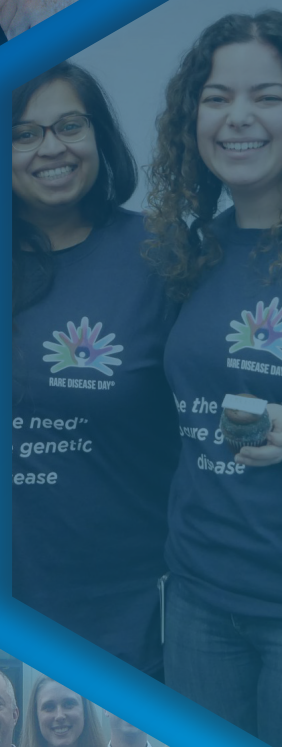
HOMOLOGY™
Medicines, Inc.

Clinical-stage company translating gene therapy and gene editing technology into one-time treatments and potential cures to transform patients' lives.

ANNUAL REPORT 2020



"In 2021, we are committed to advancing new development programs into the clinic, and we appreciate the ongoing support of the rare disease community and our dedicated team, Board of Directors and shareholders."

— Arthur Tzianabos, Ph.D.
President, Chief Executive Officer and
Director of Homology Medicines

HOMOLOGY™
Medicines, Inc.

TO OUR SHAREHOLDERS:

2020 was unlike any year in recent history, as the world was forced to deal with an unexpected global health crisis. I am proud to say that despite these difficult times, Homology was able to execute on our goals and progress our dual *in vivo* gene therapy and nuclease-free gene editing platform for patients with rare diseases. We shared additional positive data from the first-ever gene therapy trial in phenylketonuria (PKU), which was followed by a $60 million equity investment from Pfizer, and we kicked off 2021 with plans to have three clinical programs and a new development program this year.

The pheNIX trial is currently recruiting for the Phase 2 dose expansion phase, with initial data anticipated by year end. We plan to initiate another "first-ever" clinical trial in PKU, this time using our gene editing technology. Our central nervous system (CNS) pipeline has grown, as we added a gene therapy development candidate for MPS II (Hunter syndrome), which we also expect to be in the clinic this year. Underpinning these is our internal commercial GMP manufacturing process and platform, which is supplying all of our clinical and preclinical programs.

In 2020, we focused on execution and continued to build our fully integrated business. In 2021, we are committed to advancing new development programs into the clinic, and we appreciate the ongoing support of the rare disease community and our dedicated team, Board of Directors and shareholders.

HOMOLOGY'S DUAL PLATFORM AND DIFFERENTIATED APPROACH TO PKU

Treating and potentially curing PKU has been a focus of ours since Homology was founded. We believe there is significant unmet need for people living with this rare, inborn error of metabolism that could be greatly improved with a one-time treatment addressing the genetic defect. The power and differentiating aspect of Homology's technology platform, which is built on a set of adeno-associated viruses derived from human hematopoietic stem cells (AAVHSCs), is the ability to do gene therapy or gene editing, thereby having the potential to address adult and pediatric PKU patients with a one-time treatment.

In PKU, the *PAH* gene writes the instructions to make phenylalanine hydroxylase (PAH) protein, which is responsible for metabolizing phenylalanine (Phe) contained in our diet. In PKU, mutations in the *PAH* gene result in a loss of function of the PAH protein, which causes toxic levels of Phe to build up in the body and can cause severe neurological problems. Phe metabolism is also required to produce tyrosine (Tyr) and neurotransmitters. The standard-of-care for PKU is a highly restrictive, low-protein diet, and there are no treatments available that address the underlying genetic defect.

In November 2020, we shared positive data from the dose-escalation portion of the pheNIX trial with our HMI-102 gene therapy candidate for adults with PKU. HMI-102 is designed to deliver functional copies of the *PAH* gene to the liver. As of the data cut-off date*, HMI-102 was shown to be generally well-tolerated with no treatment-related serious adverse events, and these data demonstrated HMI-102's potential to restore the metabolic pathway that converts Phe to Tyr. We applied the key learnings from the dose-escalation phase to the dose expansion study, which is enrolling patients at clinical sites and has the potential to be converted to a registrational trial. We expect to share initial efficacy and safety data by year end.

We are also progressing our *in vivo* gene editing candidate HMI-103 for PKU, with plans to initiate a clinical trial in adults this year. Our ultimate goal is to develop HMI-103 for pediatric patients, as their livers grow rapidly. HMI-103 is designed to integrate the *PAH* gene into the genome utilizing the body's natural DNA repair process called homologous recombination (HR). In contrast to nuclease-based approaches, such as CRISPR-based technologies that use enzymes to cut DNA and have been shown to introduce unwanted mutations, HR is a highly precise, efficient way to edit genes without cutting DNA.

** Data cut-off date of October 19, 2020*

Our dual approach to PKU, coupled with the positive data from our pheNIX trial, led to Pfizer's equity investment in Homology.

HOMOLOGY'S EXPANDED CNS PORTFOLIO

We have characterized our AAVHSCs and published on their ability to cross the blood-brain and blood-nerve barriers. These traits, along with our team's experience in developing and launching treatments for Hunter syndrome, support the development of HMI-203. Hunter syndrome is caused by mutations in the *IDS* gene, which is responsible for producing the I2S enzyme that breaks down glycosaminoglycans (GAGs), and results in toxic lysosomal accumulation of GAGs. This leads to a shortened life expectancy, underscoring the high unmet need for a treatment that addresses both the peripheral and cognitive effects of this fatal disorder. Unlike other programs in development, HMI-203 is designed to address the underlying genetic cause of Hunter syndrome by delivering functional copies of *IDS* to the CNS and peripheral nervous system (PNS), as well as to peripheral organs, with a single intravenous administration. Data from our IND-enabling studies in a murine model showed GAG reductions in cerebrospinal fluid (CSF) and other key organs, and phenotypic correction of skeletal deformities. We look forward to advancing this program into the clinic by year end.

We continue to optimize our HMI-202 *in vivo* gene therapy for metachromatic leukodystrophy (MLD), an often fatal, rare lysosomal storage disorder that also affects the CNS, PNS and peripheral organs. We believe that by optimizing the vector, we may further enhance the therapeutic profile.

PIPELINE EXPANSION AND POWER OF THE PLATFORM

One of the advantages of our family of 15 AAVHSCs is that we can choose the best modality for a disease based on its underlying biology and the best capsid that has the right tissue tropism. We can use "capsid shuffling" to combine various properties of the capsids to address a given disease, and our dual platform provides even further flexibility by extending beyond our core areas of liver and CNS diseases. This year, we expect to nominate a development candidate that would leverage our platform capabilities in a new therapeutic area and set the stage for addressing diseases with larger patient populations. This would bring us to five development candidates that we have internally discovered and developed in under five years.

In addition, we are applying our *in vivo* editing technology to target ophthalmic diseases, and generated data that support editing across two targets, providing early proof-of-principle for our approach.

"PKU is a challenging condition, and a one-time treatment that establishes normal Phe metabolism could change the prognosis for patients with this rare genetic disorder."

— Olaf Bodamer, M.D., Ph.D., FACMG, FAAP, Park Gerald Chair in Genetics & Genomics and Associate Chief of Genetics & Genomics at Boston Children's Hospital, and principal investigator of the pheNIX trial

INTERNAL, COMMERCIAL-READY MANUFACTURING

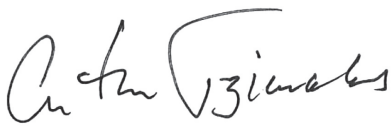
Homology invested early to build an internal 25,000-square-foot GMP manufacturing facility, which is housed within our headquarters. Its close proximity to our research and process development labs allows us to apply learnings quickly and have more control over our programs, timelines and quality. Our team's expertise has enabled us to scale our manufacturing to produce all of our clinical and preclinical supply. We were one of the first companies to scale to a 2,000-liter bioreactor in a HEK293 suspension system and our GMP commercial process and platform leverages a "plug and play" model that we have developed to allow for efficient changes to capsids or cDNA and scaling from discovery to the clinic and potentially beyond.

A LOOK AHEAD

By year end, we plan to have three clinical programs and a new development program that demonstrates the broader capability of our AAVHSC platform. Each year, our team has delivered on our goals, and I believe this year will be our strongest yet. We do not shy away from a challenge, and we are all working toward our ultimate mission to cure genetic disease.

Thank you for your continued support, and we look forward to providing updates on our programs and plans this year.

Kind regards,



Arthur Tzianabos, Ph.D.
President, Chief Executive Officer and Director of Homology Medicines

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 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, 2020

OR

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

For the transition period from to

Commission File Number: 001-38433

Homology Medicines, Inc.
(Exact name of Registrant as specified in its Charter)

Delaware	**47-3468154**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
One Patriots Park Bedford, MA	**01730**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (781) 301-7277

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, $0.0001 par value	FIXX	Nasdaq Global Select 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 Section 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 (§232.405 of this chapter) 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 whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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	☒	Small 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 ☒

The aggregate market value of the voting and non-voting stock held by non-affiliates of the registrant, as of June 30, 2020, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $511.6 million. Solely for purposes of this disclosure, shares of common stock held by executive officers, directors and certain stockholders of the registrant as of such date have been excluded because such holders may be deemed to be affiliates.

As of March 8, 2021, there were 50,487,649 shares of the registrant's common stock, par value $0.0001 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

None.

Table of Contents

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements. We intend such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, the anticipated impact of the COVID-19 pandemic on our business, anticipated use of cash, business strategy, prospective products, product approvals, research and development costs, anticipated timing and likelihood of success of clinical trials, expected timing of the release of clinical trial data, the plans and objectives of management for future operations and future results of 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," "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 Annual Report on 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 Annual Report on Form 10-K and are subject to a number of important factors that could cause actual results to differ materially from those in the forward-looking statements, including the factors described under "Summary Risk Factors" below and the sections in Item 1A., "Risk Factors" of Part I and Items 7 and 7A., "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Quantitative and Qualitative Disclosures About Market Risk," respectively, of Part II of this Annual Report on Form 10-K.

Moreover, we operate in an evolving environment. 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.

You should read this Annual Report on Form 10-K and the documents that we reference in this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements. 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.

Summary Risk Factors

Our business is subject to numerous risks and uncertainties, including those described in Part I, Item 1A. "Risk Factors" in this Annual Report on Form 10-K. You should carefully consider these risks and uncertainties when investing in our common stock. The principal risks and uncertainties affecting our business include the following:

- We have incurred significant losses since inception and anticipate that we will incur continued losses for the foreseeable future. We are not currently profitable, and we may never achieve or sustain profitability;
- We will require additional capital to fund our operations, and if we fail to obtain necessary financing, we may not be able to complete the development and commercialization of our product candidates;
- We have a limited operating history and no history of commercializing genetic medicine products, which may make it difficult to evaluate the prospects for our future viability;
- We are heavily dependent on the success of HMI-102, our most advanced product candidate, and if HMI-102 does not receive regulatory approval or is not successfully commercialized, our business may be harmed;
- We intend to identify and develop product candidates based on our novel genetic medicines platform, which makes it difficult to predict the time and cost of product candidate development. No products that utilize gene editing technology have been approved in the United States or in Europe, and there have only been a limited number of human clinical trials involving a gene editing product candidate;
- The clinical trial and regulatory approval processes are lengthy, time consuming and inherently unpredictable, and we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates;
- The COVID-19 pandemic could adversely impact our business, including our preclinical studies and clinical trials.
- Our product candidates may cause serious adverse events, side effects, toxicities or have other properties which may delay or prevent their regulatory approval, limit the commercial profile of an approved label or result in significant negative consequences following marketing approval, if any;
- adverse public perception of genetic medicine, and gene editing in particular, may negatively impact regulatory approval of, or demand for, our potential products;
- we and our contract manufacturers are subject to significant regulation with respect to manufacturing our products, and the manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity;
- even if we obtain FDA approval for our product candidates in the United States, we may never obtain approval for or commercialize it in any other jurisdiction, which would limit our ability to realize its full market potential;
- our existing collaborations are important to our business and future licenses may also be important to us, and if we are unable to maintain any of these collaborations, or if these arrangements are not successful, our business could be adversely affected; and
- if we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents which are sufficient to protect our product candidates, others could compete against us more directly, which would negatively impact our business.

PART I

Item 1. Business.

Overview

We are a clinical-stage genetic medicines company dedicated to transforming the lives of patients suffering from rare genetic diseases with significant unmet medical needs by curing the underlying cause of the disease. Our proprietary platform is designed to utilize our human hematopoietic stem cell derived adeno-associated virus vectors, or AAVHSCs, to precisely and efficiently deliver single administration genetic medicines *in vivo* either through gene therapy or nuclease-free gene editing across a broad range of genetic disorders. Our diverse set of AAVHSCs allows us to precisely target, via a single injection, a wide range of disease-relevant tissues, including the liver, central nervous system, or CNS, peripheral nervous system, or PNS, bone marrow, muscle and eye. Our genetic medicines platform is designed to provide us the flexibility to choose the method we believe is best suited from either gene therapy or gene editing for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the tissues exhibit. Our product development strategy is to continue to develop in parallel both gene therapy and gene editing, while initially leveraging the experience from our gene therapy product candidates to further advance our gene editing. We believe our dual technology platform will allow us to provide transformative cures using either modality.

The unique properties of our proprietary family of 15 novel AAVHSCs enable us to focus on a method of gene editing called gene integration, through the replacement of an entire diseased gene in the genome with a whole functional copy by harnessing the naturally occurring deoxyribonucleic acid, or DNA, repair process of homologous recombination, or HR. We believe our HR-driven gene editing approach will allow us to efficiently perform gene editing at therapeutic levels without unwanted on- and off-target modifications, and to directly measure and confirm those modifications in an unbiased manner to ensure only the intended changes are made. By utilizing the body's natural mechanism of correcting gene defects, we also avoid the need for exogenous nucleases, or bacteria-derived enzymes used in other gene editing approaches to cut DNA, that are known to significantly increase the risk of unwanted modifications.

HMI-102 for Treatment of PKU in Adult Patients

We are currently in Phase 2 of the pheNIX clinical trial with our first and lead product candidate, HMI-102, a gene therapy for the treatment of adults with phenylketonuria, or PKU. In November 2020, we reported positive safety and efficacy clinical data from the dose-escalation phase of the trial. As of the data cutoff date of October 19, 2020, six patients in the dose-escalation phase of the pheNIX trial had received HMI-102 across three dose cohorts (low-dose Cohort 1, n=2; mid-dose Cohort 2, n=2; high-dose Cohort 3, n=2). The results showed that HMI-102 was generally well-tolerated, and resulted in marked reductions in phenylalanine, or Phe, and the Phe-to-tyrosine, or Tyr, ratio, or the Phe-to-Tyr ratio, at two doses. Phe is a registrable endpoint in PKU, and the Phe-to-Tyr ratio is a clinically relevant diagnostic measurement for PKU. Based on the safety and efficacy results observed in the dose-escalation phase, we have selected and advanced two doses to the randomized, concurrently controlled, dose expansion Phase 2 portion of the pheNIX trial, which has the potential to be converted to a registrational trial. We expect to report initial clinical data from this portion of the trial by the end of 2021.

Other Product Candidates

We are currently progressing two gene therapy product development candidates for the treatment of lysosomal storage diseases: HMI-203 for the treatment of mucopolysaccharidosis type II (MPS II), or Hunter syndrome, and HMI-202 for the treatment of metachromatic leukodystrophy, or MLD.

We are in later-stage IND-enabling studies with HMI-203, an *in vivo* gene therapy product development candidate for the treatment of Hunter syndrome. HMI-203 is a potential one-time AAVHSC treatment designed to deliver functional copies of the *IDS* gene to multiple target organs, including those in the PNS and CNS, following a single I.V. administration. In preclinical studies, a single I.V. administration of HMI-203 resulted in robust biodistribution and human I2S, or hI2S, enzyme expression, leading to a significant reduction in heparan sulfate glycosaminoglycans, or GAGs, levels in the cerebrospinal fluid, brain, liver, heart, spleen, lung and kidney, compared with the vehicle-treated disease model. HMI-203 also led to significant changes in skeletal deformities compared with vehicle. We expect to initiate a Phase 1/2 dose-escalation clinical trial with HMI-203 in 2021.

We completed IND-enabling studies with HMI-202, a gene therapy CNS product development candidate for the treatment of MLD. We have generated preclinical data that have demonstrated that a single I.V. administration of HMI-202 crossed the blood-brain-barrier and blood-nerve-barrier and led to durable reduction of sulfatides in all brain regions of the disease model. We are applying the learnings from the IND-enabling studies to further optimize an HMI-202 vector that we believe may lead to a better therapeutic profile.

We are in later-stage IND-enabling studies with HMI-103, our lead gene editing product development candidate for the treatment of PKU in pediatric patients. We have generated *in vivo* preclinical data that have demonstrated Phe reduction following a single I.V. administration of the murine surrogate of HMI-103 in the PKU disease model out to 43 weeks (end of study). In addition, using quantitative molecular methods, we have demonstrated achievement of gene integration efficiencies in a humanized murine liver model that corresponded with Phe correction in the PKU murine model. These findings were peer-reviewed and published in *PLOS ONE* in May 2020. We expect to initiate a Phase 1/2 dose-escalation clinical trial with HMI-103 in 2021.

We also plan to name a development candidate in a new therapeutic area in 2021, demonstrating the broader capability of our AAVHSC platform, which we believe may allow us to target diseases with larger patient populations in the future.

We have fully integrated process development and Good Manufacturing Practice, or GMP, manufacturing capabilities that support the full breadth and flexibility of our AAVHSC capsid library. Our process development expertise covers all gene therapy and gene editing development functions and incorporates deep characterization and understanding of vector design and their consequences. Our manufacturing process is a versatile system that rapidly delivers high quality vector at scale. The manufacturing capacity within our 25,000 square foot GMP manufacturing facility includes multi-suite and multi-product capabilities to support our clinical development programs in both gene therapy and gene editing and we are now producing all of the clinical material for the pheNIX trial in this facility. Our plug and play process and manufacturing platform is a commercial manufacturing process that has successfully produced several of our product candidates. We are currently operating three 500-liter bioreactors in our internal manufacturing facility and have successfully produced GMP material at the 500-liter scale for multiple pipeline candidates. Additionally, we have successfully executed our manufacturing platform with multiple product candidates at the 2,000-liter bioreactor scale.

Our management team has a successful track record of discovering, developing and commercializing therapeutics with a particular focus on rare diseases. We have a robust intellectual property portfolio with issued composition of matter patents in the United States for our family of 15 AAVHSCs and we believe the breadth and depth of our intellectual property is a strategic asset that has the potential to provide us with a significant competitive advantage. We continue to build on our intellectual property estate through our ongoing product and platform development efforts.

Since our inception in 2015, we have raised approximately $539 million in aggregate net proceeds through our initial public offering, or IPO, in April 2018, a follow-on public offering of common stock in April 2019, proceeds from the sale of common stock under an “at-the-market” sales agreement, equity investments and preferred stock financings. Included in our net proceeds is $50.0 million from a former collaboration partner, comprised of an up-front payment of $35.0 million and a $15.0 million equity investment and a $60.0 million equity investment from Pfizer Inc., or Pfizer, through a private placement transaction. We will require additional capital in order to advance HMI-102 and our other product candidates through clinical development and commercialization. We believe that our compelling preclinical data, positive clinical data with HMI-102, scientific expertise, product development strategy, manufacturing capabilities, and robust intellectual property position us as a leader in the development of genetic medicines.

Our Opportunity in Genetic Medicines

We are currently focused on monogenic diseases where the genetic abnormality is known to occur in a single gene. The majority of monogenic diseases harbor thousands of individual mutations within the diseased gene, each resulting in a loss of function. Adding a functional gene to the cell where there is a missing or mutated gene or replacing an entire diseased gene with a whole functional gene are the optimal therapeutic approaches for addressing these monogenic disorders. This can be accomplished either through a method of gene therapy called gene transfer in slowly or non-dividing cells, or through a method of gene editing called gene integration in rapidly dividing cells.

The current focus of most nuclease-based gene editing companies is gene knockout, or knocking out a diseased gene to prevent the expression of an undesired protein. Since gene knockout does not result in a fully-corrected gene, this method can only potentially address the minority of monogenic diseases where a diseased protein requires knock-down or inactivation. Our HR-driven gene editing approach aims to achieve functional gene integration into the patient’s genome and potentially address the majority of monogenic diseases by replacing an entire diseased gene with a whole functional gene. Our gene therapy approach, on the other hand, seeks to introduce a functional copy of a defective gene into a patient’s own cells, but not incorporate such copy into the patient’s genome. This method results in the expression of the therapeutic protein of interest without changing the genome.

DNA Repair Pathways

Human cells harbor two primary independent pathways to maintain the integrity of DNA: homologous recombination, or HR, and non-homologous end joining, or NHEJ, which are described below:

- ***HR*** is a process in which cells repair DNA through highly precise incorporation of correct DNA sequences that are homologous, or matching, to the site of damage. HR has evolved to repair DNA with high fidelity and avoids the introduction of unwanted mutations at the site of correction. In the late 1990s, researchers discovered that certain AAV vectors delivered long single strands of homologous DNA to specific regions in the genome and induced the HR pathway, but their low efficiency of approximately 1% limited their use as a viable option for *in vivo* therapeutics.
- ***NHEJ*** is a less selective, error-prone process that rapidly joins the ends of broken DNA resulting in a high frequency of insertions or deletions at the break site. The discovery of nuclease-based gene editing technologies provided researchers with novel tools to specifically introduce DNA breaks into the genome. Despite high potential for error, the majority of nuclease-based gene editing approaches primarily utilize the NHEJ pathway.

We believe the major limitation of nuclease-based gene editing is the preferential utilization of the error-prone NHEJ pathway instead of the HR pathway. Because of this preference, the greatest utility of nuclease-based gene editing technologies may lie in their ability to knockout genes rather than replace an entire diseased gene in the genome with a whole functional copy. Furthermore, the use of nuclease-based gene editing technologies for insertion of a corrective sequence carries the risk of unwanted mutations from NHEJ including insertions and deletions or opposite orientation insertion of the template DNA, and also requires the separate delivery of both the nuclease and the DNA template to the same location at the same time.

We believe the unique characteristics of our genetic medicines platform will allow us to focus on the HR pathway, enabling precise nuclease-free gene integration with improved efficiency and a broader set of disease targets.

Our Approach

Our product development strategy is to continue to develop in parallel both gene therapy and gene editing modalities, and to choose the method we believe is best suited from either gene therapy or gene editing for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the tissues exhibit, all while initially leveraging the experience from our gene therapy modality to further advance our gene editing modality. Refer to Figure 1 below for a graphical depiction of our platform.

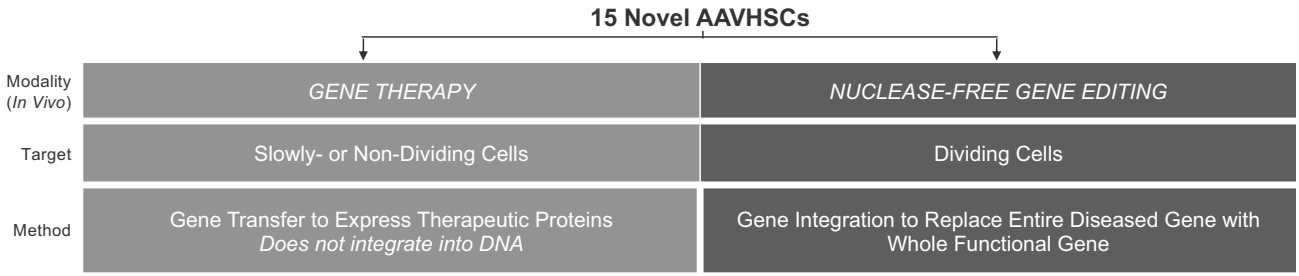


Figure 1. Our Genetic Medicines Platform.

Our novel AAVHSCs are packaged with either a gene therapy or a gene editing construct. Our gene therapy construct includes a functional copy of the gene and a promoter sequence that is designed to enable the gene to be turned on in the cell and ultimately transcribed to express the therapeutic protein of interest without integrating into the genome. Our gene editing construct includes lengthy guide sequences, or homology arms, which are designed to enable the specific alignment to the desired genomic location and then, through the natural process of HR, enable correction of the diseased gene in the genome by replacement with a whole functional copy. While others are working on identifying and testing ways to mitigate the inherent risk in working with nucleases for gene editing, our approach avoids the use of nucleases entirely. By targeting the HR pathway, our proprietary AAVHSCs mitigate the risks of nuclease-based technologies and have the potential to overcome other AAV vector limitations by combining the precision and high fidelity of HR with highly efficient in vivo gene integration, which we believe is capable of providing potential cures for a wide range of rare genetic diseases. Refer to Figure 2 below for a graphical depiction of how our AAVHSCs are designed to enable each therapeutic modality.

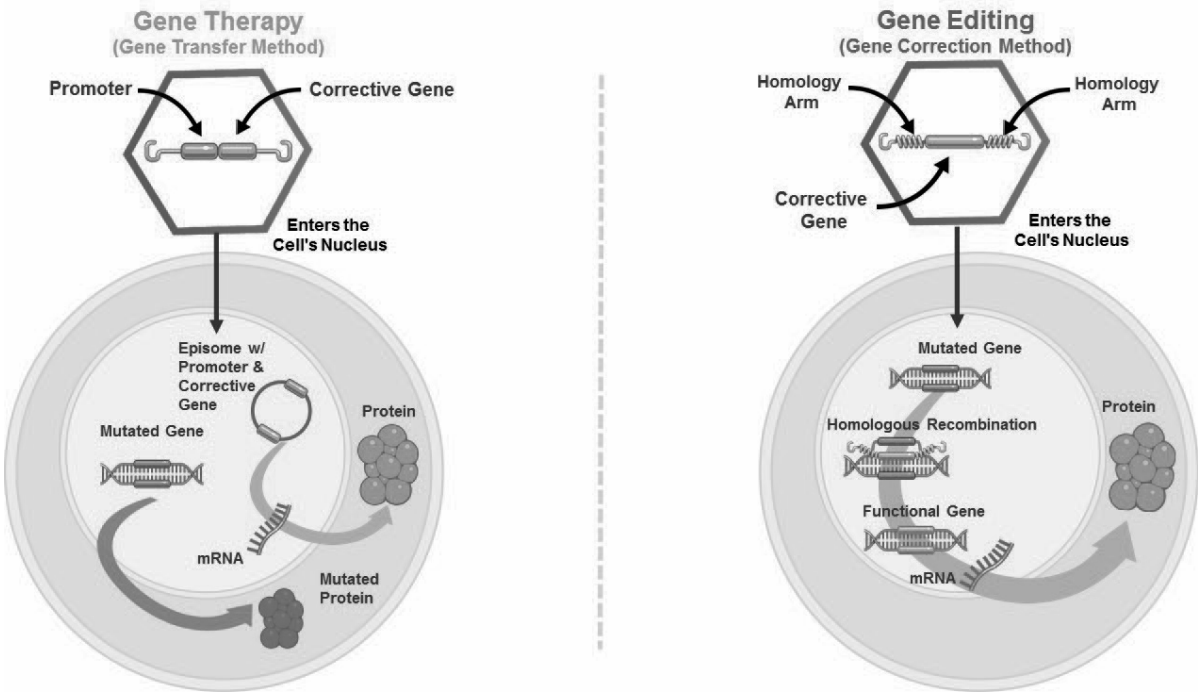


Figure 2. How our AAVHSCs are designed to enable each therapeutic modality.

We believe our approach has several key advantages that include:

- ***Our proprietary AAVHSC platform enables both gene therapy and gene editing modalities.*** Our platform provides us the flexibility to deliver genetic medicines through the best suited modality from either gene therapy or gene editing for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the tissues exhibit. Our AAVHSCs are naturally occurring as they were originally isolated from normal human CD34 cells and have the potential to result in an improved safety profile.
- ***Ability to perform nuclease-free gene editing mediated by HR with high gene integration efficiency.*** Our family of 15 novel AAVHSCs are designed to enable us to take advantage of the precise and high-fidelity process of HR-directed gene insertion for nuclease-free gene editing while achieving gene integration efficiencies that we believe are in therapeutic ranges and significantly higher than both nuclease-based and other AAV-based approaches. While nuclease-based gene editing technologies have achieved high gene knockout efficiencies in preclinical studies, which is only potentially useful for the minority of monogenic diseases, they have shown limited published evidence of gene integration efficiencies to date.
- ***Ability to introduce an entire gene into the genome or the precise repair of individual mutated nucleotides in addition to gene knockout.*** Our HR-based gene editing approach provides the flexibility to introduce an entire copy of a functional gene into the genome also known as gene integration, in addition to repairing single mutations or knocking out entire genes, thus allowing us to potentially address the significant majority of monogenic diseases.
- ***High precision and lack of unwanted off-target or on-target DNA modifications*.** Our gene editing approach leverages HR, which makes DNA repairs with high fidelity, and enables us to precisely perform gene integration without unwanted off- and on-target modifications. Furthermore, we are able to directly measure and confirm those modifications throughout the entire genome to ensure only the intended changes are made.
- ***Ability to target multiple tissues.*** In preclinical studies, intravenous administration of our family of AAVHSCs has demonstrated unique biodistribution properties across the serotypes and the ability to target a wide variety of tissues including the liver, CNS, PNS, muscle, bone marrow, eye and heart, enabling us to potentially address a broad range of monogenic diseases. The diversity of our AAVHSC library of capsids can also be expanded through targeted shuffling of the capsid sequences.
- **In vivo** ***administration with a single component delivery system.*** Our platform is designed to perform gene editing at high efficiency without the use of a nuclease, enabling us to deliver genetic medicines *in vivo* using a

single vector system that contains everything required to edit DNA. These characteristics simplify the manufacturing and delivery of our therapeutic candidates relative to existing nuclease-based gene editing approaches.

- ***Ability to target a broad range of patients given low frequency of pre-existing neutralizing antibodies.*** We believe our AAVHSCs can target a broad range of patient populations given the low prevalence of pre-existing neutralizing antibodies relative to other AAV vectors.

Our Pipeline Strategy

We believe our genetic medicines platform can be applied broadly to treat and potentially cure a wide range of genetic diseases, and we have carefully designed and prioritized our pipeline strategy to maximize this opportunity. We are initially pursuing monogenic diseases where we know exactly what we are seeking to correct and exactly which gene to insert into patients' cells. We are prioritizing monogenic diseases with significant unmet medical needs, validated regulatory pathways, well-accepted biomarkers and significant commercial opportunities. We are currently focused on developing product candidates to treat monogenic diseases in the liver, CNS and peripheral tissues, bone marrow, and the eye, given that our AAVHSCs naturally show a high degree of tropism or ability to enter cells in these organs and organ systems. These tissues are affected in many rare genetic diseases. We also plan to name a development candidate in a new therapeutic area in 2021, demonstrating the broader capability of our AAVHSC platform, which we believe may allow us to target diseases with larger patient populations in the future.

Our initial focus areas include developing product candidates for intracellular, inborn errors of metabolism and other genetic conditions that are especially well-suited to correction by our gene editing or gene therapy methods. In slow- or non-dividing cells (e.g., CNS and adult liver cells), gene therapy can potentially be curative, while rapidly dividing cells (e.g., hematopoietic CD34+ cells and pediatric liver cells) require a gene editing approach to provide a permanent correction in the genome that can be replicated with each cell division. We are purposefully deploying our proprietary AAVHSCs in certain indications first with a gene therapy approach followed by a gene editing approach, in order to maximize the likelihood of translating our platform into widespread clinical and commercial success.

We are building a deep pipeline across a wide range of diseases and tissue types to leverage the broad potential of our platform. We believe we have validated our AAVHSC platform in the liver based on the results observed in the dose-escalation portion of our Phase 1/2 trial with HMI-102, and we are also in IND-enabling studies with HMI-103, a gene editing development candidate for pediatric PKU. We have completed a comprehensive *in vivo* biodistribution study in NHPs in which all 11 of the AAVHSCs tested crossed the blood-brain-barrier and the blood-nerve-barrier, we are in IND-enabling studies with HMI-203, a gene therapy development candidate for MPS II, or Hunter syndrome, and we have recently completed IND-enabling studies with HMI-202, a gene therapy development candidate for MLD, the data from which we are using to further optimize a HMI-202 vector that we believe may lead to a better therapeutic profile. We continue our discovery efforts across multiple targets, including the liver, CNS, human stem cells and ophthalmology. We also may selectively enter into strategic alliances with pharmaceutical or biopharmaceutical companies to expand indications and accelerate development of programs where collaborators can contribute further disease-specific expertise to our platform.

