between Jaguar Health, Inc. and Ladenburg Thalmann & Co. Inc. (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed December 10, 2021, File No. 001-36714).
10.67	First Amendment to the At the Market Offering Agreement, dated February 2, 2022, by and between Jaguar Health, Inc. and Ladenburg Thalmann & Co. Inc. (incorporated by reference to Exhibit 10.1 to the Form 8-K of Jaguar Health, Inc. filed February 2, 2022, File No. 001-36714).

Exhibit No.	Description
16.1	Letter from Mayer Hoffman McCann P.C., dated November 23, 2021 (incorporated by reference to Exhibit 16.1 to the Form 8-K of Jaguar Health, Inc. filed November 23, 2021, File No. 001-36714).
21.1*	Subsidiaries of the Registrant.
23.1*	Consent of RBSM LLP, Independent Registered Public Accounting Firm.
23.2*	Consent of Mayer Hoffman McCann P.C., Independent Registered Public Accounting Firm.
31.1*	Principal Executive Officer's Certifications Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Principal Financial Officer's Certifications Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1**	Certification Pursuant to 18 U.S.C. § 1350 (Section 906 of Sarbanes-Oxley Act of 2002).
32.2**	Certification Pursuant to 18 U.S.C. § 1350 (Section 906 of Sarbanes-Oxley Act of 2002).
101.INS	Inline XBRL Instance Document
101.SCH	Inline XBRL Taxonomy Extension Schema
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase
104	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101)

* Filed herewith.

** In accordance with Item 601(b)(32)(ii) of Regulation S-K and SEC Release No. 34-47986, the certifications furnished in Exhibits 32.1 and 32.2 hereto are deemed to accompany this Form 10-K and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or deemed to be incorporated by reference into any filing under the Exchange Act or the Securities Act of 1933 except to the extent that the registrant specifically incorporates it by reference.

† Confidential treatment granted as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

‡ Management contract or compensatory plan or arrangement.

Portions of this exhibit have been omitted pursuant to Item 601 of Regulation S-K promulgated under the Securities Act because the information (i) is not material and (ii) would be competitively harmful if publicly disclosed.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

JAGUAR HEALTH, INC.

By: /s/ LISA A. CONTE
 Lisa A. Conte
 Chief Executive Officer and President

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Lisa A. Conte and Carol Lizak, jointly and severally, his or her attorneys-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this Registration Statement has been signed by the following persons in the capacities and on the date indicated.

Signature	Title	Date
<u> /s/ LISA A. CONTE </u> Lisa A. Conte	Chief Executive Officer, President and Director (Principal Executive Officer)	March 11, 2022
<u> /s/ CAROL LIZAK </u> Carol Lizak	Chief Financial Officer and Treasurer (Principal Financial and Accounting Officer)	March 11, 2022
<u> /s/ JAMES J. BOCHNOWSKI </u> James J. Bochnowski	Chairman of the Board	March 11, 2022
<u> /s/ JOHN MICEK III </u> John Micek III	Director	March 11, 2022
<u> /s/ JONATHAN B. SIEGEL </u> Jonathan B. Siegel	Director	March 11, 2022
<u> /s/ GREG J. DIVIS </u> Greg J. Divis	Director	March 11, 2022



INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM'S CONSENT

We consent to the incorporation by reference in Jaguar Health, Inc.'s Registrations Statements as follows:

- (1) Registration Statements on Form S-1 (File Nos. 333-236016, 333-232082, 333-231399, 333-232078, 333-232715, 333-233989 and No. 333-237587); and
- (2) Registration Statements on Form S-3 (File Nos. 333-238992, 333-248763, 333-220236, 333-255154, 333-256634 and 333-261283); and
- (3) Registration Statements on Form S-8 (File Nos. 333-204280, 333-215303, 333-219939, 333-225057, 333-237816, 333-256626 and 333-256629);

of our report dated March 11, 2022, with respect to our audit of the consolidated financial statements of Jaguar Health, Inc., as of December 31, 2021 and for the year ended December 31, 2021, which report is included in this Annual Report on Form 10-K of Jaguar Health, Inc., for the year ended December 31, 2021.

/s/ RBSM LLP

Larkspur, California
March 11, 2022

**PRINCIPAL EXECUTIVE OFFICER'S CERTIFICATION PURSUANT TO
SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Lisa A. Conte, certify that:

1. I have reviewed this annual report on Form 10-K of Jaguar Health, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 11, 2022

/s/ LISA A. CONTE

Lisa A. Conte

*Chief Executive Officer and President
(Principal Executive Officer)*

**PRINCIPAL FINANCIAL OFFICER'S CERTIFICATION PURSUANT TO
SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Carol Lizak, certify that:

1. I have reviewed this annual report on Form 10-K of Jaguar Health, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 11, 2022

/s/ CAROL LIZAK

Carol Lizak

Principal Financial and Accounting Officer

**CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the annual report of Jaguar Health, Inc. (the “Company”) on Form 10-K for the year ended December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the “Report”), the undersigned officer of the Company certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to such officer’s knowledge:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 11, 2022

/s/ LISA A. CONTE

Lisa A. Conte

*Chief Executive Officer and President
(Principal Executive Officer)*

**CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the annual report of Jaguar Health, Inc. (the "Company") on Form 10-K for the year ended December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned officer of the Company certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to such officer's knowledge:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 11, 2022

/s/ CAROL LIZAK

Carol. Lizak

Principal Financial and Accounting Officer