Our Product Pipeline

The current status of our programs is summarized in the table below:

Our Strategy

Our goal is to transform the lives of patients suffering from severe genetic diseases by using gene therapy and gene editing to cure the underlying cause of the disease. The critical components of our strategy to achieve this goal include:

- ***Transform the treatment paradigm for rare genetic diseases with the delivery of single-administration curative therapies.*** Utilizing our proprietary AAVHSCs, we intend to deliver genetic medicines *in vivo* via a single administration to address the underlying genetic problem in a given disease. For each of the programs in our pipeline, we have identified the mutations of a specific gene that we believe can potentially be addressed by introducing a functional copy of a defective gene via gene therapy, or by replacing an aberrant gene with a healthy one via HR-driven gene integration, resulting in specific integration into the patient's genome. Our genetic medicines platform allows us to choose the best suited modality for each disease we pursue, and we believe our nuclease-free editing approach will provide life-long clinical benefits for patients.
- ***Advance our pipeline programs through clinical proof-of-concept and commercialization.*** We are continuing to advance the Phase 1/2 pheNIX clinical trial with investigational HMI-102 gene therapy for adults with PKU at multiple sites in the U.S. and reported positive clinical data from the dose-escalation phase of the trial in November 2020. We believe that our approach of initially utilizing one of our AAVHSCs for gene therapy in adult PKU patients while, in parallel, advancing gene editing for pediatric PKU patients will maximize the efficiency of our pipeline development while providing potential solutions for the unique needs of each particular PKU patient population. Given the well-defined nature of PKU and the concentration of treatment centers, we intend to bring HMI-102, if approved, to patients through a small, targeted internal commercial organization.
- ***Continue to expand our pipeline within existing therapeutic areas and expand into new therapeutic areas.*** We are focused on applying the transformative potential of our genetic medicines platform to develop treatments for patients with monogenic diseases. Initially, we are targeting diseases occurring in the liver, the CNS and PNS, the eye and the hematopoietic system. Given the ability of our AAVHSCs to deliver to a wide range of disease-relevant tissues, we believe there are many additional indications for which our technology may be applicable, including other inborn errors of metabolism, lysosomal storage diseases, hematological diseases, and ophthalmic diseases, as well as for *in vivo* cell therapy. We may also choose to selectively collaborate to expand the indications we can pursue and accelerate development of programs where collaborators can contribute further disease-specific expertise to our platform.
- ***Strengthen our platform by leveraging our discovery and development capabilities and selectively collaborating.*** We are committed to investing in our research and development activities to expand the capabilities of our platform, specifically our AAVHSCs as well as HR gene editing technology. We are optimizing our AAVHSC genetic medicines platform with focused efforts on AAVHSC characterization, gene therapy and editing construct design and screening, and genomic assays to characterize and quantify our

editing technology. To augment our own efforts, we intend to continue to collaborate with academic institutions to pursue new scientific and therapeutic insights and strengthen our position as a leader in gene integration.

- ***Control manufacturing through our in-house capabilities.*** We have developed an internal process development platform that accommodates both gene therapy and gene editing technologies. We have constructed a 25,000 square foot GMP manufacturing facility with 1,500 liters of active capacity that is designed to accommodate all pipeline programs, and we are now producing all of the clinical material for the pheNIX trial in this facility. Additionally, we have executed our manufacturing platform with multiple product candidates at the 2,000-liter bioreactor scale. We believe the quality, reliability and scalability of our gene therapy and gene editing manufacturing approach is a core competitive advantage crucial to our long-term success and that internal manufacturing capabilities will further safeguard our intellectual property.
- ***Continue to strengthen and expand our intellectual property portfolio.*** We have exclusive worldwide rights to our technologies including issued composition of matter patents in the United States for fifteen of our novel AAVHSCs for both gene therapy and gene editing. We exclusively acquired rights to this foundational intellectual property for the AAVHSCs from City of Hope, or COH, for developing and commercializing therapeutics based on these vectors. We continue to focus on strengthening our intellectual property estate through the discovery of new AAVHSCs, further characterization around our existing AAVHSCs as well as the core technology involved in delivering our product candidates to patients. To further advance our leadership in gene therapy and nuclease-free gene editing, we actively explore opportunities to collaborate with other leading scientific institutions in the field.

Our Genetic Medicines Platform

Our proprietary genetic medicines platform is built on our novel AAVHSCs, which allow us to choose the best suited modality from either gene integration or gene therapy for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the target tissues exhibit. The unique characteristics of our platform enable nuclease-free gene editing, specifically gene integration, and broad, systemic tissue distribution. Our AAVHSCs are designed to directly integrate corrective DNA through HR with therapeutically relevant efficiencies. Our HR-based gene editing approach utilizes a single component AAV system that contains everything required to selectively edit DNA with no need for exogenous nucleases or editing machinery. This single-component system simplifies the manufacturing and delivery of our therapeutics. We believe our gene editing approach has the potential to be curative as it provides a permanent correction in the genome that is then replicated with each cell division so that new generations of cells will carry the corrected gene. Our AAVHSCs are naturally occurring and have been modified to be non-replicating to minimize potential safety issues. We believe our platform's combined attributes will allow us to develop more efficient and safer therapeutics for a wide range of genetic diseases.

Homologous Recombination—A Powerful Basis for Gene Editing

Unlike other gene editing approaches, our technology is based on the natural DNA repair process of HR and is designed to enable precise and efficient gene integration without an exogenous nuclease.

Our genetic medicines platform induces the endogenous HR cellular process using our AAVHSCs to insert replacement or corrective genes into cells that contain mutated or deleterious genes (refer to Figure 3 below). We engineer our AAVHSCs to contain long, single-stranded DNA corrective sequences highly specific to the target region in the genome. These single-stranded DNA molecules are then delivered to cells in our AAVHSC vectors, which we believe results in precise and efficient gene integration via the HR pathway. The design of our long and specific sequences, up to the 4.7 kilobase packaging limit of our AAVHSCs, is intended to significantly reduce the risk of off-target integration. Based on the packaging size of our AAVHSCs, we believe our capsids are capable of accommodating and delivering up to approximately 85% of the genes in the human genome and thus have the ability to address a significant majority of genetic disorders. We typically use homology arms as long as 1,600 base pairs of DNA to target corrective gene sequences into precise regions of the genome, in contrast to the guide sequences used in CRISPR/Cas 9-based gene editing, which are typically less than 30 base pairs in length. We also benefit from the ability of our platform to utilize HR to precisely insert gene sequences into the DNA of cells, similar to how mammalian cells repair their own DNA. In order to bring about the excision and subsequent replacement that some forms of gene editing require, those other approaches must combine multiple additional techniques and deliver into the cell the requisite cellular machinery at the right place at the same time, increasing the complexity of the task, introducing the possibility of integrating the wrong DNA due to non-HR-based repair mechanisms, and reducing the likelihood of success.

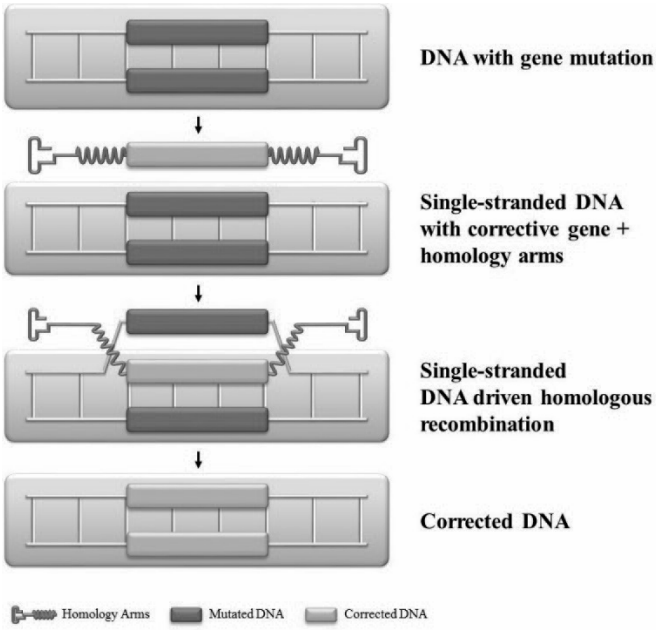


Figure 3. Schematic of homologous recombination.

Our Proprietary AAVHSCs

Our genetic medicines platform is based on a family of 15 proprietary AAVHSCs which we can deploy with either gene therapy or gene editing constructs. We have the opportunity to expand on this family through capsid shuffling. Both applications rely on a unique ability of our AAVHSCs to efficiently target multiple tissues in the body. Our AAVHSCs were isolated from human stem cells and we believe they can direct nuclease-free gene integration with higher efficiency relative to that indicated in published data for other AAV-based gene editing approaches. Our AAVHSCs display the following advantages:

Single AAVHSC Platform for Both Gene Therapy and Gene Editing Modalities

Our platform provides us the flexibility to deliver genetic medicines through the best suited modality from either gene therapy or gene editing for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the tissues exhibit.

Ability to Perform In Vivo *Nuclease-free Gene Editing Mediated by HR*

To demonstrate the utility of AAVHSC-mediated gene editing *in vivo*, we conducted a series of experiments at our headquarters. We obtained preclinical proof-of-concept for *in vivo* editing efficiency and tissue-specific expression through the

design of a promoter-less luciferase construct targeting the murine Factor 8, or *F8*, locus using AAVHSC15. *F8* is a locus in the murine genome that is known to have a strong promoter but is expressed only in the liver. The editing cassette was flanked by 800bp homology arms with sequences homologous to an insertion site within intron 6 of the murine *F8* gene. The expression cassette (hereafter mF8-Luc) also included a canonical splice acceptor sequence for splicing into the endogenous *F8* transcript and a ribosomal skipping 2A element for independent translation of the *F8* and luciferase proteins. The luciferase transcript was terminated by an SV40pA element.

AAVHSC15 packaging the promoter-less F8 targeting cassette (AAVHSC15-mF8-Luc) was administered by a single intravenous injection to albino-B6 mice to evaluate the level of targeted integration and expression from the murine *F8* locus. Six- to seven-week-old albino-B6 mice were dosed with AAVHSC15-mF8-Luc and reporter expression was followed over time. High levels of luciferase expression in livers of mice transduced under these conditions were observed. Bioluminescence increased within a week post-dosing, reached a maximum within 1-2 months and remained significantly above that observed in vehicle-treated mice until the end of the study at 470 days post-dosing (*= P<0.0001 vs vehicle). *Ex vivo* imaging of tissues harvested on Day 470 showed highest luciferase expression within liver (*=p<0.008 vs vehicle), greater than 100-fold higher than other tissues assessed (**=P<0.0001 vs other tissues), which demonstrated specificity of tissue targeting by AAVHSC15-mF8-Luc (refer to Figure 4 below). At 470 days post-dosing, vector genome levels within livers of treated mice were on average 4.7 ± 2.7 vector genomes/allele.

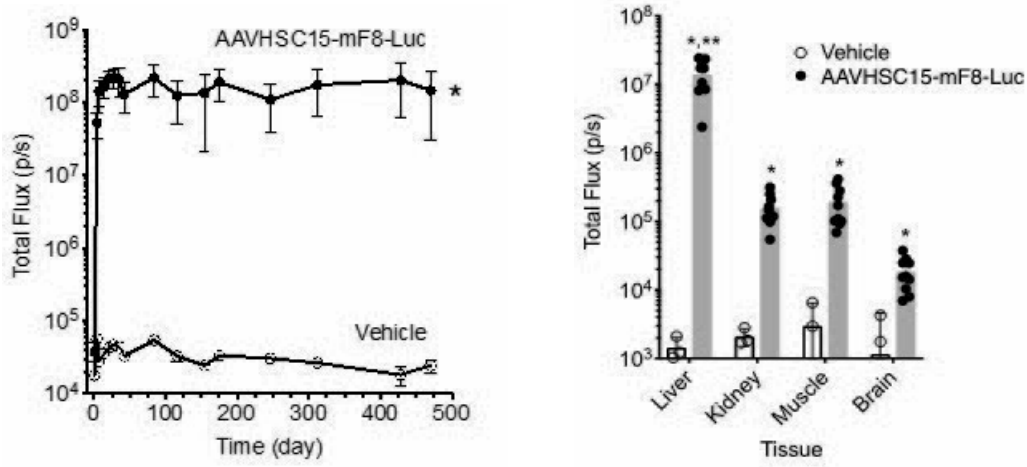


Figure 4. *In vivo* gene editing proof-of-concept at the murine F8 locus.

To molecularly characterize AAVHSC15-mF8-Luc-mediated genome editing, a ddPCR-based quantitative F8 editing assay was established. A combination of a F8 locus specific primer and probe and editing vector specific primer and probe in the FAM and HEX channel, respectively, were used to calculate the fraction of F8 loci that have an inserted luciferase transgene. Editing signal in this assay showed linear detection between 0 and 30% allele frequencies based on a standard curve of known molar ratios of edited/unedited alleles. Assay signal was specific as digestion of input DNA with HindIII prior to the ddPCR assay separated the payload from the genomic reference, causing each target to segregate independently within each droplet eliminating the editing signal.

Genomic DNA was isolated from livers of treated mice at termination of the study at 470 days post-dosing and editing of the murine F8 locus was assessed by the ddPCR editing assay. Mice treated with AAVHSC15-mF8-Luc at this initial low dose of 5e12 vg/kg showed a statistically significant increase in genome editing efficiencies with up to 2.8% of alleles edited (mean 0.8% of alleles edited with a range of editing efficiencies 0.2-2.8%; p<0.03 vs. vehicle). These data demonstrate that AAVHSC15 mediated long-term in vivo editing of the targeted locus within the liver of mice at this dose.

To assess whether expression from AAVHSC15-mF8-Luc was episomal, an AAVHSC15-Luc editing vector was prepared with the splice acceptor sequences removed (designated AAVHSC15-Δ2AmF8-Luc) but maintained an intact Met initiator codon. Relative to an IV injection of vehicle alone, injection of AAVHSC15-mF8-Luc increased luciferase expression at Days 3, 7, and 14 post-dosing, similar to the results described above. By contrast, luciferase expression was reduced >95% for mice that received an identical dose of AAVHSC15-Δ2AmF8-Luc (refer to Figure 5 below).

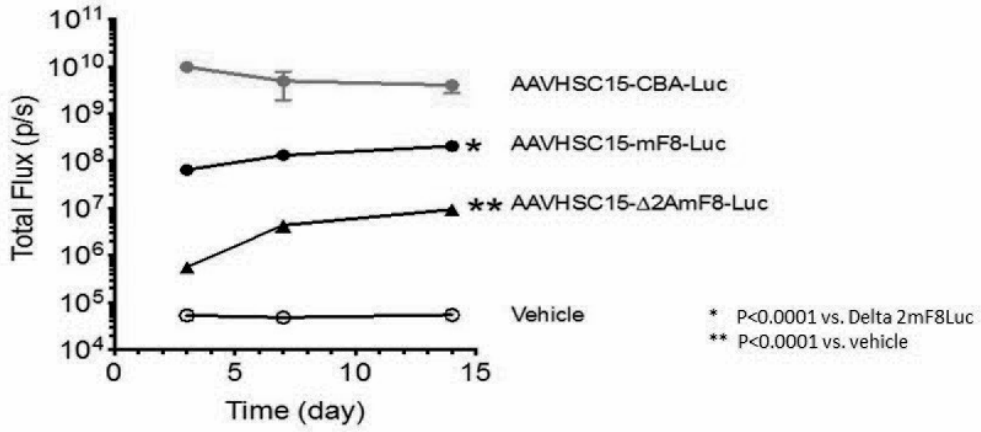


Figure 5. *In vivo* gene editing proof-of-concept at the murine F8 locus.

Ability to Introduce Entire Gene into the Genome Mediated via HR

Initial data supporting the targeted integration of entire genes using AAVHSCs into the genome have been previously published. We have expanded on those initial studies by demonstrating the targeted integration of a full-length luciferase gene into the murine F8 locus, as described above and illustrated in Figures 4 and 5. This preliminary proof of principle led to the discovery and development of a therapeutic program for pediatric PKU focused on the targeted integration of a full-length *PAH* cDNA into the human *PAH* locus. We have successfully inserted full-length cDNA encoding luciferase and PAH into two separate genomic regions *in vivo* reaching levels of efficiency required for therapeutic efficacy. HMI-103, the development candidate for pediatric PKU, is described in detail below.

The ability to introduce entire genes specifically into the genome at these efficiencies provides an opportunity to target multiple monogenic diseases where the correction of a defective gene would result in therapeutic benefit. Given that a majority of monogenic diseases harbor mutations that render the gene inactive, we believe our gene integration modality can be expanded well beyond our initial focus on liver-based inborn errors of metabolism.

High Precision and Lack of Unwanted Off-target or On-target DNA Modifications

Using next-generation sequencing technologies, we have developed methodologies to test for on-target mutations at the site of integration. Using these methods, we observed that HR using our AAVHSCs is very precise at the site of correction. We did not detect any co-incident random mutations at or above our lower limit of detection (0.5%) or inverted terminal repeat, or ITR, sequences at the site of integration.

We developed a method to enable whole genome unbiased next-generation sequencing for the detection and mapping of off-target integration sites. By leveraging the potential ability of our AAVHSCs to drive HR-based targeted integration, we can utilize next-generation sequencing technologies to identify and quantify where the inserted sequence maps. Using this method, and testing integration into the human AAVS1 locus, we estimate that 99.967% of insertions (>2.2 million reads) are at the targeted site and that the balance is within expected background of the assay. We have expanded on this assay to characterize the on-target precision of integration at the *PAH* locus in support of HMI-103, described below.

Ability to Target Multiple Tissues

In preclinical studies, intravenous administration of our family of AAVHSCs has demonstrated the ability to target a wide variety of tissues including the liver, CNS, PNS, muscle, bone marrow, eye and heart. Specifically, we have generated evidence of our AAVHSCs' ability to target a number of tissues including:

- neurons throughout the brain, spinal cord, and dorsal root ganglion by crossing the blood-brain-barrier and the blood-nerve-barrier;
- retinal ganglion cells and neurons of the retinal outer nuclear layer; we have also demonstrated the ability to target retinal tissue via intravenous injection as well as multiple layers of target cells, including photoreceptors, retinal pigment epithelial cells and horizontal cells, through sub-retinal injection;
- skeletal muscle myocytes in all skeletal muscle tissues examined, including gastrocnemius, soleus, diaphragm, esophagus, and biceps;
- cardiomyocytes throughout the heart; and
- extensive liver tropism.

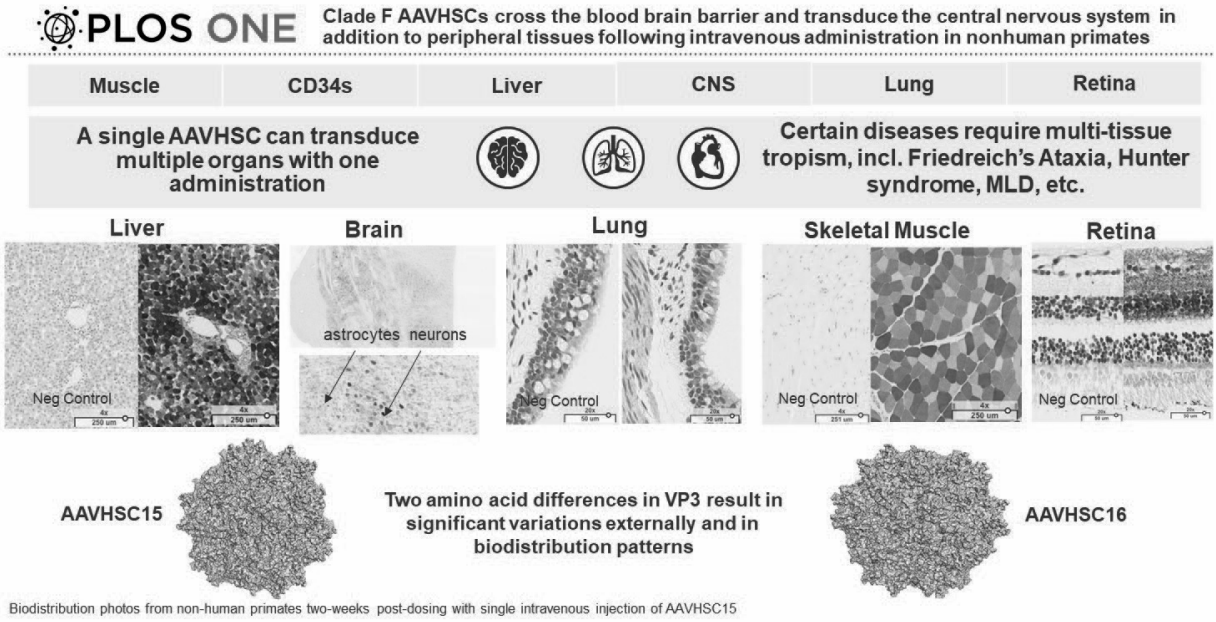


Figure 6. Our family of AAVHSCs has demonstrated the ability to target a wide variety of tissues.

In Vivo *Administration with a Single Component Delivery System*

Our platform is designed to perform gene integration at higher efficiency without the use of a nuclease, enabling us to deliver genetic medicines *in vivo* using a single vector system (refer to Figure 7 below). Existing nuclease-based gene editing technologies, when replacing a defective gene with a functional gene through gene editing, require the use of two or more different vector constructs in combination to perform their gene editing functions. One or more vector constructs house the nuclease, and the other vector construct houses the DNA template, and all vectors must reach and penetrate the specific target cell at the same time to edit the DNA. In contrast to these nuclease-based gene editing technologies, our AAVHSC technology is a single component system that contains everything required to selectively integrate DNA with no need for additional exogenous nucleases, template DNA or editing machinery.

We believe our ability to perform gene integration at efficiencies that are greater than both nuclease-based and other AAV-based approaches, coupled with our single component delivery system, enable us to administer genetic medicines *in vivo.* We believe the advantages of *in vivo* administration of therapeutics via a single component delivery system include the following:

- simpler and faster manufacturing relative to *ex vivo* resulting in reduced manufacturing costs;
- improved delivery of therapeutic as only a single vector is required to reach a cell instead of multiple vectors;
- ease of use for the patient, eliminating the need for mobilization and myeloablation, a common requirement for many *ex vivo* gene editing therapies; and
- improved safety profile, as compared to an *ex vivo* therapy.

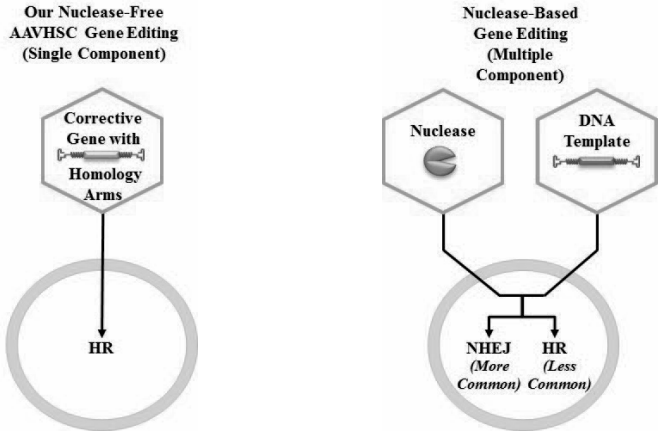


Figure 7. Our nuclease-free AAVHSC single component gene editing construct vs. nuclease-based multiple component gene editing construct for gene editing applications.

Ability to Target a Broad Range of Patients Given Low Frequency of Pre-Existing Neutralizing Antibodies

A potential concern for all AAV vectors is the presence of pre-existing neutralizing antibodies that have the potential to reduce their effectiveness. We conducted a study across 100 human serum donors representing different ethnic segments of the U.S. population. Based on the initial results, we believe the findings suggest that approximately 80% of individuals lack antibodies that recognize AAVHSCs, which is comparable to AAV9, a commonly used vector for development of other gene therapies. These findings were published in *Human Gene Therapy Clinical Development* in March 2018.

Our Product Candidates

We believe our genetic medicines platform can be applied broadly to treat and cure a wide range of genetic diseases and have carefully designed and prioritized our pipeline strategy to maximize this opportunity. We are initially pursuing diseases where the genetic abnormality is known and is found in a single gene.

HMI-102 for Treatment of PKU in Adult Patients and HMI-103 for Treatment of PKU in Pediatric Patients

Our lead program, HMI-102, is an AAVHSC vector gene therapy candidate designed to treat PAH deficiency, the underlying genetic cause of PKU. We have received orphan drug designation from the FDA and the European Medicines Agency, or EMA, for the use of AAVHSC15 expressing *PAH* for the treatment of PAH deficiency. In June 2019, we commenced enrollment of our Phase 1/2 pheNIX clinical trial with HMI-102 gene therapy for adults with classical PKU at multiple sites in the U.S. and reported positive clinical data in November 2020. We are currently in the dose expansion Phase 2 portion of the pheNIX trial. HMI-102 is intended to treat adult patients with deficiencies in PAH regardless of the specific underlying *PAH* mutation. We are also developing HMI-103, an AAVHSC vector gene editing candidate, to address the pediatric PKU population. HMI-103 is designed to replace the defective *PAH* gene through the targeted integration of a normal copy into the *PAH* genomic region. We are in IND-enabling studies with HMI-103, and we expect to initiate a Phase 1/2 dose-escalation clinical trial in 2021.

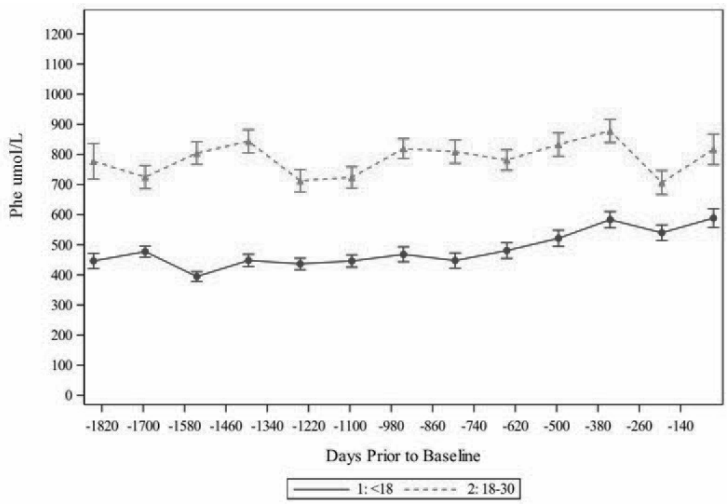
PKU Disease Overview

PKU is an inborn error of metabolism that results from mutations in the *PAH* gene. PAH is an enzyme that is normally expressed in the liver and is necessary to metabolize dietary phenylalanine, or Phe, to the amino acid tyrosine, or Tyr. Tyr is a product of Phe metabolism and a precursor to neurotransmitters, and its increase indicates increased enzymatic activity. PKU results from mutations in *PAH* that render its enzymatic activity deficient. If it is not metabolized by PAH, Phe builds up throughout the body, including in the blood and the nervous system. Approximately 75% of all dietary Phe is typically metabolized by PAH, so the absence of PAH leads directly to the pathological excess of Phe as well as a deficiency of Tyr. Excessive blood Phe and low levels of Tyr result in intellectual disability, which is possibly caused by a variety of mechanisms including effects on neuronal development, myelination, and neurotransmitter synthesis. Blood Phe is an easily measurable and translatable biomarker. It is also a validated clinical endpoint in clinical trials for PKU, facilitating both a rapid path to the clinic and characterization of therapeutic response.

Newborns in all 50 states are screened for PKU. It has been estimated that the incidence of PKU in the United States is one in 12,707, which translates to approximately 350 cases per year with an overall prevalence of 16,500. It has also been estimated that the prevalence of PKU in the European Union is 25,000. Worldwide, the estimated prevalence is 50,000 with 1,000 to 1,500 new cases annually.

The majority of patients are identified soon after birth and are primarily treated by dietary restriction of Phe. While Phe-restricted diets have dramatically reduced the intellectual deficiencies associated with this disease, they fail to address the cognitive and behavioral problems that continue throughout a patient's life. Lifetime adherence to a Phe-restricted diet is challenging and blood Phe within the recommended range is not achievable for the vast majority of patients. The inability to achieve recommended levels of Phe results in neurological as well as metabolic problems. Long-term studies in adults identify neurocognitive, psychosocial, quality of life, growth, nutrition, bone pathology and maternal PKU outcomes that are suboptimal despite early and continuous treatment with diet. In a retrospective study of PKU patients peer reviewed and published in the journal of *Molecular Genetics & Metabolism*, young children were adherent to Phe-restricted diet, whereas most adolescents (79%) did not achieve recommended Phe levels, and 88% of adults were no longer on a Phe-restricted diet. Relaxing of dietary restrictions beyond preschool years, or failure to adhere to physician-assigned diets, which is the current guideline for most adolescents and adults, results in loss of metabolic control and wide fluctuations in Phe levels that are both directly associated with progressive neurological damage.

We conducted a five-year retrospective chart review of PKU patients, which confirmed key elements of our proposed Phase 1/2 clinical trial design. Consistent findings from two PKU academic centers of excellence in the U.S. in 152 PKU patients showed that actively monitored patients, including those on restrictive low Phe diet, had Phe levels well-above the recommended threshold of 360 umol/L, based on current U.S. treatment guidelines, underscoring the need for treatments that restore the normal biochemical pathway (refer to Figure 8 below). Furthermore, we confirmed that Phe continues to be higher, even on standard of care, in the classical PKU population, defined as patients with Phe levels greater than 1200 umol/L (66% of the study population) without treatment, and was significantly elevated in the adult population compared to those patients who were less than 18 years of age. These findings were published in *Molecular Genetics and Metabolism* in December 2019.



	Combined Sites
# Patients	152
% Female / Male	51% / 49%
% Classical PKU	66%
≥18	57%

Figure 8. Retrospective five-year chart review demonstrates actively monitored adult classical PKU patients across two academic centers have Phe levels >700 umol/L.

Current Treatments

There are currently no available treatments that address the core underlying genetic biochemical defect in PKU, the deficiency of PAH.

Saproterin dihydrochloride, or Kuvan, is an FDA-approved therapy to reduce elevations in serum Phe. Saproterin is a synthetic version of BH4, a cofactor that is required for PAH activity. Treatment with BH4 can activate residual PAH enzyme activity, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients; however, clinical data suggests that saproterin is not fully effective in lowering high serum levels of Phe back to normal levels and must be used in conjunction with a low Phe diet. Worldwide sales of Kuvan were $458 million in 2020.

Pegvaliase, or Palynziq, is a pegylated plant-derived enzyme called phenylalanine ammonia lyase that was approved in the U.S. by the FDA in 2018 and in Europe by the EMA in 2019. This approach does not correct the underlying genetic disorder (PAH deficiency) and will not reconstitute the natural pathway. We believe Palynziq to have certain limitations including that it must be administered via daily injections and its label contains a black box warning that it can cause severe allergic reaction (anaphylaxis) that may be life-threatening and can happen at any time during treatment with Palynziq. The label states that patients must carry auto-injectable epinephrine with them at all times during Palynziq treatment. Patients in its Phase 3 trials did not meet the secondary efficacy endpoints for cognitive benefit. Worldwide sales of Palynziq were $171 million in 2020.

Our Gene Therapy and Gene Editing Approaches to PKU

We are taking two approaches towards developing a potential therapy for PKU. The first is a gene therapy in which a gene construct encoding human *PAH* is delivered to liver cells where it directs production of normal PAH via episomal expression driven off a liver specific promoter. The second potential therapy involves gene integration of a normal copy of the *PAH* gene into the defective gene of affected patients. We believe that the gene therapy approach offers an expedited clinical development path towards delivery of a therapeutic to adult and adolescent patients where the majority of target cells are non-dividing in the liver. We believe the gene integration approach would be more suitable in newborn and pediatric patients due to the higher rate of dividing cells as the child grows. The goal of both approaches is to enable production of functional PAH, thus restoring the normal biochemical pathway of Phe metabolism. This can reduce the abnormally high levels of Phe in the blood, while also increasing Tyr levels, the product of PAH-driven Phe metabolism. Using gene editing to correct the defective *PAH* gene in young patients has the potential to provide long-term benefit as the corrected gene will persist as cells replicate. Correcting the gene early in disease progression has the potential to normalize not only Phe levels, but also Tyr levels, the product of the Phe metabolism and a precursor to neurotransmitter synthesis. This may allow affected children to avoid many of the serious neurological consequences associated with PKU.

We believe that an effective gene therapy or gene editing treatment for PKU has the potential to eliminate the need for Phe-restricted diet and may lead to significant improvements in the morbidity and quality of life for patients. Published estimates suggest that restoration of PAH activity to 10% or more of normal levels would lead to significant improvements in serum Phe levels and potentially represent a curative therapy.

HMI-102: Our Gene Therapy Approach for PKU

We identified HMI-102 as our lead product candidate after screening multiple vector constructs. HMI-102 consists of an AAVHSC15 vector containing the coding sequence of human *PAH* under control of a promoter designed to continuously express *PAH*, specifically in the liver. We chose AAVHSC15 as the basis of this product candidate because of its tropism for the liver, the normal site for PAH protein expression.

Phase 1/2 pheNIX Clinical Trial with HMI-102

In June 2019, we commenced enrollment of our Phase 1/2 pheNIX clinical trial with HMI-102, which is designed to evaluate the safety and efficacy of the investigational gene therapy in a randomized, concurrently controlled, dose-escalation study in adult patients aged 18–55 years old with classical PKU. The dose-escalation phase of the trial was designed to evaluate safety and efficacy of ascending doses of HMI-102 to enable the selection of a dose for the randomized, concurrently controlled Part B phase of the trial, which has the potential to be converted to a registrational trial. We enrolled six patients in the dose-escalation phase across three dose cohorts (refer to Figure 9 below).

Cohort (Dose Level)	Patient #	Sex	Age	Per Protocol Baseline Phe µmol/L	Wks Post-HMI-102	Pre-Existing Underlying Immune Conditions
Cohort 1 (Low; 2E13 vg/kg)	1	F	36	1140	52 (End of Study)	-
	2	M	49	1020	52 (End of Study)	-
Cohort 2 (Mid; 6E13 vg/kg)	3	M	24	1010	48	-
	4	F	21	1060	44	Asthma
Cohort 3 (High; 1E14 vg/kg)	5	F	31	1660	28	Asthma, Eczema
	6	M	33	1060	13	-

No one failed screening due to pre-existing neutralizing antibodies (Nabs)

Baseline = Per protocol, day prior to dosing
As of data cutoff date of Oct 19, 2020

Figure 9. Baseline characteristics for patients in the dose-escalation phase of the pheNIX clinical trial.

In November 2020, we reported positive clinical data from the dose-escalation phase of the trial. Safety data from the six patients as of the cutoff date of October 19, 2020, showed HMI-102 was generally well-tolerated, and there were no treatment-related serious adverse events. There were no clinically significant changes in electrocardiogram or vital signs, no clinical signs of complement activation and no adverse events related to bilirubin. Alanine aminotransferase, or ALT, elevations, which are common in AAV-based gene therapy trials, were asymptomatic and managed with increased steroids when necessary. Efficacy data showed significant plasma Phe reductions in Cohorts 2 and 3, compared to Cohort 1 ($P<0.004$ post-hoc comparison using repeated measures MANOVA, or multivariate analysis of variance,/regression analysis), with two patients achieving target Phe levels per treatment guidelines, even while self-liberalizing diet. Compared to baseline, patients in Cohorts 2 and 3 also displayed Tyr increases and Phe-to-Tyr ratio decreases consistent with PAH enzymatic activity.

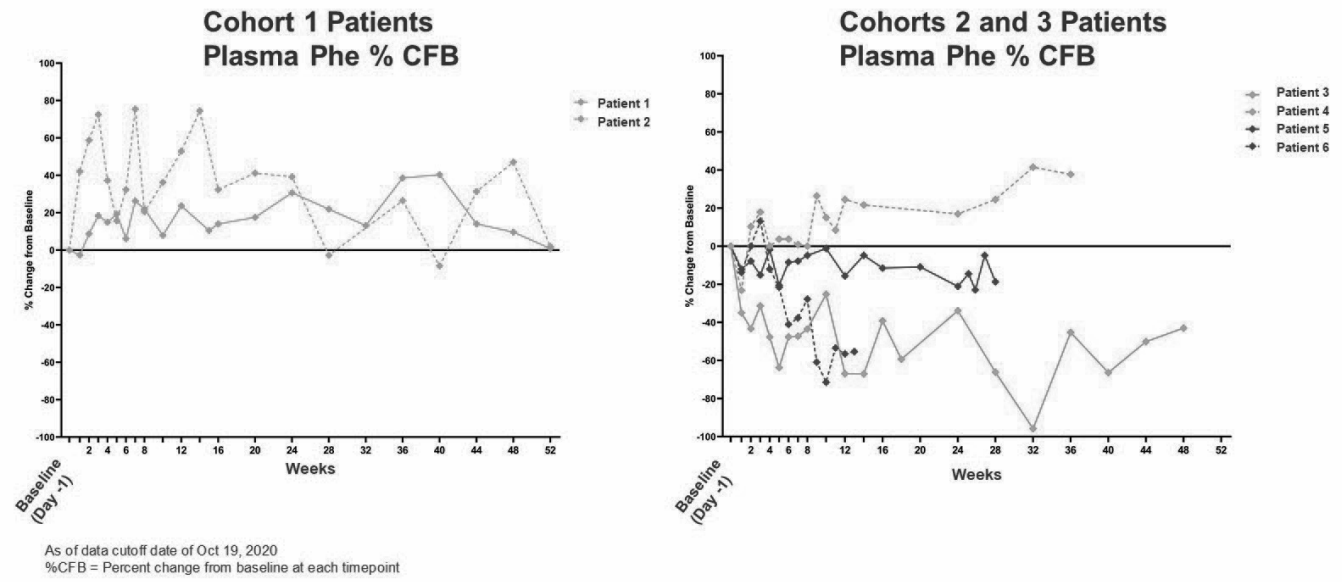


Figure 10. Data from Cohort 1 (low-dose) as compared to data from Cohort 2 (mid-dose) and Cohort 3 (high-dose) in the dose-escalation phase of the pheNIX clinical trial as of the data cutoff date of October 19, 2020.

Efficacy data from the two patients in Cohort 1 did not show any meaningful reductions in plasma Phe throughout the study, which they have completed. We believe this first and lowest dose in this dose-escalation study was insufficient to impact Phe levels. In Cohort 2, one patient experienced a marked Phe reduction from baseline level of 1,010 μmol/L, and recorded five plasma Phe values <360 μmol/L, and many of <600 μmol/L. The mean percentage change from baseline for this patient are reported in three categories: Phe, Tyr, and the Phe-to-Tyr ratio. For patients with PKU, the goal for a therapy is to lower Phe values, increase Tyr values and lower the overall Phe-to-Tyr ratio. As of the cutoff date, this patient's mean percentage change from baseline showed a 48.6% reduction in plasma Phe, an 81.1% increase in Tyr and a 70.8% decrease in the Phe-to-Tyr ratio. We believe these results are consistent with an increase in PAH enzymatic activity and increased Phe metabolism. These results were observed even while the patient self-liberalized diet, including a mean percent change from baseline of more than a 100% increase in dietary Phe intake.

The other patient in Cohort 2 did not experience a similar reduction in plasma Phe, but this patient had pre-existing immune conditions and experienced Grade 3 ALT elevation, which we believe may have affected the results. As of the cutoff date, this patient had a mean percentage change from baseline of 13% increase in plasma Phe, with a 131.1% increase in Tyr and a 45.5% decrease in the Phe-to-Tyr ratio. This also occurred while the patient self-liberalized diet with a mean percent change from baseline of 140.5% more dietary intact protein, 289% more dietary Phe intake and 75.6% decreased dietary Tyr intake. We believe the findings in this patient may be suggestive of PAH enzymatic activity sufficient to increase the patient's Tyr concentration from its low baseline, but not sufficient to reduce this patient's Phe.

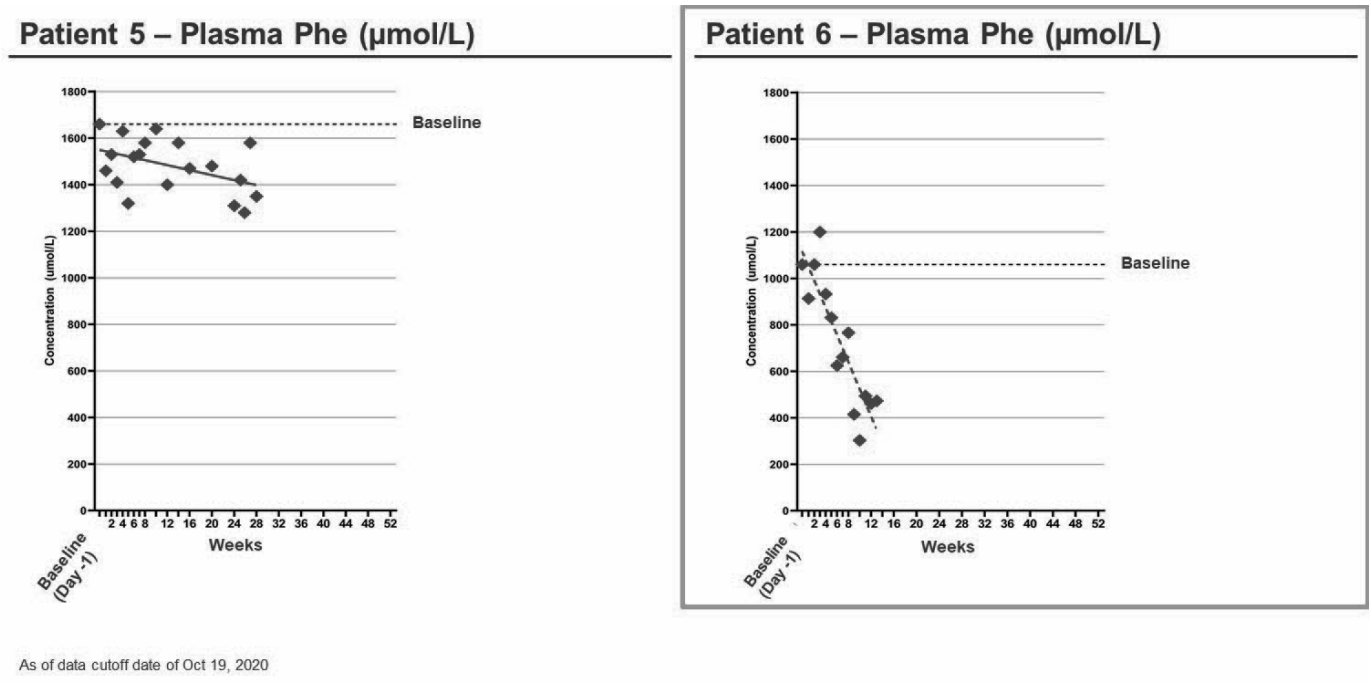


Figure 11. Data from patients 5 and 6 in Cohort 3 (high-dose) in the dose-escalation phase of the pheNIX clinical trial as of the data cutoff date of October 19, 2020.

In Cohort 3, Patient 5 had pre-existing underlying immune conditions, which we believe impacted efficacy. As of the data cutoff date, Patient 5 experienced an increase in the mean percentage change from baseline in Tyr of 22.6% and a reduction in the mean percentage change from baseline in the Phe-to-Tyr ratio of 25.4%, but did not experience a similar reduction in plasma Phe. We believe the findings in this patient may also be suggestive of PAH enzymatic activity, which was enough to improve Tyr, but not enough to reduce Phe.

Patient 6 showed a marked reduction in Phe from baseline level of 1,060 µmol/L, and recorded one plasma Phe value <360 µmol/L and several plasma Phe values <600 µmol/L through the 13 weeks of observation as of the cutoff date. The mean percentage change from baseline was a 31.4% reduction in plasma Phe, a 40.3% increase in Tyr and a 52.4% decrease in the Phe-to-Tyr ratio. These results were observed while the patient self-liberalized diet, including a mean percent change from baseline of more than 45.4% increase in dietary intact protein and a 41.8% increase in dietary Phe. This patient had the benefit of increased monitoring, which also allowed for tighter management of steroids, including additional steroids at the first observation of ALT increases.

Cohort (Dose Level)	Patient #	Mean % Change from Baseline			Diet Mean % Change from Baseline			
		Plasma Phe	Plasma Tyr	Phe-to-Tyr Ratio	Total Protein*	Intact Protein	Phe Intake	Tyr Intake
Cohort 1 (Low; 2E13 vg/kg)	1	+16.5	-0.1	+20.9	+4.5	+14.2	+0.4	-10.8
	2	+35.4	+16.1	+22.0	-3.9	+66.0	+78.5	-14.7
Cohort 2 (Mid; 6E13 vg/kg)	3	-48.6	+81.1	-70.8	-4.8	-30.0	+100.6	-1.9
	4	+13.0	+131.1	-45.5	-9.6	+140.5	+289.0	-75.6
Cohort 3 (High; 1E14 vg/kg)	5	-10.8	+22.6	-25.4	-16.9	-16.9	-18.5	-21.0
	6	-31.4	+40.3	-52.4	+8.8	+45.5	+41.8	+3.4

*Per protocol, each patient's total protein was required to be maintained at +/-25% of baseline

Figure 12. Summary data from the dose-escalation phase of the pheNIX clinical trial as of the data cutoff date of October 19, 2020.

Based on the safety and efficacy results observed in the dose-escalation phase as of the cutoff date, in early 2021 we advanced to the randomized, concurrently controlled, expansion phase of the pheNIX trial, which has the potential to be converted to a registrational trial. We selected two doses for the expansion phase: 6E13 vg/kg and 8E13 vg/kg. We expect to share initial clinical data from this portion of the trial by the end of 2021.

Preclinical Studies with HMI-102

The potential of an AAVHSC15-delivered *PAH* gene was assessed in a well-established mouse model of PKU called the Pah^{enu2}, or ENU2, mouse. This model contains a mutation in the murine *Pah* gene that results in abolished activity and elevated serum Phe levels. Baseline levels of serum Phe in these mice are approximately 1,500 micromoles per liter compared to normal levels of approximately 80 micromoles per liter, levels that are similar to those seen in classical PKU patients and normal controls, respectively. Single intravenous injections of HMI-102 into these PAH-deficient mice resulted in reductions of serum Phe to levels that are within the range for normal mice. As depicted in Figure 13, the reduction in serum Phe levels persisted for 48 weeks in treated mice on a normal protein diet, consistent with the lifespan of the model. In addition to a reduction in serum Phe, the administration of our gene therapy candidate also resulted in elevations of serum Tyr due to the restoration of the normal biochemical pathway.

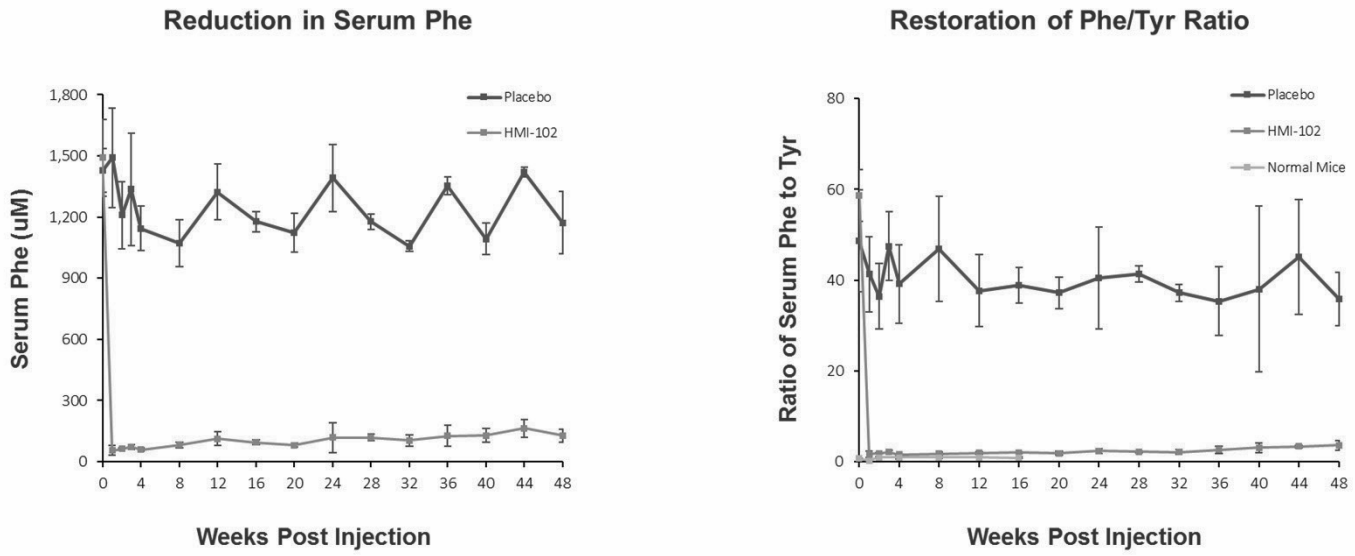


Figure 13. A single injection of HMI-102 resulted in rapid and sustained reductions in serum Phe and increased Tyr levels in PAH-deficient mice that are on a regular diet.

A subsequent study was performed to further characterize the effect of HMI-102 on normalizing levels of Phe and neurotransmitter metabolism in the brain. As shown in Figure 14, a single administration of HMI-102 in the ENU2 mouse model reduced levels of Phe in the brain to normal levels as measured at 4 weeks post-dosing. Furthermore, the brain concentrations of 5-HIAA, a metabolite of serotonin, was increased to normal levels. These results indicate that HMI-102 administration directly impacts the metabolic pathway associated with loss of PAH.

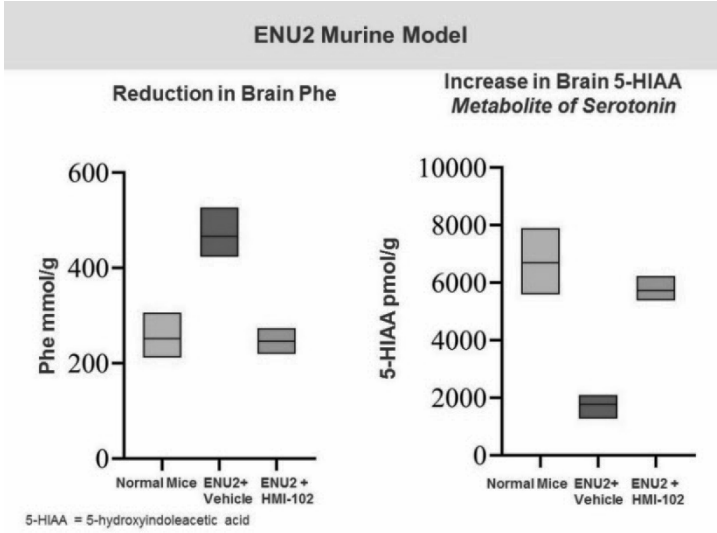


Figure 14. HMI-102 normalizes key neurological measures underscoring restoration of normal biochemical pathway.

Optimized HMI-103: Our Gene Editing Approach for PKU

In order to address the pediatric PKU population, we are developing a gene editing candidate for PKU, optimized HMI-103, that is designed to replace defective *PAH* genes with normal copies. The gene editing vector transgene is flanked by left and right homology arms, containing sequences that are identical and specific to the genomic target. The arms were designed to integrate by non-nuclease-based, AAV-mediated HR into the target human *PAH* locus. This therapy aims to correct the genetic defect within the treated liver cells then directing the expression of the PAH protein. HR-based integration via AAVHSCs is highly precise, without the introduction of insertions, deletions or viral ITRs. The corrected copy of the *PAH* gene would be retained as cells divide into daughter cells as the liver grows. Screening for PKU of all newborns in the United States allows the identification of affected individuals before serious neurological complications develop. We believe our HR approach possesses the efficacy and durability characteristics that would be appropriate to treat PKU in newly identified patients. As we further develop our expertise in treating PKU by correcting the defective *PAH* gene in the liver, we intend to develop treatments for other inborn errors of metabolism in the liver.

We have conducted *in vivo* experiments showing the integration of a human *PAH* cDNA into the human *PAH* gene locus using a humanized liver mouse model. In this model, human hepatocytes constitute the majority of the liver cells, providing an *in vivo* model to test human specific editing constructs. Injection of the human AAVHSC *PAH* gene editing candidate in this model resulted in the insertion of a codon-optimized human *PAH* cDNA into the human *PAH* locus and mRNA expression of the *PAH* cDNA. The *in vivo* integration rate at the target locus, shown in Figure 15, was calculated at a frequency of 6%. This level of editing has been shown to be sufficient to normalize Phe levels in the murine model. A second assay was also performed on DNA that was specific for human and murine hepatocytes obtained from this study. The assay provides an orthogonal approach for characterizing the frequency of targeted integration and enables testing the species-selectivity of the targeted integration. The results of this assay showed integration only in the human hepatocytes and not in the murine hepatocytes, demonstrating selectivity for the human locus. Figure 16 below shows data following I.V. administration of the murine surrogate, or the murine version of HMI-103. The human construct is designed with human-specific homology arms, so a murine surrogate is necessary for testing in the PKU murine model. As depicted, we observed that PAH gene integration was durable out to 43 weeks (end of study) and resulted in marked and durable serum Phe reduction.

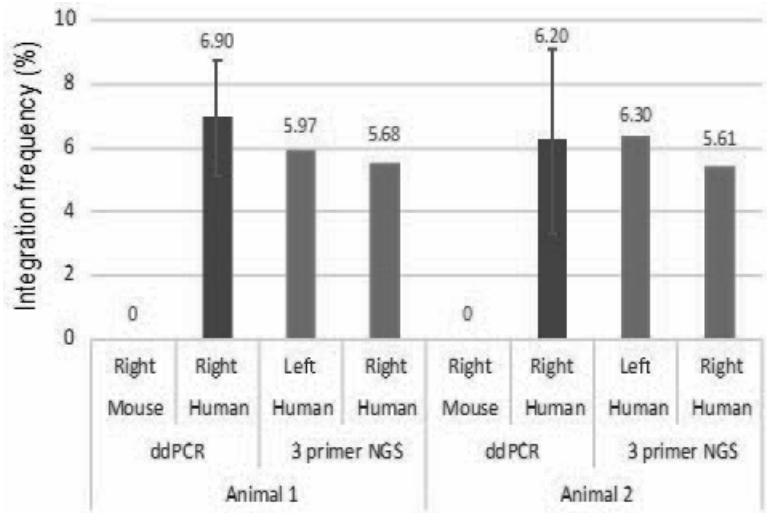


Figure 15. Human-specific AAVHSC *PAH* gene editing candidate resulted in a targeted integration rate of 6%, as measured by NGS in an *in vivo* humanized liver murine model.

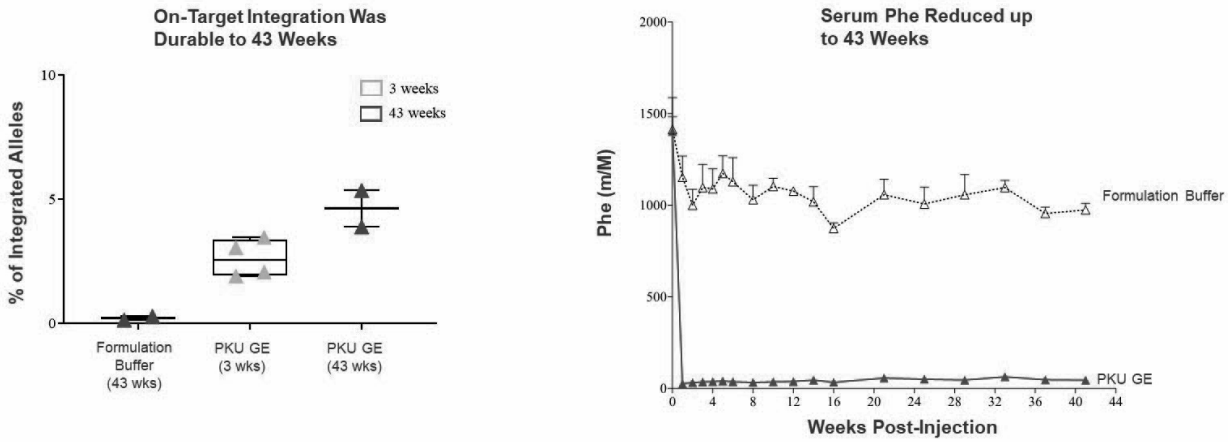


Figure 16. I.V. administration of murine surrogate (with murine homology arms) of HMI-103 showed durable gene integration in Pah^{enu2} model of PKU.

The fidelity of the integration of the cDNA into the target locus was evaluated by NGS and Nanopore sequencing. There were no *de novo* mutations detected in either homology arm target site. We also evaluated the samples for the presence of ITRs. Viral ITRs are non-homologous sequences that lie beyond the extent of the recombination event and thus should not be integrated into the target site. The integrated alleles were free of ITR sequence, consistent with HR as the main mechanism for integration. Together, these data showed that the targeted integration of the human *PAH* cDNA into the human *PAH* locus displayed sequence fidelity with no evidence of mutations.

Based on these data, we nominated HMI-103 as a product development candidate consisting of an AAVHSC15 vector and an optimized *PAH* gene construct with flanking homology arms. We continue to make progress on IND-enabling activities for the HMI-103 development program for the treatment of the pediatric PKU population and expect to initiate a Phase 1/2 dose-escalation clinical trial with HMI-103 in 2021.

Additional Product Opportunities

CNS Diseases

Our CNS programs are designed to take advantage of our AAVHSCs' natural ability to cross the blood-brain-barrier and blood-nerve-barrier in non-human primates.

HMI-203: Our Gene Therapy Approach for Hunter Syndrome

We have nominated a product development candidate, HMI-203, for the treatment of MPS II or Hunter syndrome, a rare, X-linked lysosomal storage disorder caused by mutations in the iduronate-2-sulfatase, or *IDS,* gene, which is responsible for producing the I2S enzyme that breaks down large sugar molecules, or cellular waste, called glycosaminoglycans, or GAGs. Severe Hunter syndrome results in toxic lysosomal accumulation of GAGs that causes progressive debilitation and decline in intellectual function. Hunter syndrome occurs in approximately 1 in 100,000 to 1 in 170,000 males, and the severe form leads to life expectancy of 10 to 20 years.

The standard of care for treating Hunter syndrome is enzyme replacement therapy, or ERT, which can delay some complications but does not treat CNS manifestations of Hunter syndrome since the enzyme cannot cross the blood-brain-barrier. In 2006, the recombinant form of human I2S (Elaprase), an ERT for the treatment of Hunter syndrome was approved by the FDA and subsequently approved for use internationally, and in January 2021, the recombinant form of idursulfase-beta (Hunterase), an ERT for the treatment of Hunter syndrome received manufacturing and marketing approval in Japan. However, specific treatment to address the neurological manifestations of Hunter syndrome and prevent or stabilize cognitive decline remains a significant unmet medical need.

Development candidate HMI-203 is a potential one-time AAVHSC treatment designed to deliver functional copies of the *IDS* gene to multiple target organs, including the PNS and CNS, following a single I.V. administration. We have initiated pivotal IND-enabling studies and scaled manufacturing of HMI-203 up to 500L by leveraging our commercial manufacturing platform. We expect to initiate a Phase 1/2 dose-escalation clinical trial with HMI-203 in 2021.

In preclinical studies, a single I.V. administration of HMI-203 led to robust biodistribution and sustained human I2S (hI2S) enzyme expression, which resulted in significant reductions in key Hunter syndrome biomarkers of heparan sulfate GAGs and lysosomal-associated membrane protein 1 (LAMP-1) in the brain, liver, heart, spleen, lung and kidneys compared with vehicle. Significant reductions in heparan sulfate GAGs in the cerebrospinal fluid (CSF) compared with vehicle were also observed, as well as ameliorated paw deformities, as shown by significant changes in measurements of ankle depth, paw width, paw depth and ankle width compared with vehicle. Finally, HMI-203 administration led to uptake of hI2S from the serum of the HMI-203-treated model in human cell lines, which demonstrated the potential for cell cross-correction. These data were presented at WORLD*Symposium*™ in February 2021. Refer to Figure 17 below.

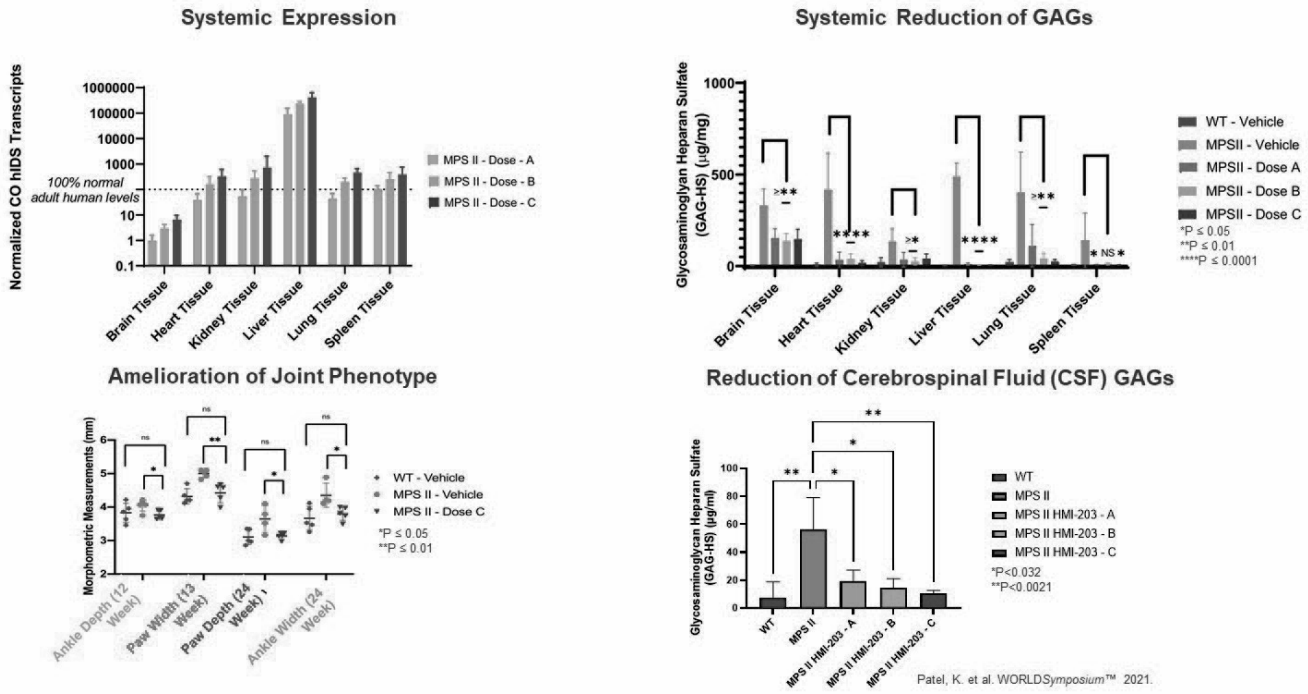


Figure 17. Single IV administration of HMI-203 demonstrated systemic expression, reduction of GAGs, and correction of phenotype in murine model.

HMI-202: Our Gene Therapy Approach for MLD

We have completed IND-enabling studies with HMI-202, our product development candidate for MLD, and we are using these data to further optimize an HMI-202 vector that we believe may lead to a better therapeutic profile. MLD is a lysosomal storage disease caused by mutation of a gene called arylsulfatase A, or *ARSA*. The protein ARSA is required for the breakdown of cellular metabolic products that in MLD accumulate in all cells of the body. Cells responsible for the production of myelin are especially sensitive to the toxic build-up of these cellular metabolic products, leading to progressive serious neurological deterioration. The late infantile form of MLD, which is the most common form, includes rapidly progressive motor and cognitive decline and loss of vision. The majority of these patients do not survive past the first decade of life.

In the United States, stem cell transplants are currently the only effective treatment for MLD, but have significant drawbacks, including the use of immunosuppression therapy, delayed onset of ARSA expression post-engraftment, conditioning regimens, and the risk of death from the stem cell transplant. In Europe, Libmeldy (autologous CD34+ cells encoding the ARSA gene), a lentiviral vector-based gene therapy for the treatment of MLD, became the first therapy approved for eligible patients with early-onset MLD in December 2020 following receipt of full (standard) market authorization by the European Commission.

We have generated preclinical data showing that a single intravenous dose of HMI-202 crossed the blood-brain-barrier and blood-nerve-barrier in a murine model and NHPs, shown in Figure 18, and had broad tissue tropism in physiologically relevant regions of the CNS and PNS, resulting in increased human ARSA enzyme activity to levels well above the therapeutic threshold when compared to average adult human enzyme activity. It is believed that levels of enzyme activity of 10 to 15% of normal could potentially be curative, based on human data from healthy subjects with enzyme activity levels in this range. These data were presented at WORLD*Symposium*™ in February 2021.

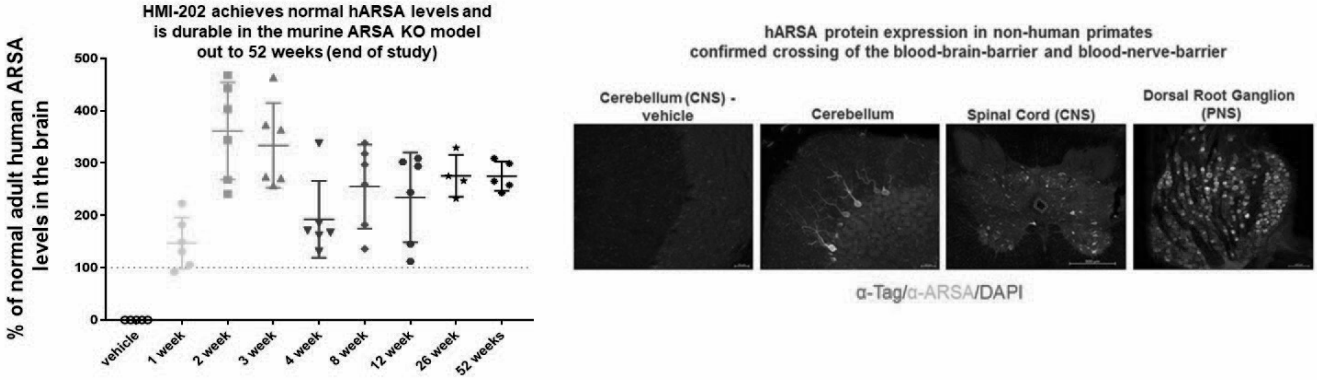


Figure 18. Single IV administration of HMI-202 crossed blood-brain-barrier and resulted in broad tissue tropism and therapeutically relevant levels of ARSA activity in the CNS of treated non-human primates.

Single IV administration of HMI-202 in the murine *Arsa* knockout model resulted in a reduction of LAMP-1 accumulation in the spinal cord and a reduction of sulfatide in the brain, both at 52 weeks post-dose (refer to Figure 19 below).

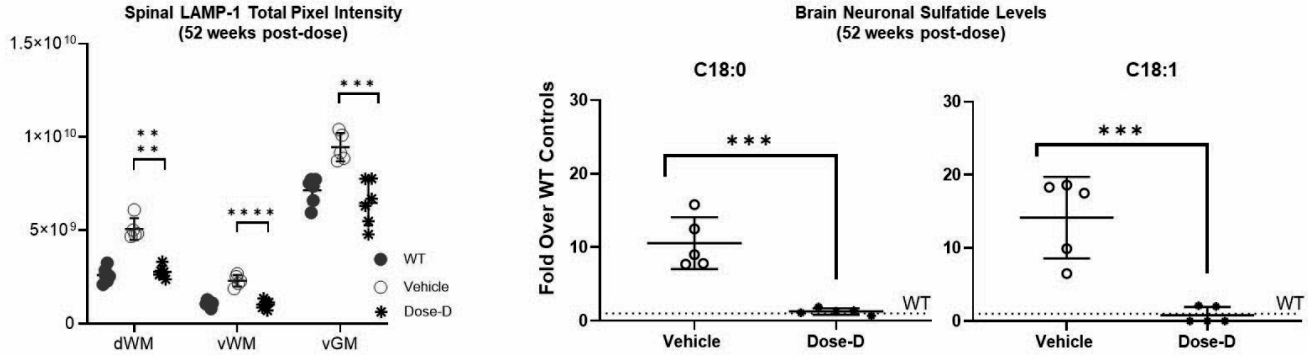


Figure 19. Single IV administration of HMI-202 resulted in reduction of LAMP-1 accumulation (52 weeks post-treatment) and reduction in sulfatide accumulation (52 weeks post-treatment) in murine model.

Other CNS Diseases

We believe our gene therapy technology has the potential to address other CNS diseases, including Friedreich's ataxia or FA. In FA, mutations in a gene called frataxin, or FXN, lead to progressive deterioration of the spinal cord leading to difficulty walking and eventual complete incapacitation and shortened lifespan. Other CNS diseases include Charcot-Marie-Tooth disease, or CMT, a group of disorders that affect the peripheral nerves, the nerves running from outside the brain and spine. The primary clinical features of this disease are slowly progressive distal weakness, muscle atrophy affecting the feet and legs and sensory loss. We also believe our gene therapy technology capable of confronting frontotemporal disorders, or forms of dementia caused by a family of brain diseases known as frontotemporal lobar degeneration. Dementia is a severe loss of thinking abilities that interferes with a person's ability to perform daily activities such as working, driving, and preparing meals. Finally, in addition to Hunter syndrome, for which we are currently advancing product development candidate HMI-203, our technology has the potential to address other lysosomal storage disorders.

Other Liver Diseases and Therapeutics

We continue to pursue the liver as a target organ given the high tropism of our AAVHSCs and the initial clinical data we have collected via our pheNIX Phase 1/2 gene therapy trial for PKU. We are pursuing potential treatments that target the liver's ability to secrete proteins into the serum. We believe that by targeting the liver with genetic medicines that act via gene therapy or gene editing, there is the potential to provide long-lasting secretion of proteins. We plan to name a development program in this therapeutic area in 2021.

Hemoglobinopathies

We are also pursuing treatment of diseases that affect blood cells such as sickle cell disease and beta thalassemia using our AAVHSC vector HR technology. We believe that our potential ability to correct the defective beta globin gene in blood precursor cells may lead to long-term functional cures for affected patients. Sickle cell disease affects over 100,000 individuals and beta thalassemia over 1,000 individuals in the United States.

Ophthalmological Diseases

A number of serious, but rare diseases of the eye such as Leber's congenital amaurosis and Choroideremia, as well as more common diseases such as macular degeneration, have been targeted using gene therapy approaches by academic groups as well as the pharmaceutical industry. We evaluated the ability of our AAVHSCs to transduce retinal cells following subretinal injection in preclinical studies in mice. Expression of green fluorescent protein, or GFP, was seen in all layers of the retina including the retinal pigment epithelium, photoreceptors and the outer nuclear layer, and the AAVHSC subretinal treatment was well-tolerated. In addition, we evaluated the ability of AAVHSC17 to transduce retinal cells in a larger animal model, a mini-pig, and observed significant transduction of all layers of the retina supporting translation across two species. We believe these studies suggest that our AAVHSCs have the potential to be useful as therapeutic vectors for treating retinal diseases in humans based on significant tropism to these target cells. We believe that these vectors have the potential to deliver long-lasting therapeutic benefit to patients that may eliminate the need for the regular and burdensome intravitreal injections that are required for many current treatments.

Manufacturing

As a company committed to curing diseases, the ability to deliver our novel therapeutic vectors to patients is critical. Therefore, we have built strong internal scientific AAV process development and manufacturing capabilities and we have invested in a GMP manufacturing facility to support our clinical development programs. We have established a commercial manufacturing platform and process that supports both gene therapy and gene editing, which is scalable from preclinical to GMP. We view the development of internal manufacturing capacity and expertise as a key competitive advantage as it allows for better control over process development timelines, costs, product quality and intellectual property, and allows us to master our unique technology. Our process development and manufacturing teams are composed of industry veterans in the field of AAV and protein technologies, as well as experts in our novel AAVHSCs, with experience in both early development and commercialization of therapeutics.

Our process development and manufacturing strategy leverages a single platform for both gene therapy and gene editing that is scalable and facilitates rapid development to the clinic. We are executing all development and process steps internally. Our development focus includes design and engineering of plasmid constructs, cell culture, transfection, purification, formulation and analytical development. We leverage our manufacturing platform across our entire pipeline, from our research programs, to our preclinical programs and now to our clinical programs. Our platform was designed from its inception to be our commercial process, allowing us to rapidly transition from research into the clinic and eventually to commercialization. Our manufacturing platform has been scaled and tested across more than 450 different constructs with more than 550 unique lots of vector successfully executed.

Our manufacturing strategy utilizes mammalian cells for our AAVHSC vector-based product candidates. All of our programs, including HMI-102 for PKU, utilize HEK293 transfection in a serum-free suspension bioreactor process. HEK293 is a well-characterized and commonly used system for many clinical-stage AAV vector products. Additionally, HEK293 cells are familiar to regulatory authorities, and commercial raw materials and reagents are readily available. Our purification leverages chromatography-based operations to provide high quality vector and ensure robust commercial-scale operations. In addition to our process development, we also internally developed 45 analytical methods to test, monitor, and characterize our products. Expertise and learnings will be leveraged across gene therapy and gene editing programs.

We have established a relationship with a contract manufacturing organization, or CMO, that has expertise in the use of HEK293 gene therapy manufacturing so that we have an external manufacturing process alongside our internal GMP manufacturing capability to supply material for our Phase 1/2 pheNIX clinical trial, as well as our upcoming additional clinical trials. For gene editing manufacturing, our strategy is to internally control the process development and manufacturing to safeguard the proprietary nature of our technology, and to continue to master all aspects of this technology.

To support clinical expansion, we have constructed a 25,000 square foot GMP manufacturing facility that accommodates both our gene therapy and gene editing pipeline programs. We are currently operating three 500-liter bioreactors and have successfully produced GMP material at the 500-liter scale for multiple pipeline candidates. Additionally, we have scaled up our manufacturing platform to a 2,000-liter bioreactor scale, which will give us the ability to produce large scale volumes and support our growing pipeline. Our manufacturing model leverages single use, disposable, closed system operations aligned to the unique characteristics of gene therapy technology to ensure flexibility, robust quality and cost effectiveness. Our internal operations also include quality control labs to facilitate product quality testing and stability.

Competition

The biotechnology and pharmaceutical industries, including in the gene therapy and gene editing fields, are characterized by rapidly advancing technologies, intense competition and a strong emphasis on intellectual property and proprietary products. While we believe that our technology, development experience and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies, and public and private research institutions that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization. Not only must we compete with other companies that are focused on gene therapy and/or gene editing technologies, any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that utilize technologies encompassing genomic medicines to create therapies, including gene therapy and gene editing. There are additional companies that are working to develop therapies in areas related to our research programs.

Our platform and product focus is the development of genetic medicines using our proprietary AAVHSCs *in vivo* either through the gene therapy or nuclease-free gene editing modality. If our current programs are approved for the indications for which we are currently planning clinical trials, they may compete with other products currently under development, including gene therapy and gene editing products or other types of therapies, such as small molecule, antibody or protein therapies. If our PKU treatments are approved, they may compete with therapies from American Gene Technologies, BioMarin, Generation Bio, Moderna, Nestlé Health Science, PTC Therapeutics, Sangamo Therapeutics and Synlogic. However, we believe that only gene therapy or gene editing approaches have the potential to restore the normal Phe biochemical pathway with a single administration. As such, the major competition in this space may be limited to American Gene Technologies, BioMarin and Sangamo Therapeutics, all of which are behind our development program according to public filings.

There are a number of companies developing nuclease-based gene editing technologies using CRISPR/Cas9, TALENs, meganucleases, Mega-TALs and ZFNs, including Beam Therapeutics, bluebird bio, Caribou Biosciences, Cellectis, CRISPR Therapeutics, Editas Medicine, Intellia Therapeutics, Precision BioSciences and Sangamo Therapeutics and non-nuclease-based technology, including LogicBio Therapeutics.

If our Hunter syndrome treatment is approved, it may compete with investigational product candidates from Avrobio, Denali Therapeutics and REGENXBIO, as well as ERTs from Takeda and/or GC Pharma. However, we believe that only a gene editing approach has the potential to address the neurological manifestations of Hunter syndrome and prevent or stabilize cognitive decline.

If our MLD treatment is approved, it may compete with therapies from Orchard Therapeutics and/or Takeda. We believe that our *in vivo* gene therapy approach for MLD could be used early in the disease progression with the potential for earlier protein expression, offering advantages over Orchard's *ex vivo* approach, as well as advantages over chronic, intrathecal ERTs, such as Takeda's approach.

In addition, many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and gene therapy industries may result in even more resources being concentrated among a smaller number of

our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our programs are likely to be their efficacy, safety, convenience and availability of reimbursement.

Furthermore, we rely upon a combination of patents and trade secret protection, as well as license and confidentiality agreements to protect the intellectual property related to our proprietary technologies, product candidate development programs and product development candidates. Our success depends in large part on our ability to secure and maintain patent protection in the United States and other countries with respect to HMI-102 and any future product development candidates. Moreover, our industry is characterized by the existence of large numbers of patents and frequent allegations of patent infringement. If, therefore, we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained or in-licensed is not sufficiently broad or if the validity of such patent is threatened, we may not be able to compete effectively in our markets, as it could create opportunities for competitors to enter the market or dissuade other companies from collaborating with us to develop products and technology, any of which would hurt our competitive position and could impair our ability to successfully commercialize our product development candidates in any indication for which they are approved. For more information regarding these competitive risks, see Item 1A. “Risk Factors—Risks Related to Our Intellectual Property.”

Intellectual Property

Our success depends in large part upon our ability to secure and maintain proprietary protection for our technologies and products and to operate without infringing the proprietary rights of others. Our policy is to protect our proprietary position by, among other methods, filing, or collaborating with our licensors to file, U.S. and foreign patent applications related to our proprietary technology, inventions, and improvements and trademarks that are important to the development and implementation of our business. We require employees who are inventors on any company-owned patent applications to assign the rights to us. Also, we use other forms of protection, particularly where we do not believe patent protection is appropriate or obtainable. We rely on trade secrets, technical know-how, and continuing innovation to develop and maintain our competitive advantage. In addition, we rely on confidentiality agreements with our employees, consultants, and other advisors to protect our proprietary information. Our policy is to require third parties that receive material confidential information to enter into confidentiality agreements with us.

Our patent portfolio includes a combination of issued patents and pending patent applications that are licensed from third parties. As of December 31, 2020, we have an exclusive license or co-exclusive license under 16 United States issued patents, two European patents and 35 patent applications, pending in the United States and internationally.

For any individual patent, the term depends on the applicable law in the country in which the patent is granted. In most countries where we have filed patent applications or in-licensed patents and patent applications, patents have a term of 20 years from the application filing date or earliest claimed non-provisional priority date. In the United States, the patent term is 20 years but may be shortened if a patent is terminally disclaimed over another patent that expires earlier. The term of a U.S. patent may also be lengthened by a patent term adjustment, in order to address administrative delays by the United States Patent and Trademark Office in granting a patent.

In the United States, the term of a patent that covers an FDA-approved drug or biologic may be eligible for patent term extension in order to restore the period of a patent term lost during the premarket FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the natural expiration of the patent. The patent term restoration period is generally equal to the regulatory review period for the approved product which period occurs after the date the patent issued, subject to certain exceptions. Only one patent may be extended for a regulatory review period for any product, and the application for the extension must be submitted prior to the expiration of the patent. In the future, we may decide to apply for restoration of patent term for one of our currently owned or licensed patents to extend its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant Biologics License Application, or BLA. Similarly, certain foreign jurisdictions also have mechanisms for extending patent term and, to the extent we have granted patents that are eligible, we may decide to apply for patent term extensions in those jurisdictions.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally equal to the regulatory review period for the approved product which period occurs after the date the patent issued, subject to certain exceptions. Only one patent may be extended for a regulatory review period for any product, and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to extend its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

For patents that might expire during the BLA review phase, the patent owner may request an interim patent term extension. If eligible, an interim patent term extension may be granted for a period of not more than one year. The patent owner may apply for not more than four subsequent interim extensions. Any interim extension granted will not be longer than the maximum period of extension allowed post-approval.

Licensed Intellectual Property

Certain of our issued patents and pending patent applications are exclusively licensed to us in all fields of use from COH. Certain of our issued patents and pending patent applications are co-exclusively licensed to us in all human therapeutic applications with and from the California Institute of Technology, or Caltech.

The City of Hope Portfolio

In April 2016, we exclusively licensed two families of patents and patent applications directed to novel AAV capsids and their manufacture and methods of use, including their use in genome editing from COH.

These two families of patents and patent applications together include eleven granted patents in the United States, two foreign granted patents, and 14 pending applications in the United States, Europe, Canada, Australia and other selected countries in Latin America and Asia. The first family of issued patents and patent applications is material to HMI-102 and relates to our novel AAV vectors and their use in cellular transduction. The eight issued U.S. patents in this family are expected to expire in 2031 and may be extended by up to five years in the United States via patent term extension depending on the regulatory pathway of the products covered by such patents. The second family includes two issued U.S. patents relating to our AAV vectors and their use in genome editing. The issued patents in this family are expected to expire in 2035 and may be extended by up to five years in the United States and in certain other countries via patent term extension depending on the regulatory pathway of the products covered by such patents.

The Caltech Portfolio

In September 2016, we co-exclusively licensed, with another commercial third party, two families of patents and patent applications directed to novel AAV capsids and vectors that demonstrate enhanced blood-brain-barrier penetration for the potential treatment of CNS diseases from Caltech.

These families of patents and patent applications include five granted patents in the United States, one granted patent in Europe, one granted patent in South Africa, and 21 pending applications in the United States, Europe, Canada, Australia and other selected countries in Latin America and Asia. The five issued U.S. patents relate to novel AAV capsids and vectors and are expected to expire in 2034. Certain other patent applications directed to novel AAV capsids and vectors, if they were to issue, may have later expirations.

Trademarks

Our trademarks Homology Medicines, HMI, the H logo, and AMENDR, are pending or registered in the United States and certain international countries. We currently own one registered trademark and four pending trademark applications in the United States, 17 registered trademarks around the world, and five pending foreign trademark applications.

Strategic Collaborations

Collaboration and License Agreement with the Novartis Institutes for BioMedical Research, Inc.

In November 2017, we entered into a collaboration and license agreement with Novartis, pursuant to which we agreed to collaborate on researching, developing, and commercializing novel genome editing products that modulate certain gene targets.

Under the terms of the agreement, we and Novartis agreed to collaborate to identify and synthesize gene editing vector candidates that modulate certain ophthalmic gene targets, against which Novartis agreed to develop licensed products. Our obligation to perform research for the targets was to continue for five years from the effective date of the agreement.

We and Novartis agreed also to collaborate to explore the applicability of our technology with respect to other gene targets. Our obligation to perform such exploratory research was extended pursuant to an amendment to the collaboration agreement and was set to conclude in May 2021.

In May 2020, Novartis confirmed an ophthalmic target for a therapeutic editing program. Additionally, in accordance with the terms of the Collaboration Agreement, Novartis' right to substitute other ophthalmic targets expired.

Subject to certain limitations pursuant to the terms of the agreement, Novartis was responsible for the internal and external costs incurred by us for the research activities as contemplated under the agreement. Novartis also agreed to pay for the development of gene editing vector candidates and licensed products.

Subject to the terms of the agreement, we were responsible for manufacturing gene editing vector candidates for certain ophthalmic gene targets for research, and gene editing vector candidates and licensed products for development and commercialization, and Novartis agreed to bear all such manufacturing costs that we incurred.

Subject to the terms of the agreement, taking into account Novartis' election to discontinue our collaboration on the sickle cell disease program, we had granted Novartis the following licenses: (i) a worldwide, non-exclusive, sublicensable license under certain of our intellectual property rights to perform Novartis' responsibilities under the applicable research plan; (ii) a worldwide, sublicensable license under certain of our intellectual property rights to conduct preclinical development activities, which license is co-exclusive (with us) during the research term, and exclusive for the remainder of the term of the agreement; (iii) a worldwide, non-exclusive, perpetual, irrevocable license, without the right to grant sublicenses, to use certain reagents generated as a result of our exploratory research activities under the agreement solely for Novartis' internal research purposes; (iv) an exclusive, royalty-bearing, sublicensable license under certain of our intellectual property rights to develop and commercialize certain gene editing vector candidates and licensed products directed to certain ophthalmic gene targets; (v) as of the effective date, a co-exclusive (with us), royalty-bearing, sublicensable, worldwide license under certain of our intellectual property rights to manufacture certain gene editing vector candidates and/or licensed products directed to certain ophthalmic gene targets, which license will be exclusive as of a certain date on which Novartis is permitted to manufacture certain gene editing vector candidates and/or licensed products pursuant to the terms of the agreement; and (vi) a non-exclusive, royalty-free, fully paid, perpetual, irrevocable, worldwide license under certain of our intellectual property rights in connection with research, development, manufacturing, commercialization or other exploitation of products or services.

Subject to the terms of the agreement, Novartis granted to us the following licenses: (i) a worldwide, non-exclusive, sublicensable license under certain of Novartis' intellectual property rights to perform certain research activities during the research term and (ii) a non-exclusive, royalty-bearing, perpetual, irrevocable, worldwide, sublicensable license under certain of Novartis' intellectual property rights that may arise under the agreement that relate to our manufacturing know-how for our manufacture of gene editing vector candidates and products created using our platform technology.

Under the terms of the agreement, we received an upfront payment of $35.0 million and Novartis also purchased shares of our Series B preferred stock for an aggregate purchase price of $15.0 million. Taking into consideration Novartis' election to discontinue our collaboration on the sickle cell disease program and the expiration of Novartis' rights to make substitutions of an ophthalmic target, we were also eligible to receive up to a total of $5.0 million upon completion of certain development candidate selection activities. In addition, we were eligible to receive up to a total of $265.0 million in milestone payments, including up to $90.0 million in development milestone payments, up to $85.0 million in regulatory milestone payments and up to $90.0 million in commercial milestone payments, with respect to the licensed products. We were also eligible to earn tiered royalties on net sales of licensed products by Novartis, its affiliates or sublicensees ranging from mid-single-digit to sub-teen double-digit percentages, which royalties were potentially subject to various reductions and offsets. If any of the exploratory research efforts were advanced into formal research and development programs, the parties agreed to negotiate the economics, including potential milestone payments for such programs.

The term of the agreement continues on a target-by-target basis until the expiration of all royalty payment obligations for the licensed products that modulate the applicable target on a country-by-country basis. Our royalty obligations under the agreement continue on a country-by-country and licensed product-by-licensed product basis until the later of (a) 10 years after the first commercial sale of such licensed product in a country, (b) the date on which such licensed product is no longer covered by certain intellectual property rights, and (c) the date on which certain regulatory exclusivity for such product expires. Either party may terminate the agreement on a target-by-target basis for the other party's material breach with respect to such target, or in the event of the other party's bankruptcy. Novartis may terminate the agreement for convenience on a target-by-target basis. We may terminate the agreement if Novartis files, or joins a third party in filing or maintaining, a patent challenge against certain of the patent rights we license to Novartis under the terms of the agreement.

On February 26, 2021, we received notice from Novartis that they had elected to terminate the agreement with respect to the ophthalmic target, which was the only remaining target under the agreement. Accordingly, the notice served as notice of Novartis' termination of the agreement in its entirety, with an effective date of August 26, 2021, which is six months from the date of the notice. Novartis has agreed to work with us to effect the orderly wind down of activities in accordance with the agreement. As a result of this notice, we have regained worldwide exclusive rights from Novartis to research, develop, manufacture and commercialize our proprietary nuclease-free gene editing technology platform for the ophthalmic target. We plan to continue to advance the program toward naming a development candidate. The companies believe that results of studies conducted under the agreement provide early proof-of-principle and support a nuclease-independent approach to editing of relevant cell types in the eye after sub-retinal injection, and are the subject of a planned presentation at an upcoming scientific meeting.

License Agreement with the California Institute of Technology

In September 2016, we entered into a license agreement with Caltech, pursuant to which Caltech granted us a co-exclusive (subject to certain reserved non-commercial rights), sublicensable, and worldwide license under certain AAV-related patents owned by Caltech for human therapeutic applications. Under this agreement, Caltech also granted us a non-exclusive, worldwide license under certain patents and other intellectual property controlled by Caltech to develop, manufacture, commercialize, and otherwise exploit products covered by such intellectual property rights for human therapeutic applications. We may grant sublicenses under the non-exclusive license to third parties to the extent necessary or useful for our, or our sublicensees', development, manufacturing, or sale of such products.

Under the Caltech agreement, we paid Caltech an initial licensing fee of $100,000. We are also required to pay Caltech up to a total of $7.2 million in milestone payments for the first licensed product; royalties, in the low single-digit percentages on net sales of licensed products, subject to a certain annual minimum royalty; and mid to high single-digit percentages of sublicensing revenues. Subject to certain exceptions, our royalty obligations under the agreement continue on a country-by-country and licensed product-by-licensed product basis until the earliest of (a) the date on which such licensed product is no longer covered by certain intellectual property rights, (b) 10 years after the first commercial sale of such licensed product, or (c) 15 years after the effective date of the agreement. As partial consideration for the licenses granted under the agreement, we issued 101,405 shares of our common stock to Caltech.

The agreement will expire upon the expiration of the last-to-expire patent that is licensed to us or as long as royalties are due under the agreement, whichever is later. We agreed to use commercially reasonable efforts to introduce commercially, and reasonably fulfill market demand for, licensed products as soon as practicable. Either party may terminate the agreement in the event of the other party's uncured material breach and in the event of the other party's bankruptcy or insolvency. We may terminate the agreement for convenience.

City of Hope License Agreement

In April 2016, we entered into a license agreement with COH, pursuant to which COH granted us an exclusive, sublicensable, worldwide license to certain AAV vector-related patents and know-how owned by COH to develop, manufacture, use and commercialize products and services covered by such patents and know-how in any and all fields. COH also granted us a non-exclusive, sublicensable, worldwide license to certain background patents owned by COH to develop, manufacture, use and commercialize licensed products and licensed services in any and all fields.

Under the agreement, we paid COH an initial licensing fee of $75,000, and made a subsequent payment of $4.5 million representing a percentage of sublicensing revenue. We are also required to pay COH an annual license maintenance fee; up to a total of $3.2 million in potential milestone fees; a royalty in the low single-digit percentages on net sales of licensed products or services, subject to certain reductions in certain circumstances, with a certain annual minimum royalty; and low double-digit percentages of sublicensing revenues. As partial consideration for the licenses granted under the agreement, we issued 154,837 shares of our common stock to COH.

The COH agreement will expire on a country-by-country and on a licensed patent-by-licensed patent basis upon the expiration of the last-to-expire valid claim of such patent in such country. We agreed to use commercially reasonable efforts to develop and commercialize licensed products and licensed services. If we fail to achieve certain diligence milestones, COH may terminate the agreement or convert the exclusive rights under the agreement from exclusive to non-exclusive. Either party may terminate the agreement in the event of the other party's material breach, subject to an opportunity to cure, and in the event of the other party's bankruptcy or insolvency. We may terminate the agreement for convenience.

Government Regulation and Product Approval

Governmental authorities in the U.S., at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, labeling, packaging, promotion, storage, advertising, distribution, marketing, post-approval monitoring and reporting and export and import of products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, are extensive and require the expenditure of substantial time and financial resources. For the purposes of this Section, the term "gene therapy" includes both traditional gene therapy products as well as gene editing and our gene integration product candidates.

FDA Approval Process

We expect our future product candidates to be regulated as biologics. Biological products, including gene therapy products, are subject to extensive regulation by the FDA under the Federal Food, Drug, and Cosmetic Act, or FDCA, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FDCA and the PHS Act and their corresponding regulations govern, among other things, the research, development, safety, testing, packaging, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of biological products.

We, along with third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Biological Products Development Process

The FDA determined that more than minimally manipulated products must be approved by the FDA through the BLA process before they may be legally marketed in the United States. The process required by the FDA before a biologic may be marketed in the United States generally involves the following:

- completion of extensive nonclinical, sometimes referred to as preclinical laboratory tests, and preclinical animal trials and applicable requirements for the humane use of laboratory animals and formulation studies in accordance with applicable regulations, including good laboratory practices, or GLP, requirements;
- submission to the FDA of an IND application, which must become effective before human clinical trials may begin;
- approval by an independent Institutional Review Board, or IRB, or ethics committee at each clinical site before the trial is commenced;
- performance of adequate and well-controlled human clinical trials according to good clinical practice, or GCP, requirements and any additional requirements needed for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- preparation and submission to the FDA of a BLA for marketing approval that includes substantive evidence of safety, purity and potency from results of nonclinical testing and clinical trials;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- completion of an FDA Advisory Committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with GMP to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity;

- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product candidate, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements, including GLP.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing and controls, information about product chemistry, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of an IND. An IND is a request for authorization from the FDA to administer an investigational new drug to humans. Some preclinical testing, such as reproductive toxicity tests and carcinogenicity in animals, may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, after which human clinical trials may begin unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin.

In addition to the IND submission process, under the National Institutes of Health, or NIH, Guidelines for Research Involving Recombinant DNA Molecules, or the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. Clinical trials involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, the efficacy measurements to be evaluated and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an independent IRB at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or a data monitoring committee, which provides guidance for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

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

- Phase I. The biological product candidate is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- Phase II. The biological product candidate is evaluated in 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, optimal dosage and dosing schedule.
- Phase III. The biological product candidate is further evaluated for dosage, clinical efficacy, potency, and safety in an expanded patient population, generally at geographically dispersed clinical study sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies may also be made a condition to approval of the BLA.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA and the investigators for serious and unexpected adverse events, any findings from other trials, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase I, Phase II and Phase III clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend or permanently discontinue a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk or the clinical study is not being conducted in accordance with FDA regulations. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product candidate has been associated with unexpected serious harm to patients. The FDA and the IRB may also halt, terminate or impose other conditions if either believes the patients are subject to unacceptable risk.

Concurrent with clinical trials, companies usually complete additional animal trials and must also develop additional information about the physical characteristics of the biological product candidate as well as finalize a process for manufacturing the product in commercial quantities in accordance with GMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. Review and Approval Processes

After the completion of clinical trials of a biological product candidate, FDA approval of a BLA must be obtained before commercial marketing and distribution of the biological product. The BLA must include results of product development, laboratory and animal trials, human trials, information on the manufacture, pharmacology, chemistry and controls of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological product candidate for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. PDUFA also imposes an annual program fee for marketed products. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first human drug application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

Within 60 days following submission of the application, the FDA reviews the submitted BLA to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is 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 of the BLA. Under PDUFA, the FDA has agreed to certain performance goals to complete the review of BLAs. For example, the FDA may give a priority review to BLAs submitted for biological products that are designed to treat a serious or life-threatening disease or condition, and if approved, would offer a significant improvement in safety or efficacy compared to marketed products. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. Under the current PDUFA agreement, these six- and ten-month review periods are measured from the "filing" date rather than the receipt date for original BLAs, which typically adds approximately two months to the timeline for review and decision from the date of submission.

The FDA reviews the BLA to determine, among other things, whether the proposed product is safe, pure and potent, or effective, for its intended use, and whether the product is being manufactured in accordance with GMP requirements to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and 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 a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. To assure GMP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

After the FDA evaluates a BLA, conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced and conducts inspections at select clinical sites, the FDA may issue an approval letter or a Complete Response Letter, or CRL. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A CRL will describe all of the deficiencies that the FDA has identified in the BLA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the CRL without first conducting required inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the CRL, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional information or clarification. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the BLA with a Risk Evaluation and Mitigation Strategy, or REMS, to ensure the benefits of the product outweigh its potential risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. The requirement for a REMS can materially affect the potential market and profitability of the product.

Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. Changes to some of the conditions established in an approved BLA, including changes in indications, product labeling, manufacturing processes or facilities, require submission and FDA approval of a new BLA or BLA supplement before the change can be implemented. A BLA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing BLA supplements as it does in reviewing BLAs. The FDA may require one or more Phase IV post-market studies or surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies.

Orphan Drug Designation

The FDA may grant orphan drug designation to drugs or biologics intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and marketing the drug or biologic for this type of disease or condition will be recovered from its sales in the United States. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and BLA user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application, including a full BLA, to market the same drug or biologic for the same

indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer with orphan exclusivity is unable to assure sufficient quantities of the approved orphan-designated product. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of a product for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if such product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. In addition, exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Rare Pediatric Disease Priority Review Voucher Program

In 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U.S. within one year following the date of approval.

For purposes of this program, a "rare pediatric disease" is a (a) serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents; and (b) rare diseases or conditions within the meaning of the Orphan Drug Act. Congress has only authorized the Rare Pediatric Disease Priority Review Voucher program until September 30, 2024. Consequently, sponsors of marketing applications approved after that date will not receive the voucher unless Congress reauthorizes the Rare Pediatric Disease Priority Review Voucher program before that time. However, even if the program is not reauthorized, if a drug candidate receives Rare Pediatric Disease Designation before October 1, 2024, the sponsor of the marketing application for such drug will be eligible to receive a voucher if the application for the designated drug is approved by the FDA before October 1, 2026.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new biological products that meet certain criteria. Specifically, new biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new biologic may request that the FDA designate the biologic as a Fast Track product at any time during the clinical development of the product. The FDA must determine if the biologic product candidate qualifies for Fast Track designation within 60 days of receipt of the sponsor's request. With regard to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it has the potential to treat a serious or life-threatening condition and, if approved, would provide a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint

that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a biological product receiving accelerated approval perform adequate and well-controlled post-marketing Phase IV clinical studies to verify the predicted clinical benefit. Failure to conduct required post-approval trials, or to confirm a clinical benefit during such post-marketing trials, will allow the FDA to withdraw the approved biologic product from the market on an expedited basis. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

In addition, under the provisions of FDASIA, enacted in 2012, the FDA established a Breakthrough Therapy Designation which is intended to expedite the development and review of products that treat serious or life-threatening diseases or conditions. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the features of Fast Track designation, as well as more intensive FDA interaction and guidance. The Breakthrough Therapy Designation is a distinct status from both accelerated approval and priority review, but these can also be granted to the same product candidate if the relevant criteria are met. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Moreover In 2017, the FDA established the Regenerative Medicine Advanced Therapy, or RMAT, designation as part of its implementation of the 21st Century Cures Act. An investigational drug is eligible for RMAT designation if: (1) it meets the definition of a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; (2) it is intended to treat, modify, reverse, or cure a serious disease or condition; and (3) preliminary clinical evidence indicates that the investigational drug has the potential to address unmet medical needs for such disease or condition. In a February 2019 final guidance, the FDA also stated that certain gene therapies that lead to a sustained effect on cells or tissues may meet the definition of a regenerative medicine therapy. RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review of BLAs and priority review. Product candidates granted RMAT designation may also be eligible for accelerated approval if the relevant statutory conditions are met.

Fast Track designation, priority review, RMAT designation and Breakthrough Therapy designation do not change the standards for approval but may expedite the development or approval process. Even if we receive one or both of these designations for our product candidates, the FDA may later decide that our product candidates no longer meet the conditions for qualification. In addition, receiving these designations may not provide us with a material commercial advantage.

Post-Approval Requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to GMP requirements, record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMP requirements and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain GMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

To help reduce the increased risk of the introduction of adventitious agents, the PHS Act emphasizes the importance of manufacturing controls for products whose attributes cannot be precisely defined. The PHS Act also provides authority to the FDA to immediately suspend biologics licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases within the United States.

The FDA closely regulates the marketing, labeling, advertising and promotion of biologics. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA 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. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. 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 or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products that are administered multiple times to an individual, the biologic and the reference biologic may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation of the abbreviated approval pathway that are still being worked out by the FDA.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

A biological product can also obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The BPCIA is complex and continues to be interpreted and implemented by the FDA. In addition, recent government proposals have sought to reduce the 12-year reference product exclusivity period. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate impact, implementation, and meaning of the BPCIA remains subject to significant uncertainty.

Other Healthcare Laws and Compliance Requirements

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims and physician and other healthcare provider payment transparency laws and regulations. If their operations are found to be in violation of any of such laws or any other governmental regulations that apply, they may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of operations, exclusion from participation in federal and state healthcare programs and individual imprisonment.

Coverage and Reimbursement

Sales of any product depend, in part, on the extent to which such product will be covered by third-party payors, such as federal, state, and foreign government healthcare programs, commercial insurance and managed healthcare organizations, and the level of reimbursement for such product by third-party payors. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. These third-party payors are increasingly reducing reimbursements for medical products, drugs and services. Moreover, for drugs and biologics administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such products. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product. Decreases in third-party reimbursement for any product or a decision by a third-party payor not to cover a product could reduce physician usage and patient demand for the product and also have a material adverse effect on sales.

Healthcare Reform

In March 2010, President Obama signed the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, each as amended, collectively known as the Affordable Care Act, which substantially changed the way healthcare is financed by both governmental and private insurers, and significantly affected the pharmaceutical industry. The Affordable Care Act contained a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement adjustments and fraud and abuse changes. Additionally, the Affordable Care Act:

- increased the minimum level of Medicaid rebates payable by manufacturers of brand name drugs from 15.1% to 23.1%;
- required collection of rebates for drugs paid by Medicaid managed care organizations;
- required manufacturers to participate in a coverage gap discount program, under which they must agree to offer 70 percent point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and
- imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell "branded prescription drugs" to specified federal government programs.

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the Affordable Care Act. The U.S. Supreme Court is currently reviewing the constitutionality of the Affordable Care Act in its entirety. Other legislative changes have been proposed and adopted since the Affordable Care Act was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year, which was temporarily suspended from May 1, 2020 through March 31, 2021, and reduced payments to several types of Medicare providers. Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted legislation 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 drug products. Individual states in the United States have also become increasingly

active in implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Privacy and Security Laws

Numerous state, federal and foreign laws, including consumer protection laws and regulations, govern the collection, dissemination, use, access to, confidentiality and security of personal information, including health-related information. In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy and security laws, including the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended, and regulations promulgated thereunder, and federal and state consumer protection laws and regulations (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure, and protection of health-related and other personal information could apply to our operations or the operations of our partners. In addition, certain state and non-U.S. laws, such as the California Consumer Privacy Act, or CCPA, the California Privacy Rights Act, or CPRA, and the General Data Protection Regulation, or GDPR, govern the privacy and security of personal data, including health-related data in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and/or criminal penalties and private litigation. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and/or criminal penalties and restrictions on data processing.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

Government Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

In addition, ethical, social and legal concerns about gene-editing technology, gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Whether or not we obtain FDA approval of a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. The requirements and process governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. Failure to comply with applicable foreign regulatory requirements, may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Clinical Trials

Certain countries outside of the United States have a similar process that requires the submission of a clinical study application, or CTA, much like the IND prior to the commencement of human clinical studies. In the European Union, or EU, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved by the national health authority and the ethics committee has granted a positive opinion in relation to the conduct of the trial in the relevant member state(s), in accordance with a country's requirements, clinical study development may proceed.

Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Conference on Harmonization, or ICH, guidelines on Good Clinical Practices, or GCP, as well as the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. Additional GCP guidelines from the European Commission, focusing in particular on traceability, apply to clinical trials of advanced therapy medicinal products, or ATMPs. If the sponsor of the clinical trial is not established within the EU, it must appoint an EU entity to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU countries, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization from the competent authority, and a positive opinion from an independent ethics committee. The CTA must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, CTAs must be submitted to the competent authority in each EU member state in which the trial will be conducted. Under the new Regulation on Clinical Trials, which is currently expected to take effect by early 2022, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only limited involvement. Any substantial changes to the trial protocol or other information submitted with the CTA must be notified to or approved by the relevant competent authorities and ethics committees. Medicines used in clinical trials must be manufactured in accordance with GMP. Other national and European Union-wide regulatory requirements may also apply.

During the development of a medicinal product, the EMA and national regulators provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use, or CHMP. A fee is incurred with each scientific advice procedure. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical trials, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future marketing authorization application of the product concerned.

Marketing Authorizations

In the European Union, medicinal products can only be placed on the market after obtaining a Marketing Authorization, or MA. To obtain regulatory approval of an investigational biological product in the EU, we must submit a marketing authorization application, or MAA. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements. The process for doing this depends, among other things, on the nature of the medicinal product.

The centralized procedure results in a single MA, issued by the European Commission, based on the opinion of the EMA's CHMP, which is valid across the entire territory of the EU. The centralized procedure is compulsory for human medicines that are: (i) derived from biotechnology processes, such as genetic engineering, (ii) contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions and viral diseases, (iii) designated orphan medicines and (iv) advanced therapy medicinal products, or ATMPs, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The centralized procedure may at the request of the applicant also be used in certain other cases. It is very likely that the centralized procedure would apply to the products we are developing. National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this national MA can be recognized in another Member State through the Mutual Recognition Procedure. If the product has not received a national MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the decentralized procedure. Under the decentralized procedure an identical dossier is submitted to the national competent authority of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State.

The Committee for Advanced Therapies, or CAT, is responsible in conjunction with the CHMP for the evaluation of ATMPs. The CAT is primarily responsible for the scientific evaluation of ATMPs and prepares a draft opinion on the quality, safety and efficacy of each ATMP for which a MAA is submitted. The CAT's opinion is then considered by the CHMP when giving its final recommendation regarding the authorization of a product in view of the balance of benefits and risks identified. Although the CAT's draft opinion is submitted to the CHMP for final approval, the CHMP may depart from the draft opinion, if it provides detailed scientific justification. The CHMP and CAT are also responsible for providing guidelines on ATMPs and have published numerous guidelines, including specific guidelines on gene therapies and cell therapies. These guidelines

provide additional guidance on the factors that the EMA will consider in relation to the development and evaluation of ATMPs and include, among other things, the preclinical studies required to characterize ATMPs; the manufacturing and control information that should be submitted in a marketing authorization application; and post-approval measures required to monitor patients and evaluate the long term efficacy and potential adverse reactions of ATMPs.

Under the centralized procedure, the maximum timeframe for the evaluation of a MAA by the EMA is 210 days. This excludes so-called clock stops, during which additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. At the end of the review period, the CHMP provides an opinion to the European Commission. If this opinion is favorable, the Commission may then adopt a decision to grant an MA. In exceptional cases, the CHMP might perform an accelerated review of a MAA in no more than 150 days (not including clock stops). Innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the breakthrough therapy designation in the U.S. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. Product developers that benefit from PRIME designation can expect to be eligible for accelerated assessment, but this is however not guaranteed. The benefits of a PRIME designation include the appointment of a CHMP rapporteur before submission of a MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review earlier in the application process. PRIME designation do not however change the standards for product approval, and there is no assurance that any such designation or eligibility will result in expedited review or approval.

MAs have an initial duration of five years. After these five years, the authorization may be renewed on the basis of a reevaluation of the risk-benefit balance. Once renewed, the MA is valid for an unlimited period unless the European Commission or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

Data and Marketing Exclusivity

The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving a MA, new chemical entities generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. The overall ten-year market exclusivity period may be extended to a maximum of eleven years if, during the first eight years a new therapeutic indication with significant clinical benefit over existing therapies is approved. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity. There is a special regime for biosimilars, or biological medicinal products that are similar to a reference medicinal product but that do not meet the definition of a generic medicinal product, for example, because of differences in raw materials or manufacturing processes. For such products, the results of appropriate preclinical or clinical trials must be provided, and guidelines from the EMA detail the type of quantity of supplementary data to be provided for different types of biological product. There are no such guidelines for complex biological products, such as gene or cell therapy medicinal products, and so it is unlikely that biosimilars of those products will currently be approved in the European Union. However, guidance from the EMA states that they will be considered in the future in light of the scientific knowledge and regulatory experience gained at the time.

Orphan Medicinal Products

The criteria for designating an "orphan medicinal product" in the EU are similar in principle to those in the United States. A medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition. The application for orphan drug designation must be submitted before the MAA. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of an MA, entitled to ten years of market exclusivity for the approved therapeutic indication. During the ten-year market exclusivity period, the EMA cannot accept a MAA, or grant a MA, or accept an application to

extend a MA, for the same indication, in respect of a similar medicinal product. An orphan medicinal product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, an MA may be granted to a similar product for the same indication at any time if (1) the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior; (2) the applicant consents to a second orphan medicinal product application; or (3) the applicant cannot supply enough orphan medicinal product.

Pediatric Development

In the European Union, MAAs for new medicinal products have to include the results of trials conducted in the pediatric population, in compliance with a pediatric investigation plan, or PIP, agreed with the EMA's Pediatric Committee, or PDCO. The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which an MA 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 are 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 MA is obtained in all Member States and study results are included in the product information, even when negative, the product is eligible for a six-months supplementary protection certificate extension (if any is in effect at the time of approval) or, in the case of orphan pharmaceutical products, a two year extension of the orphan market exclusivity is granted.

Post-Approval Requirements

Similar to the United States, both MA holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA, the European Commission and/or the competent regulatory authorities of the member states. The holder of a MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the MA. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies.

The advertising and promotion of medicinal products is also subject to laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each member state and can differ from one country to another.

Failure to comply with EU and member state laws that apply to the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products and marketing of such products, both before and after grant of the MA, manufacturing of pharmaceutical products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials, or to grant MA, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the MA, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

The aforementioned EU rules are generally applicable in the European Economic Area, or EEA, which consists of the 27 EU member states plus Norway, Liechtenstein and Iceland. With respect to the United Kingdom, following its exit from the European Union on January 31, 2020, the transition period, during which EU pharmaceutical laws continued to apply to the United Kingdom, has expired on December 31, 2020. However, the EU and the United Kingdom have concluded a trade and

cooperation agreement, or TCA, which is provisionally applicable since January 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of Good Manufacturing Practice, or GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Employees

As of December 31, 2020, we had 205 full-time employees, including 42 employees with M.D. or Ph.D. degrees. Of these full-time employees, 185 employees are engaged in research and development activities, including technical operations, clinical and regulatory and research and development. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Corporate Information

We were incorporated in Delaware in March 2015. Our principal executive offices are located at One Patriots Park, Bedford, MA 01730 and our telephone number is (781) 301-7277. Our website address is www.homologymedicines.com. Information contained on or accessible through our website is not a part of this Annual Report on Form 10-K, and the inclusion of our website address in this Annual Report on Form 10-K is an inactive textual reference only.

Available Information

We file electronically with the Securities and Exchange Commission, or SEC, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, proxy statements and other information. Our SEC filings are available to the public over the Internet at the SEC's website at http://www.sec.gov. We make available on our website at www.homologymedicines.com, under “Investors,” free of charge, copies of these reports as soon as reasonably practicable after filing or furnishing these reports with the SEC.

Item 1A. Risk Factors.

Investing in our common stock involves a high degree of risk. You should consider carefully the risks described below, together with the other information included or incorporated by reference in this Annual Report on Form 10-K. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline. Other events that we do not currently anticipate or that we currently deem immaterial may also affect our business, prospects, financial condition and results of operations.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception and anticipate that we will incur continued losses for the foreseeable future. If we are unable to achieve and sustain profitability, the market value of our common stock will likely decline. We may never achieve or maintain profitability.

We are a clinical-stage genetic medicines company with a limited operating history. We have never been profitable and do not expect to be profitable in the foreseeable future. We have incurred net losses in each year since beginning to develop our product candidates, including net losses of approximately $128.7 million and $103.9 million for the years ended December 31, 2020 and 2019, respectively. As of December 31, 2020, we had an accumulated deficit of approximately $328.4 million. In addition, we have not commercialized any products and have never generated any revenue from product sales. We have devoted most of our financial resources to research and development, including our preclinical development activities.

We expect to continue to incur significant additional operating losses for the foreseeable future as we seek to advance product candidates through preclinical and clinical development, expand our research and development activities, develop new product candidates, complete clinical trials, seek regulatory approval and, if we receive FDA approval, commercialize our products. Furthermore, the costs of advancing product candidates into each succeeding clinical phase tend to increase substantially over time. The total costs to advance any of our product candidates to marketing approval in even a single jurisdiction would be substantial. Because of the numerous risks and uncertainties associated with genetic medicines product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to begin generating revenue from the commercialization of products or achieve or maintain profitability. Our expenses will also increase substantially if and as we:

- continue our current research programs and our preclinical development of product candidates from our current research programs;
- seek to identify, assess, acquire and/or develop additional research programs and additional product candidates;
- initiate preclinical testing and clinical trials for any product candidates we identify and develop;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- further develop our genetic medicines platform;
- hire additional clinical, scientific and commercial personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts, as well as to support our operations as a public reporting company;
- acquire or in-license other commercial products, product candidates and technologies;
- make royalty, milestone or other payments under current and any future in-license agreements; and
- further expand our Good Manufacturing Practices, or GMP, manufacturing capacity.

Furthermore, our ability to successfully develop, commercialize and license our products and generate product revenue is subject to substantial additional risks and uncertainties. Each of our programs and product candidates will require additional preclinical and clinical development, potential regulatory approval in multiple jurisdictions, securing manufacturing supply, capacity and expertise, building of a commercial organization, substantial investment and significant marketing efforts before we generate any revenue from product sales. These risks are further described under "—Risks Related to Discovery, Development, Clinical Testing, Manufacturing and Regulatory Approval" and "—Risks Related to Commercialization." As a result, we expect to continue to incur net losses and negative cash flows for the foreseeable future. These net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. The amount of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues. If we are unable to develop and commercialize one or more of our product candidates either alone or with collaborators, or if revenues from any product candidate that receives marketing approval are insufficient, we will not achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability. If we are unable to achieve and then maintain profitability, the value of our equity securities will be materially and adversely affected.

We will require additional capital to fund our operations, and if we fail to obtain necessary financing, we may not be able to complete the development and commercialization of our product candidates.

We expect to spend substantial amounts to complete the development of, seek regulatory approvals for and commercialize our lead product candidate, HMI-102. We will require additional capital, which we may raise through equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources to enable us to complete the development and potential commercialization of HMI-102, HMI-103, HMI-202, HMI-203 and any other product candidates. In addition, we may not be able to enter into any collaborations that will generate significant cash. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative effect on our financial condition and our ability to pursue our business strategy. In addition, attempting to secure additional financing may divert the time and attention of our management from day-to-day activities and harm our product candidate development efforts.

Based upon our current operating plan, we believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements into the third quarter of 2022, including, subject to the impact of the

COVID-19 pandemic on our business, additional development activities related to our Phase 1/2 pheNIX clinical trial with HMI-102, the advancement of our lead gene editing product candidate, HMI-103, and our gene therapy product candidates, HMI-202 and HMI-203, the scale-up of our manufacturing processes and the expansion of our intellectual property portfolio. This estimate is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Changing circumstances could cause us to consume capital significantly faster than we currently anticipate, and we may need to spend more than currently expected because of circumstances beyond our control. Because the length of time and activities associated with successful development of HMI-102, HMI-103, HMI-202, HMI-203 and any other product candidates is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of our planned clinical trials for HMI-102 and our other product candidates;
- the outcome, timing and cost of meeting regulatory requirements established by the FDA and other comparable foreign regulatory authorities;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending potential intellectual property disputes, including patent infringement actions brought by third parties against us or HMI-102, HMI-103, HMI-202, HMI-203 or any of our product candidates;
- the effect of competing technological and market developments;
- the cost and timing of completion of commercial-scale manufacturing activities;
- the costs of operating as a public company;
- the extent to which we in-license or acquire other products and technologies;
- the cost of establishing sales, marketing and distribution capabilities for HMI-102, HMI-103, HMI-202, HMI-203 or any of our product candidates in regions where we choose to commercialize our products; and
- the initiation, progress, timing and results of our commercialization of HMI-102, HMI-103, HMI-202, HMI-203 or any of our product candidates, if approved for commercial sale.

We cannot be certain that additional funding will be available on acceptable terms, or at all. Moreover, market volatility resulting from the COVID-19 pandemic or other factors could also adversely impact our ability to access capital as and when needed. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of HMI-102, HMI-103, HMI-202, HMI-203 or other product candidates or potentially discontinue operations.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial revenue, we may finance our cash needs through a combination of equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements. We do not currently have any committed external source of funds. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, including under our effective Registration Statement on Form S-3, the ownership interests of our shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

We have a limited operating history and no history of commercializing genetic medicine products, which may make it difficult to evaluate the prospects for our future viability.

We were established and began operations in 2015. Our operations to date have been limited to financing and staffing our company, developing our technology and identifying and developing our product candidates. We have not yet demonstrated an ability to successfully complete any clinical trials, including large-scale, pivotal clinical trials, obtain marketing approval, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Typically, it takes about six to ten years to develop a new drug from the time it enters Phase 1 clinical trials to when it is approved for treating patients, but in many cases, it may take longer. Consequently, predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing genetic medicine products.

In addition, as a business with a limited operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will eventually need to transition from a company with a research focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

As we continue to build our business, we expect our financial condition and operating results may fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any particular quarterly or annual period as indications of future operating performance.

We are heavily dependent on the success of HMI-102, our most advanced product candidate, and if HMI-102 does not receive regulatory approval or is not successfully commercialized, our business may be harmed.

To date, we have invested a significant portion of our efforts and financial resources in the development of HMI-102. Our future success and ability to generate product revenue is substantially dependent on our ability to successfully develop, obtain regulatory approval for and successfully commercialize this product candidate. We currently have no products that are approved for commercial sale and may never be able to develop marketable products. We expect that a substantial portion of our efforts and expenditures over the next few years will be devoted to HMI-102, which will require additional clinical development, management of clinical and manufacturing activities, regulatory approval in multiple jurisdictions, securing manufacturing supply, building of a commercial organization, substantial investment and significant marketing efforts before we can generate any revenues from any commercial sales. Accordingly, our business currently depends heavily on the successful development, regulatory approval and commercialization of HMI-102, which may never occur if HMI-102 is ultimately shown to not be associated with phenylalanine hydroxylase enzymatic activity and increased Phe metabolism, or if HMI-102 were associated with serious adverse events, or if it were found to not be efficacious. Therefore, we cannot be certain that HMI-102 will be successful in our current Phase 1/2 pheNIX trial or future clinical trials, receive regulatory approval or be successfully commercialized even if we receive regulatory approval. Even if we receive approval to market HMI-102 from the FDA or other regulatory authorities, we cannot be certain that our product candidate will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives. Additionally, the research, testing, manufacturing, labeling, approval, sale, marketing and distribution of genetic medicine products are and will remain subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries that each have differing regulations. We are not permitted to market HMI-102 in the United States until it receives approval of a Biologics License Application, or BLA, from the FDA, or in any foreign countries until it receives the requisite approval from such countries.

We have not submitted a BLA to the FDA or comparable applications to other regulatory authorities and do not expect to be in a position to do so for the foreseeable future.

HMI-102 is our most advanced product candidate, and because our other product candidates are based on similar technology, if HMI-102 shows unexpected adverse events or a lack of efficacy in the indications we intend to treat, or if we experience other regulatory or developmental issues, our development plans and business could be significantly harmed. Further, competitors may be developing products with similar technology and may experience problems with their products that could identify problems that would potentially harm our business.

We may not be successful in our efforts to identify additional product candidates.

Part of our strategy involves identifying novel product candidates. The process by which we identify product candidates may fail to yield product candidates for clinical development for a number of reasons, including those discussed in these risk factors and also:

- we may not be able to assemble sufficient resources to acquire or discover additional product candidates;
- competitors may develop alternatives that render our potential product candidates obsolete or less attractive;
- potential product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- potential product candidates may, on further study, be shown to have harmful side effects, toxicities or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance;
- potential product candidates may not be effective in treating their targeted diseases;
- the market for a potential product candidate may change so that the continued development of that product candidate is no longer reasonable;
- a potential product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; or
- the regulatory pathway for a potential product candidate is too complex and difficult to navigate successfully or economically.

In addition, we may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases that may later prove to have greater commercial potential, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights. If we are unable to identify additional suitable product candidates for clinical development, this would adversely impact our business strategy and our financial position and share price and could potentially cause us to cease operations.

We will need to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

We will need to significantly expand our organization, and we may have difficulty identifying, hiring and integrating new personnel. Future growth would impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

Many of the biotechnology companies that we compete against for qualified personnel and consultants have greater financial and other resources, different risk profiles and a longer history in the industry than we do. If we are unable to continue to attract and retain high-quality personnel and consultants, the rate and success at which we can discover and develop product candidates and operate our business will be limited.

We may be required to make significant payments in connection with our license agreements with each of the City of Hope and the California Institute of Technology.

Under our license agreements with each of City of Hope Medical Center, or COH, and California Institute of Technology, or Caltech, we are subject to significant obligations, including payment obligations upon achievement of specified milestones and royalties on product sales, as well as other material obligations, including potential payments to COH if we were to sublicense the COH technology to additional strategic collaborators. If these payments become due, we may not have sufficient funds available to meet our obligations or we may have to direct funds from other development efforts, and as a result, our development efforts may be materially harmed.

Risks Related to Discovery, Development, Clinical Testing, Manufacturing and Regulatory Approval

We intend to identify and develop product candidates based on our novel genetic medicines platform, which makes it difficult to predict the time and cost of product candidate development. No products that utilize gene editing technology have been approved in the United States or in Europe, and there have only been a limited number of human clinical trials involving a gene editing product candidate. Moreover, none of those trials has involved our nuclease-free gene editing technology.

We have concentrated our research and development efforts on our genetic medicines platform, which uses both nuclease-free gene editing and gene therapy technologies. Our future success depends on the successful development of this novel therapeutic approach. To date, no product that utilizes gene editing has been approved in the United States or Europe. There have been a limited number of clinical trials of gene editing technologies, however no product candidates have been approved, and none of these clinical trials involved product candidates that utilize our novel gene correction editing technology. In addition, because our programs are all in the research, preclinical or early-clinical stage, we have not yet been able to fully assess safety in humans, and there may be long-term effects from treatment with any of our future product candidates that we cannot predict at this time. Any gene correction editing product candidates we may develop will act at the level of DNA, and, because animal DNA differs from human DNA, it will be difficult for us to test our future product candidates in animal models for either safety or efficacy. Also, animal models may not exist for some of the diseases we expect to pursue. Our genetic medicines platform is based on a family of 15 proprietary AAVHSCs which we can deploy with either gene editing or gene therapy constructs. Both applications rely on a unique ability of our AAVHSCs to efficiently target multiple tissues in the body. The mechanism of action by which these vectors target particular tissues is still not completely understood. Therefore, it is difficult for us to determine that our vectors will be able to properly integrate corrective DNA in or deliver gene transfer constructs to enough tissue cells to reach therapeutic levels. We cannot be certain that our AAVHSCs will be able to meet safety and efficacy levels needed to be therapeutic in humans or that they will not cause significant adverse events or toxicities. Furthermore, studies conducted by a third party in non-human primates suggests that intravenous delivery of certain AAV vectors at very high doses may result in severe toxicity. To date, we have not observed the severe toxicities described in these publications after intravenous administration in non-human primates with our naturally occurring AAVHSC vectors, and we have not seen these toxicities in our product candidates. However, we cannot be certain that we will be able to avoid triggering toxicities in our future preclinical or clinical studies. Any such results could impact our ability to develop a product candidate. As a result of these factors, it is more difficult for us to predict the time and cost of product candidate development, and we cannot predict whether the application of our genetic medicines platform, or any similar or competitive gene therapy or gene editing platforms, will result in the identification, development, and regulatory approval of any medicines, or that other genetic medicine technologies will not be considered better or more attractive for the development of medicines. There can be no assurance that any development problems we experience in the future related to our genetic medicines platform or any of our research programs will not cause significant delays or unanticipated costs, or that such development problems can be solved. We may also experience delays in developing a sustainable, reproducible, and scalable manufacturing process or transferring that process to commercial partners. Any of these factors may prevent us from completing our preclinical studies or any clinical trials that we may initiate or commercializing any product candidates we may develop on a timely or profitable basis, if at all.

Because gene therapy and gene editing are novel and the regulatory landscape that governs any product candidates we may develop is uncertain and continues to change, we cannot predict the time and cost of obtaining regulatory approval, if we receive it at all, for any product candidates we may develop.

Regulatory requirements governing products created with genome editing technology or involving gene therapy treatment have changed frequently and will likely continue to change in the future. Approvals by one regulatory authority may not be indicative of what any other regulatory authority may require for approval, and there is substantial, and sometimes uncoordinated, overlap in those responsible for regulation of gene therapy products, cell therapy products and other products created with genome editing technology. For example, the FDA established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research, or CBER, with responsibility for the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. These and

other regulatory review agencies, committees and advisory groups and any requirements and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional preclinical studies or clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval limitations or restrictions.

Additionally, under NIH Guidelines supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

In the European Union, or EU, the EMA, has a Committee for Advanced Therapies, or CAT, that, in conjunction with the CHMP, is responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products, or ATMPs. ATMPs include gene therapy medicines, somatic-cell therapy medicines and tissue-engineered medicines. The role of the CAT is to prepare a draft opinion on an application for marketing authorization for a gene therapy medicinal candidate that is submitted to the EMA. The CAT's opinion is considered by the CHMP when giving its final recommendation regarding the authorization of a product in view of the balance of benefits and risks identified. Although the CAT's draft opinion is submitted to the CHMP for final approval, the CHMP may depart from the draft opinion, if it provides detailed scientific justification. In the EU, the development and evaluation of a gene therapy medicinal product must be considered in the context of the relevant EU guidelines. The CHMP and CAT are also responsible for providing guidelines on ATMPs and have published numerous guidelines, including specific guidelines on gene therapies and cell therapies. These guidelines provide additional guidance on the factors that the EMA will consider in relation to the development and evaluation of ATMPs and include, among other things, the preclinical studies required to characterize ATMPs; the manufacturing and control information that should be submitted in a marketing authorization application; and post-approval measures required to monitor patients and evaluate the long term efficacy and potential adverse reactions of ATMPs. Although these guidelines are not legally binding, we believe that our compliance with them is likely necessary to gain and maintain approval for any of our product candidates. In addition, the EMA may issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines. Similarly complex regulatory environments exist in other jurisdictions in which we might consider seeking regulatory approvals for our product candidates, further complicating the regulatory landscape. As a result, the procedures and standards applied to gene therapy products and cell therapy products may be applied to any of our gene therapy or genome editing product candidates, but that remains uncertain at this point.

The clinical trial requirements of the FDA, the EMA and other regulatory authorities and the criteria these regulators use to evaluate the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for product candidates created with novel genome editing technology such as ours can be more lengthy, rigorous and expensive than the process for other better known or more extensively studied product candidates and technologies. Since we are developing novel treatments for diseases in which there is little clinical experience with new endpoints and methodologies, there is heightened risk that the FDA, the EMA or comparable regulatory authorities may not consider the clinical trial endpoints to provide clinically meaningful results, and the resulting clinical data and results may be more difficult to analyze. This may be a particularly significant risk for many of the genetically defined diseases for which we may develop product candidates alone or with collaborators due to small patient populations for those diseases, and designing and executing a rigorous clinical trial with appropriate statistical power is more difficult than with diseases that have larger patient populations. Regulatory authorities administering existing or future regulations or legislation may not allow production and marketing of products utilizing genome editing technology in a timely manner or under technically or commercially feasible conditions. Even if our product candidates obtain required regulatory approvals, such approvals may later be withdrawn as a result of changes in statute or regulations or the interpretation of new available data by applicable regulatory agencies.

Changes in applicable regulatory guidelines may lengthen the regulatory review process for our product candidates, require additional studies or trials, increase development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of such product candidates, or lead to significant post-approval limitations or restrictions. Additionally, adverse developments in clinical trials conducted by others of gene therapy products or products created using genome editing technology, or adverse public perception of the field of genome editing, may cause the FDA, the EMA and other regulatory authorities to revise the requirements for approval of any product candidates we may develop or limit the use of products utilizing genome editing technologies, either of which could materially harm our business. Furthermore, regulatory action or private litigation could result in expenses, delays or other impediments to our research programs or the development or commercialization of current or future product candidates.

As we advance product candidates, we will be required to consult with these regulatory and advisory groups and comply with all applicable guidelines, rules and regulations. If we fail to do so, we may be required to delay or terminate development of such product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a product candidate to market could decrease our ability to generate sufficient product revenue to maintain our business.

Clinical trials are expensive, time-consuming, difficult to design and implement, and involve an uncertain outcome.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biotechnology and genetic medicines industries have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Even if our current and future clinical trials are completed as planned, we cannot be certain that their results will establish the safety, purity, potency and/or effectiveness of HMI-102 for PKU or any other potential indication to the satisfaction of the FDA or other regulatory authorities, even if we believe that such trials were successful.

To date, we have not completed any clinical trials required for the approval of HMI-102 or any of our product candidates. Although we have initiated our Phase 1/2 pheNIX trial for HMI-102, we may experience delays in conducting any clinical trials and we do not know whether planned clinical trials will begin on time, need to be redesigned, recruit and enroll patients on time or be completed on schedule, or at all. Clinical trials can be delayed or terminated for a variety of reasons, including delays or failures related to:

- the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical studies;
- obtaining regulatory approval to commence a trial;
- reaching an agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining institutional review board, or IRB, and ethics committee approval at each site;
- recruiting suitable patients to participate in a trial;
- developing and validating the companion diagnostic to be used in a clinical trial, if applicable;
- having patients complete a trial or return for post-treatment follow-up;
- clinical sites deviating from trial protocol or dropping out of a trial;
- addressing patient safety concerns that arise during the course of a trial;
- adding a sufficient number of clinical trial sites; or
- manufacturing sufficient quantities of product candidate for use in clinical trials.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates or significantly increase the cost of such trials, including:

- we may receive feedback from regulatory authorities that requires us to modify the design of our clinical trials;
- clinical trials of our product candidates may produce negative safety and/or efficacy data or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

- we or our investigators might have to suspend or terminate clinical trials of our product candidates for various reasons, including non-compliance with regulatory requirements, a finding that our product candidates have undesirable side effects or other unexpected characteristics, or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate, and we may not have funds to cover the costs;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate; and
- any future collaborators that conduct clinical trials may face any of the above issues, and may conduct clinical trials in ways they view as advantageous to them but that are suboptimal for us.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- incur unplanned costs;
- be delayed in obtaining marketing approval for our product candidates or not obtain marketing approval at all;
- obtain marketing approval in some countries and not in others;
- obtain marketing approval for indications or patient populations that are not as broad as intended or desired;
- obtain marketing approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

In addition, disruptions caused by the COVID-19 pandemic may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials. For example, we have experienced, and may continue to experience, delays in enrolling our Phase 1/2 pheNIX trial as a result of the COVID-19 pandemic. We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by the Data Safety Monitoring Board, or DSMB, for such trial or by the FDA or other regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Furthermore, we may rely on CROs and clinical trial sites to ensure the proper and timely conduct of clinical trials, and while we would have agreements governing their committed activities, we would have limited influence over their actual performance, as described in "—Risks Related to Our Dependence on Third Parties."

Our most advanced product candidate, HMI-102, will require extensive clinical testing before we are prepared to submit a BLA for regulatory approval. We cannot predict with any certainty if or when we might complete the development of HMI-102 and submit a BLA for regulatory approval of HMI-102 or whether any such BLA will be approved by the FDA. We may seek feedback from the FDA or other regulatory authorities on our clinical development program, and the FDA or such regulatory authorities may not provide such feedback on a timely basis, or such feedback may not be favorable, which could further delay our development programs.

If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of HMI-102 could be harmed, and our ability to generate revenues from HMI-102 may be delayed. In addition, any delays in our clinical trials could increase our costs, slow down the development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and results of operations. In addition, many of the factors that cause, or lead to, a delay in the

commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Adverse public perception of genetic medicine, and gene editing in particular, may negatively impact regulatory approval of, or demand for, our potential products.

Some of our potential therapeutic products involve editing the human genome. The clinical and commercial success of our potential products will depend in part on public acceptance of the use of gene editing and gene therapy for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy and gene editing are unsafe, unethical, or immoral, and, consequently, our products may not gain the acceptance of the public or the medical community. Adverse public attitudes may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of product candidates we may develop in lieu of, or in addition to, existing treatments with which they are already familiar and for which greater clinical data may be available.

In addition, gene editing technology is subject to public debate and heightened regulatory scrutiny due to ethical concerns relating to the application of gene editing technology to human embryos or the human germline. For example, in April 2015, Chinese scientists reported on their attempts to edit the genome of human embryos to modify the gene for hemoglobin beta. This is the gene in which a mutation occurs in patients with the inherited blood disorder beta thalassemia. Although this research was purposefully conducted in embryos that were not viable, the work prompted calls for a moratorium or other types of restrictions on gene editing of human eggs, sperm, and embryos. The Alliance for Regenerative Medicine in Washington, D.C. has called for a voluntary moratorium on the use of gene editing technologies in research that involved altering human embryos or human germline cells. Similarly, the NIH has announced that it would not fund any use of gene editing technologies in human embryos, noting that there are multiple existing legislative and regulatory prohibitions against such work, including the Dickey-Wicker Amendment, which prohibits the use of appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. Laws in the United Kingdom prohibit genetically modified embryos from being implanted into women, but embryos can be altered in research labs under license from the Human Fertilisation and Embryology Authority. Research on embryos is more tightly controlled in many other European countries.

Although we do not use our technologies to edit human embryos or the human germline, such public debate about the use of gene editing technologies in human embryos and heightened regulatory scrutiny could prevent or delay our development of product candidates. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair our development and commercialization of product candidates or demand for any products we may develop. Adverse events in our preclinical studies or clinical trials or those of our competitors or of academic researchers utilizing gene therapy or gene editing technologies, even if not ultimately attributable to product candidates we may discover and develop, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of potential product candidates we may identify and develop, stricter labeling requirements for those product candidates that are approved, a decrease in demand for any such product candidates and a suspension or withdrawal of approval by regulatory authorities of our product candidates.

A Breakthrough Therapy Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek a Breakthrough Therapy Designation for our product candidates if the clinical data support such a designation for one or more product candidates. A breakthrough therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug, or biologic in our case, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For product candidates that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Biologics designated as breakthrough therapies by the FDA may also be eligible for priority review.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under non-expedited FDA review procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. The same principles apply to a possible PRIME designation by the EMA in the EU.

A Fast Track Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our product candidates will receive marketing approval.

On May 1, 2019, we received Fast Track Designation for HMI-102 for the prevention or treatment of neurocognitive defects due to phenylalanine hydroxylase deficiency through normalization of circulating phenylalanine levels, and we intend to seek such designation for some or all of our other product candidates. If a drug or biologic, in our case, is intended for the treatment of a serious or life-threatening condition and the biologic demonstrates the potential to address unmet medical needs for this condition, the biologic sponsor may apply for FDA Fast Track Designation. The sponsor of a Fast Track product candidate has opportunities for more frequent interactions with the applicable FDA review team during product development and, once a BLA is submitted, the product candidate may be eligible for priority review. A Fast Track product candidate may also be eligible for rolling review, where the FDA may consider for review sections of the BLA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the BLA, the FDA agrees to accept sections of the BLA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the BLA. The FDA has broad discretion whether or not to grant this designation. Even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Many biologics that have received Fast Track Designation have failed to obtain approval.

We may also seek accelerated approval for products that have obtained Fast Track Designation. Under the FDA's accelerated approval program, the FDA may approve a biologic for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. For biologics granted accelerated approval, post-marketing confirmatory trials are required to describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence and, in some cases, the FDA may require that the trial be designed and/or initiated prior to approval. Moreover, the FDA may withdraw approval of any product candidate or indication approved under the accelerated approval pathway in an expedited manner if, for example:

- the trial or trials required to verify the predicted clinical benefit of the product candidate fail to verify such benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the biologic;
- other evidence demonstrates that the product candidate is not shown to be safe or effective under the conditions of use; or
- we fail to conduct any required post-approval trial of the product candidate with due diligence.

We have received orphan drug designation for HMI-102 and HMI-202, and we intend to seek orphan drug designation for our other product candidates, but any orphan drug designations we receive may not confer marketing exclusivity or other expected benefits.

We have received orphan drug designation for HMI-102 in the United States and Europe for the use of AAVHSC15 expressing *PAH* for the treatment of PAH deficiency. In addition, we have received orphan drug designation for HMI-202 in the United States and Europe for the use of AAVHSC15 expressing human arylsulfatase A for the treatment of metachromatic leukodystrophy, or MLD. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity. Orphan drug exclusivity in the United States provides that the FDA may not

approve any other applications, including a full BLA, to market the same drug for the same indication for seven years, except in limited circumstances. The applicable exclusivity period is ten years in Europe. The European exclusivity period can be reduced to six years if, at the end of the fifth year a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified.

Even if we, or any future collaborators, obtain orphan drug designation for a product candidate, we, or they, may not be able to obtain or maintain orphan drug exclusivity for that product candidate. We may not be the first to obtain marketing approval of any product candidate for which we have obtained orphan drug designation for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical products. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Further, even if we, or any future collaborators, obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may be approved for the same indication. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same indication if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care or the manufacturer of the product with orphan exclusivity is unable to maintain sufficient product quantity. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process, nor does it prevent competitors from obtaining approval of the same product candidate as ours for indications other than those in which we have been granted orphan drug designation. The same principles are valid for the EU as well.

We have received rare pediatric disease designation for HMI-202, and we may seek rare pediatric disease designation for our other product candidates, however, there is no guarantee that we will obtain such designation, and even if we do, there is no guarantee that FDA approval will result in a priority review voucher.

In 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" that meets certain criteria may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U.S. within one year following the date of approval.

We have received rare pediatric disease designation for HMI-202 for the treatment of MLD, and we may seek rare pediatric disease designation for our other product candidates; however, we may not be able to obtain such designation. If we are able to obtain rare pediatric disease designation for our other product candidates, there is no guarantee that we will be able to obtain a priority review voucher, even if the designated product candidate is approved by the FDA. Moreover, Congress included a sunset provision in the statute authorizing the rare pediatric disease priority review voucher program. Specifically, the FDA may not award the voucher to sponsors of marketing applications unless either (i) the drug has received rare pediatric disease designation as of September 30, 2024, and is then approved by the FDA no later than September 30, 2026; or (ii) Congress reauthorizes the program. Even though we received rare pediatric disease designation for HMI-202 by the current statutory deadline of September 30, 2024, we may not receive the voucher if we do not obtain approval by September 30, 2026. Even if legislation is enacted that extends the date by which approval of the rare pediatric disease-designated drug must obtain approval to receive a priority review voucher, we may not obtain approval by that date, and even if we do, we may not obtain a priority review voucher.

A Regenerative Medicine Advanced Therapy designation by the FDA, or Advanced Therapy Medicinal Product designation by the EMA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.

We may seek a Regenerative Medicine Advanced Therapy, or RMAT, designation for HMI-102 or our other product candidates. In 2017, the FDA established the RMAT designation as part of its implementation of the 21st Century Cures Act. An investigational drug is eligible for RMAT designation if: (1) it meets the definition of a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; (2) it is intended to treat, modify, reverse, or cure a serious disease or condition; and (3) preliminary clinical evidence indicates that the investigational drug has the potential to address

unmet medical needs for such disease or condition. In a February 2019 final guidance, the FDA also stated that certain gene therapies that lead to a sustained effect on cells or tissues may meet the definition of a regenerative medicine therapy. RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review of BLAs and priority review. Product candidates granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate. RMAT-designated product candidates that receive accelerated approval may, as appropriate, fulfill their post-approval requirements through the submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence (such as electronic health records); through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.

RMAT designation does not change the standards for product approval, and there is no assurance that such designation or eligibility for such designation will result in expedited review or approval or that the approved indication will not be narrower than the indication covered by the RMAT designation. Additionally, RMAT designation can be revoked if the criteria for eligibility cease to be met as clinical data emerges.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and product candidates. We completed the build-out of a GMP manufacturing facility to support our clinical development programs in both gene therapy and gene editing and commenced manufacturing activities in April 2019. However, if we experience delays or are unable to scale our internal manufacturing capabilities, we will need to contract with manufacturers that can produce the preclinical, clinical and commercial supply of our products. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities.

All entities involved in the preparation of therapeutics for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical studies must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's current good laboratory practices, or GLP, and GMP regulations enforced by the FDA through its facilities inspection program. Some of our contract manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA or other regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. An alternative manufacturer would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical studies, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed, or we could lose potential revenue.

If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. We may encounter delays in enrolling, or be unable to enroll, a sufficient number of patients to complete any of our clinical trials, and even once enrolled we may be unable to retain a sufficient number of patients to complete any of our trials. The enrollment of patients depends on many factors, including:

- the patient eligibility criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to study sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved for the indications we are investigating;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial site.

Delays or failures in planned patient enrollment or retention may result in increased costs, program delays or both, which could have a harmful effect on our ability to develop HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidates, or could render further development impossible.

Our product candidates may cause serious adverse events or undesirable side effects or have other properties which may delay or prevent their regulatory approval, limit the commercial profile of an approved label, or, result in significant negative consequences following marketing approval, if any.

Serious adverse events or undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects, toxicities or unexpected characteristics, including death. A significant risk in any gene editing product is that the edit will be "off-target" (or "on-target," but unwanted) and cause serious adverse events, undesirable side effects, toxicities or unexpected characteristics. For example, off-target cuts could lead to disruption of a gene or a genetic regulatory sequence at an unintended site in the DNA, or, in those instances where we also provide a segment of DNA to serve as a repair template, it is possible that following off-target cut events, DNA from such repair template could be integrated into

the genome at an unintended site, potentially disrupting another important gene or genomic element. We cannot be certain that off-target editing will not occur in any of our planned or future clinical studies. There is also the potential risk of delayed adverse events following exposure to gene editing therapy, due to the potential for persistent biological activity of the genetic material or other product components used to carry the genetic material.

If unacceptable side effects arise in the development of our product candidates, we, the FDA, the IRBs or ethics committees at the institutions in which our studies are conducted or DSMB, could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We expect to have to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may harm our business, financial condition and prospects significantly.

If any of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by any such product, including during any long-term follow-up observation period recommended or required for patients who receive treatment using our products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- we may be required to recall a product or change the way such product is administered to patients;
- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product;
- regulatory authorities may require additional warnings on the label, such as a “black box” warning or contraindication;
- we may be required to implement a Risk Evaluation and Mitigation Strategy, or REMS, or create a medication guide outlining the risks of such side effects for distribution to patients;
- the product could become less competitive;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate’s clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that neither HMI-102, HMI-103, HMI-202, HMI-203, nor any other product candidates we may seek to develop in the future will ever obtain regulatory approval. Neither we nor any future collaborator is permitted to market any of our product candidates in the United States until we receive regulatory approval of a BLA from the FDA. It is possible that the FDA may refuse to file for substantive review any BLAs that we submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates.

Prior to obtaining approval to commercialize a product candidate in the United States or abroad, we or our collaborators must demonstrate with substantial evidence from well-controlled clinical trials, and to the satisfaction of the FDA or foreign regulatory authorities, that such product candidates are safe and effective, or in the case of biologics, safe, pure, and potent, for their intended uses. Results from nonclinical studies and clinical trials can be interpreted in different ways. Even if we believe

the nonclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and other regulatory authorities. The FDA may also require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or post-approval, or it may object to elements of our clinical development program. Depending on the extent of these or any other FDA-required studies, approval of any BLA or application that we submit may be delayed by several years or may require us to expend significantly more resources than we have available.

Of the large number of potential products in development, only a small percentage successfully complete the FDA or foreign regulatory approval processes and are commercialized. The lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market our product candidates, which would significantly harm our business, results of operations and prospects.

In addition, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post-marketing clinical trials, including Phase 4 clinical trials, and/or the implementation of a REMS, which may be required to ensure safe use of the drug after approval. The FDA or the applicable foreign regulatory agency also may approve a product candidate for a more limited indication or patient population than we originally requested, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA to review and or approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies, in particular the EMA, following its relocation to Amsterdam and related reorganization, may also slow the time necessary for new drugs and biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Separately, in response to the global pandemic of COVID-19, on March 10, 2020 the FDA announced its intention to postpone most foreign inspections of manufacturing facilities and products through April 2020, and subsequently, on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, on July 10, 2020 the FDA announced its intention to resume certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA intends to use this risk-based assessment system to identify the categories of regulatory activity that can occur within a given geographic area, ranging from mission critical inspections to resumption of all regulatory activities. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Even if we obtain FDA approval for HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidates in the United States, we may never obtain approval for or commercialize them in any other jurisdiction, which would limit our ability to realize their full market potential.

In order to market any products in any particular jurisdiction, we must establish and comply with numerous and varying regulatory requirements on a country-by-country basis regarding safety and efficacy. Approval by the FDA in the United States does not ensure approval by regulatory authorities in other countries or jurisdictions. However, the failure to obtain approval in one jurisdiction may negatively impact our ability to obtain approval elsewhere. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country.

Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and increased costs for us and

require additional preclinical studies or clinical trials which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. We do not have any product candidates approved for sale in any jurisdiction, including in international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of any product we develop will be unrealized.

Even if we receive regulatory approval of our product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising and promotional activities for such product, among other things, will be subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, establishment registration and drug listing requirements, continued compliance with GMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and GCP requirements for any clinical trials that we conduct post-approval. Manufacturers of drug products and their facilities are subject to continual review and periodic, unannounced inspections by the FDA and other regulatory authorities for compliance with cGMP regulations and standards.

In addition, any marketing approvals that we may receive for our product candidates may contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, and may include burdensome post-approval study or risk management requirements. For example, the FDA may require a REMS in order to approve our product candidates, which could entail requirements for a medication guide, physician training and communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on manufacturing such products;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or holds on clinical trials;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure or detention; or
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate. We also 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. For example, the results of the 2020 U.S. Presidential Election may impact our business and industry. Namely, the Trump administration took several executive actions, including the issuance of a number of Executive

Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict whether or how these orders will be implemented, or whether they will be rescinded and replaced under the Biden administration. The policies and priorities of the new administration are unknown and could materially impact the regulations governing our product candidates. 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 be subject to enforcement action and we may not achieve or sustain profitability.

The FDA and other regulatory authorities actively enforce the laws and regulations prohibiting the promotion of off-label uses.

If any of our product candidates are approved and we are found to have improperly promoted off-label uses of those products, we may become subject to significant liability. The FDA and other regulatory authorities strictly regulate the promotional claims that may be made about prescription products, such as our product candidates, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for a product candidate, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The U.S. federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

Potential product liability lawsuits against us could cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

The use of our product candidates, including HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. On occasion, large judgments have been awarded in class action lawsuits based on products that had unanticipated adverse effects. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation and significant negative media attention;
- withdrawal of participants from our clinical trials;
- significant costs to defend the related litigation and related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- inability to commercialize HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- decreased demand for HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, if approved for commercial sale; and
- loss of revenue.

Our insurance policies are expensive and protect us only from some business risks, which leaves us exposed to significant uninsured liabilities.

We do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include general liability, employment practices liability, property, auto, workers' compensation, umbrella, and directors' and officers' insurance.

Any additional product liability insurance coverage we acquire in the future, may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If we obtain marketing approval for HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, we intend to acquire insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. A successful product liability claim or series of claims brought against us could cause our share price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business, including preventing or limiting the commercialization of any product candidates we develop. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

We also expect that operating as a public company will continue to make it more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified people to serve on our board of directors, our board committees or as executive officers. We do not know if we will be able to maintain existing insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which would adversely affect our cash position and results of operations.

Our employees and independent contractors, including principal investigators, CROs, consultants, vendors, and any third parties we may engage in connection with development and commercialization may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

Misconduct by our employees and independent contractors, including principal investigators, CROs, consultants, vendors, and any third parties we may engage in connection with development and commercialization, could include intentional, reckless or negligent conduct or unauthorized activities that violate: (i) the laws and regulations of the FDA, EMA rules and regulations and other similar regulatory requirements, including those laws that require the reporting of true, complete and accurate information to such authorities; (ii) manufacturing standards; (iii) data privacy, security, fraud and abuse and other healthcare laws and regulations; or (iv) laws that require the reporting of true, complete and accurate financial information and data. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, creation of fraudulent data in preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with such laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid, other U.S. federal healthcare programs or healthcare programs in other jurisdictions, individual imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations.

Our business and operations would suffer in the event of system failures.

Our computer systems, as well as those of our CROs and other contractors and consultants, are vulnerable to damage from computer viruses, unauthorized access, natural disasters (including hurricanes), terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product candidate development programs. For example, the loss of preclinical or clinical trial data from completed, ongoing or planned trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability and the further development of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate could be delayed.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, clinical trial data, proprietary business information, personal data and personally identifiable information of our clinical trial subjects and employees, in our data centers and on our networks. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or internal bad actors, or breached due to employee error, a technical vulnerability, malfeasance or other disruptions. Attacks upon information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. As a result of the COVID-19 pandemic, we may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Although, to our knowledge, we have not experienced any such material security breach to date, any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, significant regulatory penalties, and such an event could disrupt our operations, damage our reputation, and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and delay our clinical development of our product candidates.

Initial, "top-line" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we publicly disclose initial, top-line or preliminary data from our clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the initial, top-line or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Initial, top-line or preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the initial, top-line or preliminary data we previously published. As a result, initial, top-line and preliminary data should be viewed with caution until the final data are available.

From time to time, we also disclose data from our preclinical studies and clinical trials. Initial or preliminary data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between initial or preliminary data and final data could significantly harm our business prospects. Further, disclosure of initial or preliminary data by us or by our competitors could result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure.

If the top-line or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to timely capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Risks Related to Healthcare Laws and Other Legal Compliance Matters

Enacted and future healthcare legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and may affect the prices we may set.

In the United States, the EU and other jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes and proposed changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, was enacted, which substantially changed the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA, those of greatest importance to the pharmaceutical and biotechnology industries include the following:

- an annual, non-deductible fee payable by any entity that manufactures or imports certain branded prescription drugs and biologic agents (other than those designated as orphan drugs), which is apportioned among these entities according to their market share in certain government healthcare programs;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- 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;
- extension of a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- establishment of a Center for Medicare Innovation at the Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been judicial, executive, and Congressional challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, on December 14, 2018, a U.S. District Court Judge in the Northern District of Texas ruled that the entire ACA is invalid based primarily on the fact that the Tax Cuts and Jobs Act of 2017 repealed the tax-based shared responsibility payment imposed by the ACA, on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate." On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the district court's decision that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court is currently reviewing the case, although it is unclear how the Supreme Court will rule. It is also unclear how other efforts, if any, to challenge, repeal or replace the ACA will affect or our business or financial condition.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2021, unless additional action is taken by Congress. In January 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. These new laws or any other similar laws introduced in the future may result in additional reductions in Medicare and other healthcare funding, which could negatively affect our customers and accordingly, our financial operations.

Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, CMS may develop new payment and delivery models, such as bundled payment models. In addition, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. We expect that additional U.S. federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. federal government will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Legally-mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates or put pressure on our product pricing.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. The delivery of healthcare in the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of healthcare and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize our product candidates, if approved.

In markets outside of the United States and EU, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States, the EU or any other jurisdiction. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our product candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

Our business operations and current and future relationships with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers will be subject to applicable healthcare regulatory laws, which could expose us to penalties.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers, may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute our product candidates, if approved. Such laws include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or providing any remuneration (including any kickback, bribe, or certain rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under U.S. federal and state healthcare programs such as Medicare and Medicaid. 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;
- the U.S. federal false claims and civil monetary penalties laws, including the civil False Claims Act, which, among other things, impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the U.S. federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a

false record or statement material to a false or fraudulent claim, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

- HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services; similar to the U.S. federal Anti-Kickback Statute, 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;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and regulations implemented thereunder, which also impose certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without appropriate authorization by covered entities subject to the rule, such as health plans, healthcare clearinghouses and healthcare providers as well as their business associates that perform certain services involving the use or disclosure of individually identifiable health information;
- the FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;
- the U.S. Public Health Service Act, which prohibits, among other things, the introduction into interstate commerce of a biological product unless a biologics license is in effect for that product;
- the U.S. federal legislation commonly referred to as the Physician Payments Sunshine Act, enacted as part of the ACA, and its implementing regulations, which requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report annually to the government information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain healthcare professionals beginning in 2022, and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;
- analogous U.S. state laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. For example, California recently enacted legislation, the CCPA, which went into effect January 1, 2020. The CCPA, among other things, creates new data privacy obligations for covered companies and provides new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also creates a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. Although the law includes limited exceptions, including for "protected health information" maintained by a covered entity or business associate, it may regulate or impact our processing of personal information depending on the context. Further, the CPRA was also recently voted into law by California residents. The CPRA significantly amends the CCPA and imposes additional data protection obligations on covered companies doing business in California, including additional consumer rights processes and opt outs for certain uses of sensitive data. It also creates a new California data protection agency specifically tasked to enforce the law, which would likely result in increased regulatory scrutiny of California businesses in the areas of data protection and security. The substantive requirements for businesses subject to the CPRA will go into effect on January 1, 2023, and become enforceable on July 1, 2023;
- similar healthcare laws and regulations in the EU and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers. For instance, in the EU, interactions between pharmaceutical companies and healthcare professionals and healthcare organizations, are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct both at EU level and Member States level. The provision of benefits or advantages to physicians to induce or encourage

the prescription, recommendation, endorsement, purchase, supply, order or use of pharmaceutical products is prohibited in the EU. Relationships with healthcare professionals and associations are subject to stringent anti-gift statutes and anti-bribery laws, the scope of which differs across the EU. In addition, national "Sunshine Acts" may require pharmaceutical companies to report/publish transfers of value provided to healthcare professionals and associations on a regular (e.g. annual) basis; and

- similar laws governing the privacy and security of certain protected information, in the EU and other jurisdictions including the General Data Protection Regulation, or GDPR, which imposes obligations and restrictions on the collection and use of personal data relating to individuals located in the European Economic Area (including health data). Further, the United Kingdom's decision to leave the EU has created uncertainty with regard to the status of the UK as an "adequate country" for the purposes of data transfers outside the EEA. From January 1, 2021, companies have to comply with the GDPR and also the United Kingdom GDPR, or UK GDPR, which, together with the amended UK Data Protection Act 2018, retains the GDPR in UK national law. The UK GDPR mirrors the fines under the GDPR, e.g. fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. The relationship between the United Kingdom and the EU in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data protection laws and regulations will develop in the medium to longer term, and how data transfers to and from the United Kingdom will be regulated in the long term. Currently there is a four to six-month grace period agreed in the EU and United Kingdom Trade and Cooperation Agreement, ending June 30, 2021 at the latest, whilst the parties discuss an adequacy decision. However, it is not clear whether (and when) an adequacy decision may be granted by the European Commission enabling data transfers from EU member states to the United Kingdom long term without additional measures. These changes may lead to additional costs and increase our overall risk exposure.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid or similar programs in other countries or jurisdictions, disgorgement, individual imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment, which could affect our ability to operate our business. Further, defending against any such actions can be costly, time-consuming and may require significant personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

We are subject to environmental, health and safety laws and regulations, and we may become exposed to liability and substantial expenses in connection with environmental compliance or remediation activities.

Our operations, including our development, testing and manufacturing activities, are subject to numerous environmental, health and safety laws and regulations. These laws and regulations govern, among other things, the controlled use, handling, release and disposal of and the maintenance of a registry for, hazardous materials and biological materials, such as chemical solvents, human cells, carcinogenic compounds, mutagenic compounds and compounds that have a toxic effect on reproduction, laboratory procedures and exposure to blood-borne pathogens. If we fail to comply with such laws and regulations, we could be subject to fines or other sanctions.

As with other companies engaged in activities similar to ours, we face a risk of environmental liability inherent in our current and historical activities, including liability relating to releases of or exposure to hazardous or biological materials. Environmental, health and safety laws and regulations are becoming more stringent. We may be required to incur substantial expenses in connection with future environmental compliance or remediation activities, in which case, the production efforts of our third-party manufacturers or our development efforts may be interrupted or delayed.

Risks Related to Commercialization

We face significant competition in an environment of rapid technological change, and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer or more advanced or effective than ours, which may harm our financial condition and our ability to successfully market or commercialize any product candidates we may develop.

The development and commercialization of new genetic medicine products is highly competitive. Moreover, the gene editing field is characterized by rapidly changing technologies, significant competition, and a strong emphasis on intellectual property. We will face competition with respect to any product candidates that we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies, and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization.

There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we have research programs, including PKU, MLD, Hunter syndrome, hemoglobinopathies and ophthalmological diseases. Some of these competitive products and therapies are based on scientific approaches that are similar to our approach, and others are based on entirely different approaches.

Our platform and product focus is the development of genetic medicines using our proprietary AAVHSCs *in vivo* either through the gene therapy or nuclease-free gene editing modality. If our current programs are approved for the indications for which we are currently planning clinical trials, they may compete with other products currently under development, including gene editing and gene therapy products or other types of therapies, such as small molecule, antibody or protein therapies. If our PKU treatments are approved, they may compete with therapies from American Gene Technologies, BioMarin, Censa Pharmaceuticals, Generation Bio, Nestlé Health Science, Sangamo Therapeutics and Synlogic. However, we believe that only gene therapy or gene editing approaches have the potential to restore the normal Phe biochemical pathway with a single administration. If our Hunter syndrome treatment is approved, it may compete with therapies from Shire and/or GC Pharma. If our MLD treatment is approved, it may compete with therapies from Orchard Therapeutics and/or Shire. *In vivo* gene therapy approaches provide potential advantages over *ex vivo* approaches. There are a number of companies developing nuclease-based gene editing technologies using CRISPR/Cas9, TALENs, meganucleases, Mega-TALs and ZFNs, including but not limited to Beam Therapeutics, bluebird bio, Caribou Biosciences, Cellectis, CRISPR Therapeutics, Editas Medicine, Intellia Therapeutics, Precision BioSciences, Prime Therapeutics and Sangamo Therapeutics and non-nuclease-based technology, including LogicBio Therapeutics.

Many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop or that would render any products that we may develop obsolete or non-competitive. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomic or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

The successful commercialization of our product candidates will depend in part on the extent to which governmental authorities and health insurers establish adequate coverage, reimbursement levels and pricing policies. Failure to obtain or maintain coverage and adequate reimbursement for our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

The availability and adequacy of coverage and reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford prescription medications such as our product candidates, assuming FDA approval. Our ability to achieve acceptable levels of coverage and reimbursement for products by governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize our product candidates. Assuming we obtain coverage for our product candidates by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. Moreover, for drugs and biologics administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such products. We cannot be sure that coverage and reimbursement in the United States, the EU or elsewhere will be available for our product candidates or any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services, and many third-party payors may refuse to provide coverage and reimbursement for particular drugs or biologics when an equivalent generic drug, biosimilar or a less expensive therapy is available. It is possible that a third-party payor may consider our product candidates as substitutable and only offer to reimburse patients for the less expensive product. Even if we show improved efficacy or improved convenience of administration with our product candidates, pricing of existing third-party therapeutics may limit the amount we will be able to charge for our product candidates. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in our product candidates. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates, and may not be able to obtain a satisfactory financial return on our product candidates.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, third-party payors, including private and governmental payors, such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered. The Medicare and Medicaid programs increasingly are used as models in the United States for how private payors and other governmental payors develop their coverage and reimbursement policies for drugs and biologics. Some third-party payors may require pre-approval of coverage for new or innovative devices or drug therapies before they will reimburse healthcare providers who use such therapies. We cannot predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

No uniform policy for coverage and reimbursement for products exists among third-party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases on short notice, and we believe that changes in these rules and regulations are likely.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe and other countries have and will continue to put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medical products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our product candidates may be reduced compared with the United States and may be insufficient to generate commercially-reasonable revenue and profits.

Even if a pharmaceutical product obtains a marketing authorization in the EU, there can be no assurance that reimbursement for such product will be secured on a timely basis or at all. Governments influence the price of medicinal products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Member states are free to restrict the range of pharmaceutical products for which their national health insurance systems provide reimbursement, and to control the prices and reimbursement levels of pharmaceutical

products for human use. 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. Member states may approve a specific price or level of reimbursement for the pharmaceutical product, or alternatively adopt a system of direct or indirect controls on the profitability of the company responsible for placing the pharmaceutical product on the market, including volume-based arrangements, caps and reference pricing mechanisms. 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 healthcare costs in general, particularly prescription medicines, 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 a commercial pressure on pricing within a country.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and biologics and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products.

Even if HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate receives marketing approval, it may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success.

If HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If it does not achieve an adequate level of acceptance, we may not generate significant product revenues or become profitable. The degree of market acceptance of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, if approved for commercial sale, will depend on a number of factors, including but not limited to:

- the safety, efficacy and potential advantages compared to alternative treatments;
- effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement;
- product labeling or product insert requirements of the FDA, EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our product together with other medications.

Because we expect sales of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, if approved, to generate substantially all of our product revenues for a substantial period, the failure of this product to find market acceptance would harm our business and could require us to seek additional financing.

If we are unable to establish sales, marketing and distribution capabilities either on our own or in collaboration with third parties, we may not be successful in commercializing HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, if approved. Moreover, provisions in our agreements with Pfizer may inhibit our ability to enter into future collaborations with third parties.

We do not have any infrastructure for the sales, marketing or distribution of our products, and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so.

We expect to build a focused sales, distribution and marketing infrastructure to market HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate in the United States and EU, if approved. There are significant expenses and risks involved with establishing our own sales, marketing and distribution capabilities, including our ability to hire, retain and appropriately incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities could delay any product launch, which would adversely impact the commercialization of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate. Additionally, if the commercial launch of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

We do not anticipate having the resources in the foreseeable future to allocate to the sales and marketing of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidates in certain markets overseas. Therefore, our future sales in these markets will largely depend on our ability to enter into and maintain collaborative relationships for such capabilities, the collaborator's strategic interest in the product and such collaborator's ability to successfully market and sell the product. We intend to pursue collaborative arrangements regarding the sale and marketing of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, if approved, for certain markets overseas; however, we cannot assure that we will be able to establish or maintain such collaborative arrangements, or if able to do so, that they will have effective sales forces.

If we are unable to build our own sales force or negotiate a collaborative relationship for the commercialization of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, we may be forced to delay the potential commercialization of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate or reduce the scope of our sales or marketing activities for HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate. If we elect to increase our expenditures to fund commercialization activities ourselves, we will need to obtain additional capital, which may not be available to us on acceptable terms, or at all. We could enter into arrangements with collaborative partners at an earlier stage than otherwise would be ideal and we may be required to relinquish rights to HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate or otherwise agree to terms unfavorable to us, any of which may have an adverse effect on our business, operating results and prospects.

Moreover, we have granted Pfizer a right of first refusal to acquire rights (whether through license, asset sale or otherwise) to develop or commercialize HMI-102 and/or HMI-103. This right of first refusal provision may inhibit our ability to enter into future collaborations with third parties.

If we are unable to establish adequate sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate, and may not become profitable and may incur significant additional losses. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If we obtain approval to commercialize any products outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

If HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate is approved for commercialization, we intend to enter into agreements with third parties to market it in certain jurisdictions outside the United States. We expect that we will be subject to additional risks related to international pharmaceutical operations, including:

- different regulatory requirements for drug and biologic approvals and rules governing drug and biologic commercialization and country-specific regulations of gene therapies in foreign countries;
- complex and restrictive import/export regulations;
- reduced protection for intellectual property rights;
- foreign reimbursement, pricing and insurance regimes;
- potential noncompliance with the U.S. Foreign Corrupt Practices Act, the U.K. Bribery Act 2010 and similar anti-bribery and anticorruption laws in other jurisdictions; and
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad.

We have no prior experience in these areas. In addition, there are complex regulatory, tax, labor and other legal requirements imposed by both the EU and many of the EU member states with which we will need to comply. Many U.S.-based biotechnology companies have found the process of marketing their own products in Europe to be very challenging.

Any product candidates for which we intend to seek approval as biologic products may face competition sooner than anticipated.

The Patient Protection and Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our biological products.

There is a risk that any of our product candidates approved as a biological product under a BLA would not qualify for the 12-year period of exclusivity or that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

Risks Related to Our Dependence on Third Parties

We currently contract with third parties for the manufacture of certain materials for our research programs, preclinical and clinical studies. This reliance on third parties increases the risk that we will not have sufficient quantities of such materials, product candidates, or any medicines that we may develop and commercialize, or that such supply will not be available to us at an acceptable cost or in compliance with regulatory requirements, which could delay, prevent, or impair our development or commercialization efforts.

We currently rely on third-party manufacturers for the manufacture of certain materials for research programs, preclinical and clinical studies. We do not have long-term supply agreements with all of the third-party manufacturers, and we purchase our required supply on a purchase order basis. We recently completed the build-out of a GMP manufacturing facility to support our clinical development programs in both gene therapy and gene editing and commenced manufacturing activities in 2019. However, if we experience delays or are unable to scale our internal manufacturing capabilities, we will need to contract with manufacturers that can produce the clinical and commercial supply of our product candidates.

We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the possible breach of the manufacturing agreement by the third party;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us; and
- reliance on the third party for regulatory compliance, quality assurance, safety, and pharmacovigilance and related reporting.

Third-party manufacturers may not be able to comply with GMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocations, seizures or recalls of product candidates or medicines, operating restrictions, and criminal prosecutions,

any of which could significantly and adversely affect supplies of our medicines and harm our business, financial condition, results of operations, and prospects. Moreover, as a result of the COVID-19 pandemic, third-party manufacturers may be affected, which could disrupt their activities and as a result we could face difficulty sourcing key components necessary to produce supply of our product candidates, which may negatively affect our preclinical and clinical development activities.

Any medicines that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under GMP regulations and that might be capable of manufacturing for us. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval.

Our current and anticipated future dependence upon others for the manufacture of any product candidates we may develop or medicines may adversely affect our future profit margins and our ability to commercialize any medicines that receive marketing approval on a timely and competitive basis.

We intend to continue to rely on third parties to conduct, supervise and monitor our clinical trials. If those third parties do not successfully carry out their contractual duties, or if they perform in an unsatisfactory manner, it may harm our business.

We intend to continue to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials, and we expect to have limited influence over their actual performance.

We intend to continue to rely upon CROs to monitor and manage data for our clinical programs, as well as the execution of future nonclinical studies. Our reliance on CROs for clinical development activities limits our control over these activities, but we will remain responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs will be required to comply with GLP and GCP, which are regulations and guidelines enforced by the FDA and are also required by the competent authorities of the EU member states of the European Economic Area and comparable foreign regulatory authorities in the form of International Conference on Harmonization guidelines for any of our product candidates that are in preclinical and clinical development. The Regulatory authorities enforce GCP through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with GCP, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements. In addition, our clinical trials must be conducted with product produced under GMP regulations. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of subjects, we may be required to repeat clinical trials, which would delay the regulatory approval process.

Our CROs will not be our employees, and we will not control whether or not they devote sufficient time and resources to our future clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials, or other product development activities which could harm our competitive position. We face the risk of potential unauthorized disclosure or misappropriation of our intellectual property by CROs, which may reduce our trade secret protection and allow our potential competitors to access and exploit our proprietary technology. If our CROs do not successfully carry out their contractual duties or obligations or fail to meet expected deadlines, including as a result of the impact of the COVID-19 pandemic, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize any product candidate that we develop. As a result, our financial results and the commercial prospects for any product candidate that we develop would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

If our relationship with any CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves substantial cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we intend to carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have an adverse impact on our business, financial condition and prospects.

We may collaborate with third parties for the development and commercialization of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate. We may not succeed in establishing and maintaining collaborative relationships, which may significantly limit our ability to develop and commercialize HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate successfully, if at all.

We may seek collaborative relationships for the development and commercialization of HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate. Failure to obtain a collaborative relationship for HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate may significantly impair the potential for the product candidate. We also will need to enter into collaborative relationships to provide funding to support our other research and development programs. The process of establishing and maintaining collaborative relationships is difficult, time-consuming and involves significant uncertainty, such as:

- a collaboration partner may shift its priorities and resources away from our product candidates due to a change in business strategies, or a merger, acquisition, sale or downsizing;
- a collaboration partner may seek to renegotiate or terminate their relationships with us due to unsatisfactory clinical results, manufacturing issues, a change in business strategy, a change of control or other reasons;
- a collaboration partner may cease development in therapeutic areas which are the subject of our strategic collaboration;
- a collaboration partner may not devote sufficient capital or resources towards our product candidates;
- a collaboration partner may change the success criteria for a product candidate thereby delaying or ceasing development of such candidate;
- a significant delay in initiation of certain development activities by a collaboration partner will also delay payment of milestones tied to such activities, thereby impacting our ability to fund our own activities;
- a collaboration partner could develop a product that competes, either directly or indirectly, with our product candidate;
- a collaboration partner with commercialization obligations may not commit sufficient financial or human resources to the marketing, distribution or sale of a product;
- a collaboration partner with manufacturing responsibilities may encounter regulatory, resource or quality issues and be unable to meet demand requirements;
- a collaboration partner may terminate a strategic alliance;
- a dispute may arise between us and a partner concerning the research, development or commercialization of a product candidate resulting in a delay in milestones, royalty payments or termination of an alliance and possibly resulting in costly litigation or arbitration which may divert management attention and resources; and
- a partner may use our products or technology in such a way as to invite litigation from a third party.

If any collaborator fails to fulfill its responsibilities in a timely manner, or at all, our research, clinical development, manufacturing or commercialization efforts related to that collaboration could be delayed or terminated, or it may be necessary for us to assume responsibility for expenses or activities that would otherwise have been the responsibility of our collaborator. If we are unable to establish and maintain collaborative relationships on acceptable terms or to successfully transition terminated collaborative agreements, we may have to delay or discontinue further development of one or more of our product candidates, undertake development and commercialization activities at our own expense or find alternative sources of capital. Moreover, any collaborative partners we enter into agreements with in the future may shift their priorities and resources away from our product candidates or seek to renegotiate or terminate their relationships with us. For example, in February 2021, we received written notice from Novartis that Novartis elected to terminate our collaboration agreement with Novartis with respect to the only remaining ophthalmic target under the agreement. Accordingly, the notice served to terminate the agreement in its entirety. The termination of the collaboration agreement will be effective on August 26, 2021.

We do not have multiple sources of supply for all of the components used in HMI-102 and our other product candidates. If we were to lose a supplier, it could have a material adverse effect on our ability to complete the development of HMI-102. If we obtain regulatory approval for HMI-102, we would need to expand the supply of its components in order to commercialize them.

We do not have multiple sources of supply for all of the components used in the manufacturing of HMI-102. We also do not have long-term supply agreements with any of our component suppliers. We are currently evaluating manufacturers that will commercially manufacture HMI-102. It is our expectation that we will only qualify one initial supplier that will need to be approved by the FDA. If for any reason we are unable to obtain product from the manufacturer we select, we would have to qualify new manufacturers. We may not be able to establish additional sources of supply for our product candidates, or may be unable to do so on acceptable terms. Manufacturing suppliers are subject to GMP quality and regulatory requirements, covering manufacturing, testing, quality control and record keeping relating to our product candidates and subject to ongoing inspections by the regulatory agencies. Failure by any of our suppliers to comply with applicable regulations may result in long delays and interruptions in supply. Manufacturing suppliers are also subject to local, state and federal regulations and licensing requirements. Failure by any of our suppliers to comply with all applicable regulations and requirements may result in long delays and interruptions in supply.

The number of suppliers of the raw material components of our product candidates is limited. In the event it is necessary or desirable to acquire supplies from alternative suppliers, we might not be able to obtain them on commercially reasonable terms, if at all. It could also require significant time and expense to redesign our manufacturing processes to work with another company.

As part of any marketing approval, a manufacturer of HMI-102 is required to be licensed by the FDA prior to commercialization. This licensing process normally includes inspections by regulatory authorities that must be successful prior to them being licensed. Failure of manufacturing suppliers to successfully complete these regulatory inspections will result in delays. If supply from the approved supplier is interrupted, there could be a significant disruption in commercial supply. An alternative vendor would need to be qualified through a BLA amendment or supplement which could result in further delay. The FDA or other regulatory agencies outside of the United States may also require additional studies if a new supplier is relied upon for commercial production. Switching vendors may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

If we are unable to obtain the supplies we need at a reasonable price or on a timely basis, it could have a material adverse effect on our ability to complete the development of HMI-102 and our other product candidates or, if we obtain regulatory approval for HMI-102 or our other product candidates, to commercialize them.

If we fail to comply with our obligations in the agreements under which we in-license or acquire development or commercialization rights to products, technology or data from third parties, including those for HMI-102, we could lose such rights that are important to our business.

We are a party to agreements with Caltech for certain AAV vector-related patents owned by Caltech for human therapeutic applications, or the Caltech License, and COH for certain AAV vector-related patents and know-how, and we may enter into additional agreements, including license agreements, with other parties in the future that impose diligence, development and commercialization timelines, milestone payments, royalties, insurance and other obligations on us.

For example, in exchange for the rights granted to us under the Caltech License, we are obligated to pay Caltech up to a total of $7.2 million in milestone payments for the first licensed product, royalties, in the low single-digit percentages, on net sales of licensed products subject to a certain annual minimum royalty, and mid-single- to high single-digit percentages of sublicensing revenues. If we fail to comply with our obligations under the Caltech License, or any of our other collaborators, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product candidate that is covered by these agreements, which could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our proprietary technologies, product candidate development programs and product candidates. Our success depends in large part on our ability to secure and maintain patent protection in the United States and other countries with respect to HMI-102, HMI-103, HMI-202, HMI-203 and any future product candidates. We seek to protect our proprietary position by filing or collaborating with our licensors to file patent applications in the United States and abroad related to our proprietary technologies, development programs and product candidates. The patent prosecution process is expensive and time-consuming, and we may not be able to 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 our research and development output before it is too late to obtain patent protection. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our proprietary products and technology, including HMI-102, HMI-103, HMI-202, HMI-203 or any other product candidate in the United States or in other foreign countries, in whole or in part. Alternately, our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technology or from developing competing products and technologies. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which can prevent a patent from issuing from a pending patent application or later invalidate or narrow the scope of an issued patent. Even if patents do successfully issue and even if such patents cover HMI-102, HMI-103, HMI-202, HMI-203 or any future product candidate, third parties may challenge their validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated, or held unenforceable. Any successful challenge to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates or companion diagnostic that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate and companion diagnostic under patent protection could be reduced.

If the patent applications we hold or have in-licensed with respect to our development programs and product candidates fail to issue, if their validity, breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for HMI-102, HMI-103, HMI-202, HMI-203 or any future product candidate, it could dissuade companies from collaborating with us to develop product candidates, encourage competitors to develop competing products or technologies and threaten our ability to commercialize future product candidates. Any such outcome could have a materially adverse effect on our business.

The patent position of biotechnology and pharmaceutical companies is highly uncertain, involves complex legal and factual questions, and is characterized by the existence of large numbers of patents and frequent litigation based on allegations of patent or other intellectual property infringement or violation. In addition, the laws of jurisdictions outside the United States may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. Since patent applications in the United States and other jurisdictions are confidential for a period of time after filing, we cannot be certain that we were the first to file for patents covering our inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in the issuance of patents, or may result in the issuance of patents which fail to protect our technology or products, in whole or in part, or which fail to effectively prevent others from commercializing competitive technologies and products.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Thus, even if our patent applications issue as patents, they may not issue in a form that will provide us with meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Moreover, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Without patent protection for our current or future product candidates, we may be open to competition from generic versions of such products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Third parties may assert claims against us alleging infringement of their patents and proprietary rights, or we may need to become involved in lawsuits to defend or enforce our patents, either of which could result in substantial costs or loss of productivity, delay or prevent the development and commercialization of our product candidates, prohibit our use of proprietary technology or sale of products or put our patents and other proprietary rights at risk.

Our commercial success depends, in part, upon our ability to develop, manufacture, market and sell our product candidates without alleged or actual infringement, misappropriation or other violation of the patents and proprietary rights of third parties. Litigation relating to infringement or misappropriation of patent and other intellectual property rights in the pharmaceutical and biotechnology industries is common, including patent infringement lawsuits, interferences, oppositions and reexamination proceedings before the U.S. Patent and Trademark Office, or USPTO, and corresponding foreign patent offices. The various markets in which we plan to operate are subject to frequent and extensive litigation regarding patents and other intellectual property rights. In addition, many companies in intellectual property-dependent industries, including the biotechnology and pharmaceutical industries, have employed intellectual property litigation as a means to gain an advantage over their competitors. Numerous United States, EU and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates, and as the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the intellectual property rights of third parties. Some claimants may have substantially greater resources than we do and may be able to sustain the costs of complex intellectual property litigation to a greater degree and for longer periods of time than we could. In addition, patent holding companies that focus solely on extracting royalties and settlements by enforcing patent rights may target us.

We may be subject to third-party claims including infringement, interference or derivation proceedings, post-grant review and inter partes review before the USPTO or similar adversarial proceedings or litigation in other jurisdictions. Even if such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, and the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our compositions, formulations, or methods of treatment, prevention or use, the holders of any such patents may be able to prohibit our use of those compositions, formulations, methods of treatment, prevention or use or other technologies, effectively blocking our ability to develop and commercialize the applicable product candidate until such patent expires or is finally determined to be invalid or unenforceable or unless we obtained a license.

In addition, defending such claims would cause us to incur substantial expenses and, if successful, could cause us to pay substantial damages if we are found to be infringing a third party's patent rights. These damages potentially include increased damages and attorneys' fees if we are found to have infringed such rights willfully. Further, if a patent infringement suit is brought against us or our third-party service providers, our development, manufacturing or sales activities relating to the product or product candidate that is the subject of the suit may be delayed or terminated. As a result of patent infringement claims, or in order to avoid potential infringement claims, we may choose to seek, or be required to seek, a license from the third party, which may require payment of substantial royalties or fees, or require us to grant a cross-license under our intellectual property rights. These licenses may not be available on reasonable terms or at all. Even if a license can be obtained on reasonable terms, the rights may be nonexclusive, which would give our competitors access to the same intellectual property rights. If we are unable to enter into a license on acceptable terms, we could be prevented from commercializing one or more of our product candidates, or forced to modify such product candidates, or to cease some aspect of our business operations, which could harm our business significantly. We might also be forced to redesign or modify our product candidates so that we no longer infringe the third-party intellectual property rights, which may result in significant cost or delay to us, or which redesign or modification could be impossible or technically infeasible. Even if we were ultimately to prevail, any of these events could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business. In addition, if the breadth or strength of protection provided the patents and patent applications we own or in-license is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

If we or one of our licensors were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the United States and in Europe, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Third parties might allege unenforceability of our patents because during prosecution of the patent an individual connected with such prosecution withheld relevant information, or made a misleading statement. The outcome of proceedings involving assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity of patents, for example, we cannot be certain that there is no invalidating prior art of which we and the

patent examiner were unaware during prosecution, but that an adverse third party may identify and submit in support of such assertions of invalidity. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Our patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without infringing our patents or other intellectual property rights.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, 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. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors view these announcements in a negative light, the price of our common stock could be adversely affected. Such litigation or proceedings could substantially increase our operating losses and reduce our resources available for development activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have an adverse effect on our ability to compete in the marketplace.

We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third-party patent which might adversely affect our ability to develop, manufacture and market our product candidates.

We cannot guarantee that any of our or our licensors' patent searches or analyses, including but not limited to the identification of relevant patents, analysis of the scope of relevant patent claims or determination of the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States, Europe and elsewhere that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. For example, in the United States, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States, EU and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our product candidates could be filed by others without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or the use of our product candidates. After issuance, the scope of patent claims remains subject to construction as determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidates. We may incorrectly determine that our product candidates are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States, the EU or elsewhere that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our product candidates. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates.

If we fail to correctly identify or interpret relevant patents, we may be subject to infringement claims. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay monetary damages, we may be temporarily or permanently prohibited from commercializing our product candidates. We might, if possible, also be forced to redesign our product candidates in a manner that no longer infringes third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

Changes in patent laws or patent jurisprudence could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology and genetic medicines industries involve both technological complexity and legal complexity. Therefore, obtaining and enforcing biotechnology and genetic medicines patents is costly, time-consuming and inherently uncertain. In addition, the America Invents Act, or the AIA, which was passed in September 2011, resulted in significant changes to the U.S. patent system.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned from a "first-to-invent" to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. Under a "first-to-file" system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on the invention

regardless of whether another inventor had made the invention earlier. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application and diligent in filing patent applications, but circumstances could prevent us from promptly filing patent applications on our inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action.

Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. It is not clear what, if any, impact the AIA will have on the operation of our business. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors' patent applications and the enforcement or defense of our or our licensors' issued patents.

We may become involved in opposition, interference, derivation, inter partes review or other proceedings challenging our or our licensors' patent rights, and the outcome of any proceedings are highly uncertain. An adverse determination in any such proceeding could reduce the scope of, or invalidate, our owned or in-licensed patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Additionally, 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, and there are other open questions under patent law that courts have yet to decisively address. 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 Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways and could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. In addition, the European patent system is relatively stringent in the type of amendments that are allowed during prosecution, but, the complexity and uncertainty of European patent laws has also increased in recent years. Complying with these laws and regulations could limit our ability to obtain new patents in the future that may be important for our business.

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.

The USPTO and European and other patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO and European and other patent agencies over the lifetime of a patent. While an inadvertent failure to make payment of such fees or to comply with such provisions can in many cases be cured by additional payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance with such provisions will result in the abandonment or lapse of the patent or patent application, and the 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 within prescribed time limits. If we or our licensors fail to maintain the patents and patent applications covering our product candidates or if we or our licensors otherwise allow our patents or patent applications to be abandoned or lapse, it can create opportunities for competitors to enter the market, which would hurt our competitive position and could impair our ability to successfully commercialize our product candidates in any indication for which they are approved.

We enjoy only limited geographical protection with respect to certain patents and we may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents covering our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive

than those in the United States. In-licensing patents covering our product candidates in all countries throughout the world may similarly be prohibitively expensive, if such opportunities are available at all. And in-licensing or filing, prosecuting and defending patents even in only those jurisdictions in which we develop or commercialize our product candidates may be prohibitively expensive or impractical. Competitors may use our and our licensors' technologies in jurisdictions where we have not obtained patent protection or licensed patents to develop their own products and, further, may export otherwise infringing products to territories where we and our licensors have patent protection, but enforcement is not as strong as that in the United States or the EU. These products may compete with our product candidates, and our or our licensors' patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

In addition, we may decide to abandon national and regional patent applications while they are still pending. The grant proceeding of each national or regional patent is an independent proceeding which may lead to situations in which applications may be rejected by the relevant patent office, while substantively similar applications are granted by others. For example, relative to other countries, China has a heightened requirement for patentability and specifically requires a detailed description of medical uses of a claimed drug. Furthermore, generic drug manufacturers or other competitors may challenge the scope, validity or enforceability of our or our licensors' patents, requiring us or our licensors to engage in complex, lengthy and costly litigation or other proceedings. Generic drug manufacturers may develop, seek approval for and launch generic versions of our products. It is also quite common that depending on the country, the scope of patent protection may vary for the same product candidate or technology.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws or regulations in the United States and the EU, and many companies have encountered significant difficulties in protecting and defending proprietary rights in such jurisdictions. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets or other forms of intellectual property, which could make it difficult for us to prevent competitors in some jurisdictions from marketing competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, are likely to result in substantial costs and divert our efforts and attention from other aspects of our business, and additionally could put at risk our or our licensors' patents of being invalidated or interpreted narrowly, could increase the risk of our or our licensors' patent applications not issuing, or could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, while damages or other remedies may be awarded to the adverse party, which may be commercially significant. If we prevail, damages or other remedies awarded to us, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate, which may have an adverse effect on our ability to successfully commercialize our product candidates in all of our expected significant foreign markets. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished and we may face additional competition in those jurisdictions.

In some jurisdictions, compulsory licensing laws compel patent owners to grant licenses to third parties. In addition, some countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors are forced to grant a license to third parties under patents relevant to our business, or if we or our licensors are prevented from enforcing patent rights against third parties, our competitive position may be substantially impaired in such jurisdictions.

If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of marketing exclusivity for our product candidates, our business may be materially harmed.

The term of any individual patent depends on applicable law in the country where the patent is granted. In the United States, provided all maintenance fees are timely paid, a patent generally has a term of 20 years from its application filing date or earliest claimed non-provisional filing date. Extensions may be available under certain circumstances, but the life of a patent and, correspondingly, the protection it affords is limited. Even if we or our licensors obtain patents covering our product candidates, when the terms of all patents covering a product expire, our business may become subject to competition from competitive medications, including generic medications. Given the amount of time required for the development, testing and regulatory review and approval of new product candidates, patents protecting such candidates may expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

In the United States, a patent that covers an FDA-approved drug or biologic may be eligible for a term extension designed to restore the period of the patent term that is lost during the premarket regulatory review process conducted by the FDA. Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, which permits a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. In the EU, our product candidates may be eligible for term extensions based on similar legislation. In either jurisdiction, however, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Even if we are granted such extension, the duration of such extension may be less than our request. If we are unable to obtain a patent term extension, or if the term of any such extension is less than our request, the period during which we can enforce our patent rights for that product will be in effect shortened and our competitors may obtain approval to market competing products sooner. The resulting reduction of years of revenue from applicable products could be substantial.

Our proprietary rights may not adequately protect our technologies and product candidates, and do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- others may be able to make products that are the same as or similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed;
- others, including inventors or developers of our owned or in-licensed patented technologies who may become involved with competitors, may independently develop similar technologies that function as alternatives or replacements for any of our technologies without infringing our intellectual property rights;
- we or our licensors or our other collaboration partners might not have been the first to conceive and reduce to practice the inventions covered by the patents or patent applications that we own, license or will own or license;
- we or our licensors or our other collaboration partners might not have been the first to file patent applications covering certain of the patents or patent applications that we or they own or have obtained a license, or will own or will have obtained a license;
- we or our licensors may fail to meet obligations to the U.S. government with respect to in-licensed patents and patent applications funded by U.S. government grants, leading to the loss of patent rights;
- it is possible that our pending patent applications will not result in issued patents;
- it is possible that there are prior public disclosures that could invalidate our or our licensors' patents;
- issued patents that we own or exclusively license may not provide us with any competitive advantage, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights, or in countries where research and development safe harbor laws exist, and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- ownership, validity or enforceability of our or our licensors' patents or patent applications may be challenged by third parties; and
- the patents of third parties or pending or future applications of third parties, if issued, may have an adverse effect on our business.

We depend on proprietary technology licensed from others. If we lose our existing licenses or are unable to acquire or license additional proprietary rights from third parties, we may not be able to continue developing our products.

We currently in-license certain intellectual property from COH and Caltech. In the future we may in-license intellectual property from other licensors. We rely on certain of these licensors to file and prosecute patent applications and maintain patents and otherwise protect the intellectual property we license from them. We have limited control over these activities or any other intellectual property that may be related to our in-licensed intellectual property. For example, we cannot be certain that such activities by these licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents and other intellectual property rights. We have limited control over the manner in which

our licensors initiate an infringement proceeding against a third-party infringer of the intellectual property rights, or defend certain of the intellectual property that is licensed to us. It is possible that the licensors' infringement proceeding or defense activities may be less vigorous than had we conducted them ourselves. The licensing and acquisition of third-party intellectual property rights is a competitive practice, and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their larger size and cash resources or greater clinical development and commercialization capabilities. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire.

If we fail to comply with our obligations under our patent licenses with third parties, we could lose license rights that are important to our business.

We are a party to license agreements with COH and Caltech, pursuant to which we in-license patents and technology for our product candidates. These existing licenses impose various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations or otherwise materially breach a license agreement, our licensors may have the right to terminate the license, in which event we would not be able to develop or market the products covered by such licensed intellectual property. In addition, any claims asserted against us by our licensors may be costly and time-consuming, divert the attention of key personnel from business operations or otherwise have a material adverse effect on our business.

Our reliance on third parties may require us to share our trade secrets, which increases the possibility that our trade secrets will be misappropriated or disclosed, and confidentiality agreements with employees and third parties may not adequately prevent disclosure of trade secrets and protect other proprietary information.

We consider proprietary trade secrets, confidential know-how and unpatented know-how to be important to our business. We may rely on trade secrets and confidential know-how to protect our technology, especially where patent protection is believed by us to be of limited value. However, trade secrets and confidential know-how are difficult to protect, and we have limited control over the protection of trade secrets and confidential know-how used by our licensors, collaborators and suppliers. Because we expect to rely on third parties to manufacture HMI-102, HMI-103, HMI-202, HMI-203 and any future product candidates, and we expect to collaborate with third parties on the development of HMI-102, HMI-103, HMI-202, HMI-203 and any future product candidates, we may, at times, share trade secrets with them. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development collaborations or similar agreements. Under such circumstances, trade secrets and confidential know-how can be difficult to maintain as confidential.

To protect this type of information against disclosure or appropriation by competitors, our policy is to require our employees, consultants, contractors and advisors to enter into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with us prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. However, current or former employees, consultants, contractors and advisers may unintentionally or willfully disclose our confidential information to competitors, and confidentiality agreements may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. The need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our competitive position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have an adverse effect on our business and results of operations. Enforcing a claim that a third party obtained illegally and is using trade secrets and/or confidential know-how is expensive, time consuming and unpredictable, and the enforceability of confidentiality agreements may vary from jurisdiction to jurisdiction.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected. We currently own one registered trademark and four pending trademark applications in the United States, as well as 17 registered trademarks and five pending trademark applications in other countries around the world. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our unregistered trademarks or trade names. Over the long term, if we are unable to successfully register our trademarks and trade names and establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

We may need to license additional intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

The growth of our business may depend in part on our ability to acquire or in-license additional proprietary rights. For example, our programs may involve product candidates that may require the use of additional proprietary rights held by third parties. Our product candidates may also require specific formulations to work effectively and efficiently. These formulations may be covered by intellectual property rights held by others. We may develop products containing our compositions and pre-existing pharmaceutical compositions. These pharmaceutical products may be covered by intellectual property rights held by others. We may be required by the FDA or comparable foreign regulatory authorities to provide a companion diagnostic test or tests with our product candidates. These diagnostic test or tests may be covered by intellectual property rights held by others. We may be unable to acquire or in-license any relevant third-party intellectual property rights that we identify as necessary or important to our business operations. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which would harm our business. We may need to cease use of the compositions or methods covered by such third-party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe on such intellectual property rights which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license under such intellectual property rights, any such license may be non-exclusive, which may allow our competitors access to the same technologies licensed to us.

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

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. Although we seek to protect our ownership of intellectual property rights by ensuring that our agreements with our employees, collaborators and other third parties with whom we do business include provisions requiring such parties to assign rights in inventions to us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Even if we are successful, litigation could result in substantial cost and reputational loss and be a distraction to our management and other employees.

Risks Related to Employee Matters and Managing Growth and Other Risks Related to Our Business

The COVID-19 pandemic caused by the novel strain of coronavirus could adversely impact our business, including our preclinical studies and clinical trials.

In 2020, a strain of novel coronavirus disease, COVID-19, was declared a pandemic and spread across the world, including throughout the United States, Europe and Asia. The pandemic and government measures taken in response have also had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred, supply chains have been disrupted, and facilities and production have been suspended.

In response to the spread of COVID-19, most office-based employees continue to work from home, and we have limited the number of staff in our research and development laboratories and in our manufacturing facility to key personnel. For those employees on-site, we have developed shift schedules for our laboratories and manufacturing facility and a modified office layout and traffic flow pattern to increase spacing capabilities, reduce inter-office risks and allow for business continuity. We have increased cleaning protocols throughout our entire facility, limited visitors to only those who are critical to our ongoing operations and have cancelled all business travel. In addition, we have developed our own on-site COVID-19 surveillance testing for employees to help promote health and safety. Disruptions caused by the COVID-19 pandemic have resulted, and may continue to result, in delays in enrolling our Phase 1/2 pheNIX clinical trial. In addition, we could experience additional disruptions in conducting or completing the Phase 1/2 pheNIX trial or other planned preclinical and clinical trials and could incur unforeseen costs as a result of preclinical study or clinical trial delays. Many of our clinical sites are not currently accepting new patients for enrollment in clinical trials and have placed limitations on patients already enrolled in clinical trials from visiting the clinical sites for follow-up monitoring visits. While we have entered into arrangements with third parties to provide remote patient visits and monitoring, we may still experience delays with the pheNIX trial. All of our ongoing and planned preclinical studies at external CROs are progressing and we have accelerated shipments of reagents and supplies to avoid any disruption of activities. However, it is possible that the COVID-19 pandemic may have an impact in the future on our CROs' ability to complete critical studies required for the progression of these programs. Moreover, while we currently do not anticipate any interruptions in our manufacturing process, it is possible that the COVID-19 pandemic and response efforts may have an impact in the future on our and/or our third-party suppliers and CMOs' ability to manufacture our product candidates or materials needed for our preclinical studies and clinical trials. If the COVID-19 pandemic continues to spread in the United States and elsewhere, we may experience disruptions that could severely impact our business, preclinical studies and clinical trials, including:

- delays in receiving approval from local regulatory authorities to initiate our planned clinical trials;
- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including interruption in global shipping that may affect the transport of clinical trial materials;
- changes in local regulations as part of a response to the COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue the clinical trials altogether;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others, or interruption of clinical trial subject visits and study procedures, the occurrence of which could affect the integrity of clinical trial data;
- risk that participants enrolled in our clinical trials will acquire COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events;
- interruptions or delays in preclinical studies due to restricted or limited operations at our research and development laboratory facility;
- delays in necessary interactions with local regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government employees;
- limitations in employee resources that would otherwise be focused on the conduct of our clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people;
- refusal of the FDA to accept data from clinical trials in affected geographies; and
- impacts from prolonged remote work arrangements, such as increased cybersecurity risks and strains on our business continuity plans.

The COVID-19 pandemic continues to rapidly evolve. The extent to which the pandemic impacts our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted

with confidence, such as the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions, the effectiveness of vaccines and vaccine distribution efforts, the ultimate impact of COVID-19 on financial markets and the global economy, and the effectiveness of other actions taken in the United States and other countries to contain and treat the disease.

While the potential economic impact brought by and the duration of the COVID-19 pandemic may be difficult to assess or predict, the widespread pandemic has resulted in, and may continue to result in, significant disruption of global financial markets, which could reduce our ability to access capital and negatively affect our liquidity. In addition, the recession or market correction resulting from the spread of COVID-19 could materially affect our business.

Our future success depends on our ability to retain our key personnel and to attract, retain and motivate qualified personnel.

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the development, regulatory, commercialization and business development expertise of Arthur Tzianabos, Ph.D., our President and Chief Executive Officer, and Albert Seymour, Ph.D., our Chief Scientific Officer, as well as the other principal members of our management, scientific and clinical teams. Although we have formal employment agreements with our executive officers, these agreements do not prevent them from terminating their employment with us at any time.

If we lose one or more of our executive officers or key employees, our ability to implement our business strategy successfully could be seriously harmed. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize product candidates successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be engaged by entities other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to develop and commercialize product candidates will be limited.

We or the third parties upon whom we depend may be adversely affected by natural disasters, public health emergencies and other natural catastrophic events, and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Natural disasters could severely disrupt our operations and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, public health emergency, such as the COVID-19 pandemic, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our manufacturing facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business. For example, following Hurricane Maria, shortages in production and delays in a number of medical supplies produced in Puerto Rico resulted, and any similar interruption due to a natural disaster affecting us or any of our third-party manufacturers could materially delay our operations.

Risks Related to Our Common Stock

Our executive officers and directors and their respective affiliates, if they choose to act together, will continue to have the ability to control or significantly influence all matters submitted to stockholders for approval.

Our executive officers and directors and their respective affiliates, in the aggregate, hold shares representing approximately 20.9% of our outstanding voting stock as of December 31, 2020. As a result, if these stockholders choose to act together, they would be able to control or significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control or significantly influence the election of directors, the composition of our management and approval of any merger, consolidation or sale of all or substantially all of our assets.

A significant portion of our total outstanding shares are eligible, or will soon become eligible, to be sold into the market, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Based on filings with the SEC, as of November 6, 2020, holders of an aggregate of approximately 10.0 million shares of our common stock have rights, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders, until the rights terminate pursuant to the terms of the investors' rights agreement, as amended, between us and such holders. We have also registered all shares of common stock that we may issue under our equity compensation plans, which can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements, if applicable.

Additionally, on November 9, 2020, we entered into a stock purchase agreement with Pfizer, pursuant to which Pfizer purchased 5.0 million shares of our common stock through a private placement transaction. The shares of common stock sold in the Pfizer private placement are subject to a one-year lock-up from closing, during which time Pfizer is prohibited from selling or otherwise disposing of such shares. Pfizer also has rights, subject to specified conditions, to require us to file a Registration Statement on Form S-3 to register the shares of common stock sold in the Pfizer private placement. Once any such registration statement is declared effective, these shares can be freely sold on the public market.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company until the last day of the fiscal year following the fifth anniversary of the closing of the initial public offering of our common stock. However, if certain events occur prior to the end of such five-year period, including if we become a "large accelerated filer," our annual gross revenues exceed $1.07 billion or we issue more than $1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company prior to the end of such five-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We cannot predict whether investors will find our common stock less attractive if we rely on 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 reduced or more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have elected to take advantage of this extended transition period.

Provisions in our restated certificate of incorporation and amended and restated bylaws and under Delaware law could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our restated certificate of incorporation and our amended and restated bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions include those establishing:

- 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 filling 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 be used to significantly dilute the ownership of a hostile acquirer;
- the ability of our board of directors to alter our bylaws without obtaining stockholder approval;
- the required approval of the holders of at least two-thirds of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws or repeal the provisions of our 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.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Our certificate of incorporation designates the Court of Chancery of the State of Delaware, subject to certain exceptions, as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders and our bylaws designate the federal district courts of the United States as the exclusive forum for actions arising under the Securities Act of 1933, as amended, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our restated certificate of incorporation specifies that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions involving claims brought against us by stockholders. In addition, our bylaws provide that the federal district courts of the United States are the exclusive forum for any complaint raising a cause of action arising under the Securities Act of 1933, as amended. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our restated certificate of incorporation and bylaws described above. We believe these choice of forum provisions benefit us by providing increased consistency in the application of Delaware law by

chancellors particularly experienced in resolving corporate disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. However, the provision may have the effect of discouraging lawsuits against our directors, officers, employees and agents as it may limit any stockholder's ability to bring a claim in a judicial forum that such stockholder finds favorable for disputes with us or our directors, officers, employees or agents. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our restated certificate of incorporation or bylaws to be inapplicable or unenforceable in such action. If a court were to find the choice of forum provisions contained in our restated certificate of incorporation or bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition or results of operations.

Our ability to use net operating losses and research and development credits to offset future taxable income or income tax liabilities may be subject to certain limitations.

As of December 31, 2020, we had federal and state net operating loss carryforwards, or NOLs, of approximately $265.1 million and $271.5 million, respectively. Our state NOLs, and federal NOLs generated in taxable years beginning before January 1, 2018 are subject to expiration and will expire at various dates through 2040. As of December 31, 2020, we also had federal and state research and development and other tax credit carryforwards, or credits, including the orphan drug credit, of approximately $34.2 million and $7.2 million, respectively, available to reduce future income tax liabilities. The federal and state credits expire at various dates through 2040. These NOLs and credits could expire unused and be unavailable to offset future taxable income or income tax liabilities, to the extent subject to expiration. In addition, in general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change NOLs or credits to offset future taxable income or income tax liabilities. For these purposes, an ownership change generally occurs where the aggregate change in stock ownership of one or more stockholders or groups of stockholders owning at least 5% of a corporation's stock exceeds 50 percentage points over a three-year period. Our existing NOLs or credits may be subject to limitations arising from previous ownership changes, if any. In addition, future changes in our stock ownership, many of which are outside of our control, could result in an ownership change. Our NOLs or credits may also be impaired under state law. Accordingly, even if we attain profitability, we may not be able to utilize a material portion of our NOLs or credits. Furthermore, NOLs generated in periods beginning after December 31, 2017 may be carried forward indefinitely but may only be used to offset 80% of our taxable income in years beginning after December 31, 2020, which may require us to pay federal income taxes in future years despite generating federal NOLs in prior years.

Because we do not anticipate paying any cash dividends on our common shares in the foreseeable future, capital appreciation, if any, would be your sole source of gain.

We have never declared or paid any cash dividends on our common shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. As a result, capital appreciation, if any, of our common shares would be your sole source of gain on an investment in our common shares for the foreseeable future.

General Risk Factors

The market price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock.

Our stock price is likely to be volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your shares of common stock at or above the price at which you purchased them. The market price for our common stock may be influenced by many factors, including:

- the success of competitive products or technologies;
- actual or expected changes in our growth rate relative to our competitors;
- results of clinical trials of our product candidates or those of our competitors;
- developments related to our existing or any future collaborations;

- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- regulatory or legal developments in the United States and other countries;
- development of new product candidates that may address our markets and make our product candidates less attractive;
- changes in physician, hospital or healthcare provider practices that may make our product candidates less useful;
- announcements by us, our collaborators or our competitors of significant acquisitions, strategic collaborations, joint ventures or capital commitments;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- failure to meet or exceed financial estimates and projections of the investment community or that we provide to the public;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- actual or expected changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biopharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We have incurred and expect to continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, we have incurred and expect to continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and have made some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we have engaged in a process to document and evaluate our internal control over financial reporting, which has been both costly and challenging. We will need to continue to dedicate internal resources, engage outside consultants, adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing whether such controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could cause us to need to restate our previously issued financial statements and result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.

In the future, we may enter into transactions to acquire other businesses, products or technologies. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and nondisruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

We currently occupy approximately 67,000 square feet of office, research and development laboratory and manufacturing space in Bedford, Massachusetts, under a lease that expires in 2027. We are subletting approximately 23,000 square feet of office and laboratory space at our prior facility in Bedford, Massachusetts to a single tenant, under a lease that expires in 2021. We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

We are not subject to any material legal proceedings.

Item 4. Mine Safety Disclosures.

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 has been publicly traded on the Nasdaq Global Select Market under the symbol "FIXX" since March 28, 2018. Prior to that time, there was no public market for our common stock.

Holders

As of March 1, 2021, there were approximately 17 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not expect to pay any cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any future financing instruments.

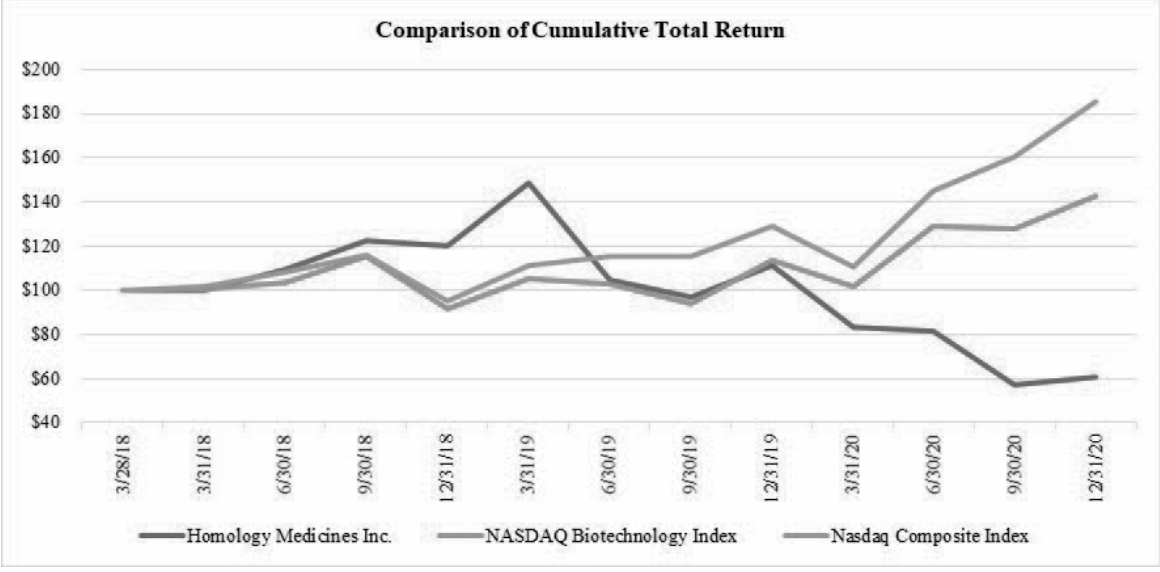
Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12, *Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters*, of this Annual Report on Form 10-K.

Stock Performance Graph

This performance graph shall not be deemed "soliciting material" or to be "filed" with the SEC for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act of 1933, as amended (the "Securities Act"), or the Exchange Act.

The graph set forth below compares the cumulative total stockholder return on our common stock between March 28, 2018 (the date our common stock commenced trading on the Nasdaq Global Select Market) and December 31, 2020, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes an initial investment of $100 on March 28, 2018 in our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any. The comparisons in the graph are not intended to forecast or be indicative of possible future performance of our common stock.



Recent Sales of Unregistered Securities; Purchases of Equity Securities by the Issuer or Affiliated Purchaser

We did not repurchase any of our equity securities during the quarter ended December 31, 2020. Other than as disclosed in our Current Report on Form 8-K filed with the SEC on November 9, 2020, we did not sell any equity securities during the year ended December 31, 2020 that were not registered under the Securities Act.

Use of Proceeds

Not applicable.

Item 6. Selected Financial Data.

The selected financial data presented below is derived from our audited consolidated financial statements. The selected financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Item 7 of Part II to this Annual Report on Form 10-K. The selected financial data in this section are not intended to replace our consolidated financial statements and the related notes. Our historical results are not necessarily indicative of our future results.

	For the Years Ended December 31,				
(in thousands, except share and per share data)	2020	2019	2018	2017	2016
			(as revised)		
Consolidated Statements of Operations Data:					
Collaboration revenue	$ 2,702	$ 1,666	$ 5,322	$ —	$ —
Operating expenses:					
Research and development	100,392	89,398	47,948	21,378	5,695
General and administrative	32,573	22,211	17,300	8,279	4,305
Total operating expenses	132,965	111,609	65,248	29,657	10,000
Loss from operations	(130,263)	(109,943)	(59,926)	(29,657)	(10,000)
Other income (expense)					
Changes in fair value of convertible preferred stock tranche liability	—	—	—	(876)	1,929
Interest income	1,569	6,027	4,349	542	24
Total other income (expense)	1,569	6,027	4,349	(334)	1,953
Net loss	$ (128,694)	$ (103,916)	$ (55,577)	$ (29,991)	$ (8,047)
Net loss per share-basic and diluted (1)	$ (2.80)	$ (2.47)	$ (1.95)	$ (12.10)	$ (4.23)
Weighted average common shares outstanding-basic and diluted (1)	45,910,787	42,117,690	28,551,807	2,479,432	1,900,531

(1) See Note 13 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K for an explanation of the method used to calculate basic and diluted net loss per common share and the weighted average number of shares used in the computation of the per share amounts.

	As of December 31,				
(in thousands)	2020	2019	2018	2017	2016
			(as revised)		
Consolidated Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 217,431	$ 262,388	$ 214,737	$ 129,659	$ 11,392
Total assets	263,737	310,567	259,094	137,530	14,219
Total liabilities	67,742	52,060	62,739	39,222	6,719
Total stockholders' equity (deficit)	195,995	258,507	196,355	(39,454)	(9,892)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	263,737	310,567	259,094	137,530	14,219

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our "Selected Consolidated Financial Data" and our consolidated financial statements, related notes and other financial information included elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties such as our plans, objectives, expectations and intentions. As a result of many important factors, including those set forth in the section captioned "Risk Factors" and elsewhere in this Annual Report on Form 10-K, our actual results could differ materially from the results described in, or implied by, these forward-looking statements. A discussion of the year ended December 31, 2019 compared to the year ended December 31, 2018 has been reported previously in our Annual Report on Form 10-K for the year ended December 31, 2019, filed with the SEC on March 12, 2020, under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations."

Overview

We are a clinical-stage genetic medicines company dedicated to transforming the lives of patients suffering from rare genetic diseases with significant unmet medical needs by curing the underlying cause of the disease. Our proprietary platform is designed to utilize our human hematopoietic stem cell derived adeno-associated virus vectors, or AAVHSCs, to precisely and efficiently deliver single administration genetic medicines *in vivo* either through gene therapy or nuclease-free gene editing across a broad range of genetic disorders. Our diverse set of AAVHSCs allows us to precisely target, via a single injection, a wide range of disease-relevant tissues, including the liver, central nervous system, or CNS, peripheral nervous system, or PNS, bone marrow, muscle and eye. Our genetic medicines platform is designed to provide us the flexibility to choose the method we believe is best suited from either gene therapy or gene editing for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the tissues exhibit. Our product development strategy is to continue to develop in parallel both gene therapy and gene editing, while initially leveraging the experience from our gene therapy product candidates to further advance our gene editing. We believe our dual technology platform will allow us to provide transformative cures using either modality.

The unique properties of our proprietary family of 15 novel AAVHSCs enable us to focus on a method of gene editing called gene integration, through the replacement of an entire diseased gene in the genome with a whole functional copy by harnessing the naturally occurring deoxyribonucleic acid, or DNA, repair process of homologous recombination, or HR. We believe our HR-driven gene editing approach will allow us to efficiently perform gene editing at therapeutic levels without unwanted on- and off-target modifications, and to directly measure and confirm those modifications in an unbiased manner to ensure only the intended changes are made. By utilizing the body's natural mechanism of correcting gene defects, we also avoid the need for exogenous nucleases, or bacteria-derived enzymes used in other gene editing approaches to cut DNA, that are known to significantly increase the risk of unwanted modifications.

HMI-102 for Treatment of PKU in Adult Patients

We are currently in Phase 2 of the pheNIX clinical trial with our first and lead product candidate, HMI-102, a gene therapy for the treatment of adults with phenylketonuria, or PKU. In November 2020, we reported positive safety and efficacy clinical data from the dose-escalation phase of the trial. As of the data cutoff date of October 19, 2020, six patients in the dose-escalation phase of the pheNIX trial had received HMI-102 across three dose cohorts (low-dose Cohort 1, n=2; mid-dose Cohort 2, n=2; high-dose Cohort 3, n=2). The results showed that HMI-102 was generally well-tolerated, and resulted in marked reductions in phenylalanine, or Phe, and the Phe-to-tyrosine, or Tyr, ratio, or the Phe-to-Tyr ratio, at two doses. Phe is a registrable endpoint in PKU, and the Phe-to-Tyr ratio is a clinically relevant diagnostic measurement for PKU. Based on the safety and efficacy results observed in the dose-escalation phase, we have selected and advanced two doses to the randomized, concurrently controlled, dose expansion Phase 2 portion of the pheNIX trial, which has the potential to be converted to a registrational trial. We expect to report initial clinical data from this portion of the trial by the end of 2021.

Other Product Candidates

We are currently progressing two gene therapy product development candidates for the treatment of lysosomal storage diseases: HMI-203 for the treatment of mucopolysaccharidosis type II (MPS II), or Hunter syndrome, and HMI-202 for the treatment of metachromatic leukodystrophy, or MLD.

We are in later-stage IND-enabling studies with HMI-203, an *in vivo* gene therapy product development candidate for the treatment of Hunter syndrome. HMI-203 is a potential one-time AAVHSC treatment designed to deliver functional copies of the *IDS* gene to multiple target organs, including those in the PNS and CNS, following a single I.V. administration. In preclinical studies, a single I.V. administration of HMI-203 resulted in robust biodistribution and human I2S, or hI2S, enzyme expression, leading to a significant reduction in heparin sulfate glycosaminoglycans, or GAGs, levels in the cerebrospinal fluid, brain, liver, heart, spleen, lung and kidney, compared with the vehicle-treated disease model. HMI-203 also led to significant changes in skeletal deformities compared with vehicle. We expect to initiate a Phase 1/2 dose-escalation clinical trial with HMI-203 in 2021.

We completed IND-enabling studies with HMI-202, a gene therapy CNS product development candidate for the treatment of MLD. We have generated preclinical data that demonstrates that a single I.V. administration of HMI-202 crossed the blood-brain-barrier and blood-nerve-barrier and led to durable reduction of sulfatides in all brain regions of the disease model. We are applying the learnings from the IND-enabling studies to further optimize an HMI-202 vector that may lead to a better therapeutic profile.

We are in later-stage IND-enabling studies with HMI-103, our lead gene editing product development candidate for the treatment of PKU in pediatric patients. We have generated *in vivo* preclinical data demonstrating Phe reduction following a single I.V. administration of the murine surrogate of HMI-103 in the PKU disease model out to 43 weeks (end of study). In addition, using quantitative molecular methods, we have demonstrated achievement of gene integration efficiencies in a humanized murine liver model that corresponded with Phe correction in the PKU murine model. These findings were peer-reviewed and published in *PLOS ONE* in May 2020. We expect to initiate a Phase 1/2 dose-escalation clinical trial with HMI-103 in 2021.

We also plan to name a development candidate in a new therapeutic area in 2021, demonstrating the broader capability of our AAVHSC platform, which we believe may allow us to target diseases with larger patient populations in the future.

On November 9, 2020, we entered into a stock purchase agreement, or the Stock Purchase Agreement, with Pfizer Inc., or Pfizer, pursuant to which Pfizer purchased 5,000,000 shares of our common stock through a private placement transaction at a purchase price of $12.00 per share, for an aggregate purchase price of $60.0 million. For additional information, see "Liquidity and Capital Resources."

On February 26, 2021, we received notice from Novartis Institutes of BioMedical Research, Inc., or Novartis, that they had elected to terminate the collaboration and license agreement with respect to the ophthalmic target, which was the only remaining target under the agreement. Accordingly, the notice served as notice of Novartis' termination of the agreement in its entirety, with an effective date of August 26, 2021, which is six months from the date of the notice. Novartis has agreed to work with us to effect the orderly wind down of activities in accordance with the agreement. As a result of this notice, we have regained worldwide exclusive rights from Novartis to research, develop, manufacture and commercialize our proprietary nuclease-free gene editing technology platform for the ophthalmic target. We plan to continue to advance the program toward naming a development candidate. The companies believe that results of studies conducted under the agreement provide early proof-of-principle and support a nuclease-independent approach to editing of relevant cell types in the eye after sub-retinal injection, and are the subject of a planned presentation at an upcoming scientific meeting. See Note 15 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K for additional information regarding the Novartis collaboration and license agreement.

We have fully integrated process development and Good Manufacturing Practice, or GMP, manufacturing capabilities that support the full breadth and flexibility of our AAVHSC capsid library. Our process development expertise covers all gene therapy and gene editing development functions and incorporates deep characterization and understanding of vector design and their consequences. Our manufacturing process is a versatile system that rapidly delivers high quality vector at scale. The manufacturing capacity within our 25,000 square foot GMP manufacturing facility includes multi-suite and multi-product capabilities to support our clinical development programs in both gene therapy and gene editing and we are now producing all of the clinical material for the pheNIX trial in this facility. Our plug and play process and manufacturing platform is a commercial manufacturing process that has successfully produced several of our product candidates. We are currently operating three 500-liter bioreactors in our internal manufacturing facility and have successfully produced GMP material at the 500-liter scale for multiple pipeline candidates. Additionally, we have successfully executed our manufacturing platform with multiple product candidates at the 2,000-liter bioreactor scale.

Our management team has a successful track record of discovering, developing and commercializing therapeutics with a particular focus on rare diseases. We have a robust intellectual property portfolio with issued composition of matter patents in the United States for our family of 15 AAVHSCs and we believe the breadth and depth of our intellectual property is a strategic asset that has the potential to provide us with a significant competitive advantage. We continue to build on our intellectual property estate through our ongoing product and platform development efforts.

Since our inception in 2015, we have raised approximately $539 million in aggregate net proceeds through our initial public offering, or IPO, in April 2018, a follow-on public offering of common stock in April 2019, proceeds from the sale of common stock under an "at-the-market" sales agreement, equity investments and preferred stock financings. Included in our net proceeds is $50.0 million from a former collaboration partner, comprised of an up-front payment of $35.0 million and a $15.0 million equity investment and a $60.0 million equity investment from Pfizer Inc., or Pfizer, through a private placement transaction. We will require additional capital in order to advance HMI-102 and our other product candidates through clinical development and commercialization. We believe that our compelling preclinical data, positive clinical data with HMI-102,

scientific expertise, product development strategy, manufacturing capabilities, and robust intellectual property position us as a leader in the development of genetic medicines.

We were incorporated and commenced operations in 2015. Since our incorporation, we have devoted substantially all of our resources to organizing and staffing our company, business planning, raising capital, developing our technology platform, advancing our lead product candidate, HMI-102 for the treatment of PKU, through IND-enabling studies and into a Phase 1/2 clinical trial, advancing HMI-103, HMI-203, and HMI-202 into IND-enabling studies, researching and identifying additional product candidates, developing and implementing manufacturing processes and internal manufacturing capabilities, building out our manufacturing and research and development space, enhancing our intellectual property portfolio, and providing general and administrative support for these operations. To date, we have financed our operations primarily through the sale of common stock, through the sale of preferred stock, and through funding from our collaboration partner.

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the foreseeable future, if at all. We recognized $2.7 million and $1.7 million in collaboration revenue for the years ended December 31, 2020 and 2019, respectively. Since inception, we have incurred significant operating losses. Our net losses for the years ended December 31, 2020 and 2019 were $128.7 million and $103.9 million, respectively. As of December 31, 2020, we had an accumulated deficit of $328.4 million.

Our total operating expenses were $133.0 million and $111.6 million for the years ended December 31, 2020 and 2019, respectively. We expect our operating expenses to continue to increase in connection with our ongoing development activities related to our product candidates. Specifically, we anticipate that our expenses will increase due to costs associated with our Phase 1/2 pheNIX clinical trial with HMI-102, development activities including IND-enabling studies and clinical trials associated with our other product candidates, including HMI-103, our gene editing product candidate for PKU, HMI-203, our gene therapy product candidate for Hunter syndrome, HMI-202, our gene therapy product candidate for MLD, for which we are focusing on optimization of the vector, and research activities in additional therapeutic areas to expand our pipeline, hiring additional personnel in manufacturing, research, clinical and regulatory, quality and other functional areas, increased expenses incurred with contract manufacturing organizations, or CMOs, to supply us with product for our clinical studies, costs to manufacture product for preclinical and clinical studies in our internal manufacturing facility and other costs including the maintenance and expansion of our intellectual property portfolio. In addition, we expect to continue to incur additional costs associated with operating as a public company.

We have incurred significant capital expenditures for the buildout of a facility we have leased, including research and development labs, office space and manufacturing suites and the procurement of equipment and furniture for this facility and in support of our product development candidates and research initiatives. We expect to incur additional capital expenditures in support of our research and development activities and our manufacturing facility.

Because of the numerous risks and uncertainties associated with the development of our current and any future product candidates and our platform and technology and because the extent to which we may enter into collaborations with third parties for development of any of our product candidates is unknown, we are unable to predict the timing and amount of increased operating expenses and capital expenditures associated with completing the research and development of our product candidates. Our future capital requirements will depend on many factors, including:

- the costs, timing, and results of our ongoing research and development efforts, including clinical trials, on HMI-102;
- the costs, timing, and results of our ongoing research and development efforts for HMI-103, HMI-202 and HMI-203, all of which are in IND-enabling studies;
- the costs, timing, and results of our research and development efforts for current and future product candidates in our gene therapy and gene editing pipeline;
- the costs and timing of process development and manufacturing scale-up activities, and the adequacy of supply of our product candidates for preclinical studies and clinical trials through CMOs and internal manufacturing;
- the costs and timing of capital expenditures for potential additional manufacturing capacity and related equipment and furniture;
- the costs and timing of preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims, including any claims by third parties that we are infringing upon their intellectual property rights;

- the effect of competitors and market developments; and
- our ability to establish and maintain strategic collaborations, licensing or other agreements and the financial terms of such agreements for our product candidates.

We believe that our existing cash and cash equivalents will enable us to fund our current projected operating expenses and capital expenditure requirements into the third quarter of 2022, including, subject to the impact of the COVID-19 pandemic on our business, additional development activities related to our Phase 1/2 pheNIX clinical trial with HMI-102, the advancement of HMI-103, our lead gene editing product candidate for PKU, through IND-enabling studies and into a Phase 1/2 clinical trial, HMI-203, our lead *in vivo* gene therapy product candidate for Hunter syndrome, through IND-enabling studies and into a Phase 1/2 clinical trial, and HMI-202, an *in vivo* gene therapy product candidate for MLD, through additional preclinical studies as we focus on optimizing the program's vector, the continued scale-up of our manufacturing processes and the expansion of our intellectual property portfolio. We have based these estimates on assumptions that may prove to be imprecise, and we may use our available capital resources sooner than we currently expect. See "Liquidity and Capital Resources." Adequate additional funds may not be available to us on acceptable terms, or at all. For example, the trading prices for our and other biopharmaceutical companies' stock have been highly volatile as a result of the COVID-19 pandemic. As a result, we may face difficulties raising capital through sales of our common stock and any such sales may be on unfavorable terms. See "Risk Factors—The COVID-19 pandemic caused by the novel strain of coronavirus could adversely impact our business, including our preclinical studies and clinical trials." in Item 1A of this Annual Report on Form 10-K. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect rights as a shareholder. Any future debt financing or preferred equity or other financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require the issuance of warrants, which could potentially dilute the ownership interests of our shareholders.

If we raise additional funds through collaborations, strategic alliances, or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce, or terminate our product development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Because of the numerous risks and uncertainties associated with drug development, we are unable to predict when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenue from product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

Impact of the COVID-19 Pandemic

We are closely monitoring how the spread of the COVID-19 pandemic is affecting our employees, our Phase 1/2 pheNIX clinical trial, preclinical studies, manufacturing and overall operations. In response to the spread of COVID-19, we have taken steps to minimize the impact on our operations.

Operations – To protect the health of our employees and the third parties with whom we interact, most office-based employees continue to work from home, while essential staffing levels in our operations remain in place, including key personnel in our laboratories and manufacturing facility. For those employees on-site, we have developed shift schedules for our laboratories and manufacturing facility and a modified office layout and traffic flow pattern to increase spacing capabilities, reduce inter-office risks and allow for business continuity. We have increased cleaning protocols throughout our entire facility, limited visitors to only those who are critical to our ongoing operations and have cancelled all business travel. In addition, we have developed our own on-site COVID-19 surveillance testing for employees to help promote health and safety.

Phase 1/2 pheNIX clinical trial – We are currently in Phase 2 of our Phase 1/2 pheNIX clinical trial and are working with trial sites to mitigate potential COVID-19-related disruptions in order to help ensure the safety of patients and healthcare professionals. In addition, we have deployed home-health services which include home visits for patient monitoring and reporting, as well as the utilization of a centralized laboratory for testing enrolled patients. Despite our best efforts, disruptions caused by the COVID-19 pandemic have resulted, and may continue to result, in delays in enrolling our Phase 1/2 pheNIX clinical trial. In addition, we could experience additional disruptions in conducting or completing this trial or other planned clinical trials and the incurrence of unforeseen costs as a result of these delays. We will continue to evaluate the impact of the ongoing global pandemic on the pheNIX trial and will make adjustments, as needed.

Preclinical studies – IND-enabling studies are continuing in support of our HMI-103 and HMI-203 programs and we have made operational changes to mitigate the risk of potential disruptions caused by the COVID-19 pandemic. All of our ongoing and planned preclinical studies at external CROs are progressing and we have accelerated shipments of reagents and supplies to avoid any disruption of activities. However, it is possible that the COVID-19 pandemic may have an impact in the future on our CROs' ability to complete critical studies required for the progression of these programs. In addition, any planned or potential meetings with the FDA or other regulatory authorities about any of our development programs could be delayed as these regulatory bodies respond to the ongoing pandemic.

Manufacturing – We continue to operate our manufacturing facility at or near normal levels. We have on-hand all of the drug product needed for the expansion phase of the pheNIX clinical trial. In addition, during the first quarter of 2020, we began to accelerate the procurement of raw materials for future manufacturing, research and development needs to minimize potential supply chain interruptions. While we currently do not anticipate any interruptions in our manufacturing process, it is possible that the COVID-19 pandemic and response efforts may have an impact in the future on our and/or our third-party suppliers and CMOs' ability to manufacture our product candidates or materials needed for our preclinical studies and clinical trials.

At this time, there is significant uncertainty relating to the trajectory of the COVID-19 pandemic and impact of related responses and as a result, we expect that the COVID-19 pandemic may impact our business, revenues, results of operations and financial condition. The impact of COVID-19 on our future results will largely depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the duration of the pandemic, travel restrictions and social distancing in the United States and other countries, business closures or business disruptions, the ultimate impact of COVID-19 on financial markets and the global economy, the effectiveness of vaccines and vaccine distribution efforts and the effectiveness of other actions taken in the United States and other countries to contain and treat the disease. See "Risk Factors— The COVID-19 pandemic caused by the novel strain of coronavirus could adversely impact our business, including our preclinical studies and clinical trials." in Item 1A of this Annual Report on Form 10-K.

Components of Our Results of Operations

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the foreseeable future. We recorded $2.7 million in collaboration revenue for the year ended December 31, 2020 (see Notes 15 and 16 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K for additional information regarding revenue recognition discussions).

Operating Expenses

Our operating expenses since inception have consisted solely of research and development costs and general and administrative costs.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts, and the development of our product candidates, and include:

- salaries, benefits and other related costs, including stock-based compensation expense, for personnel engaged in research and development functions;
- expenses incurred under agreements with third parties, including contract research organizations, or CROs, and other third parties that conduct research, preclinical activities and clinical trials on our behalf as well as CMOs and our internal technical operations team that manufacture our product candidates for use in our preclinical testing, our Phase 1/2 pheNIX clinical trial and additional potential future clinical trials;
- costs of outside consultants, including their fees and related travel expenses;
- the costs of laboratory supplies and acquiring, developing and manufacturing preclinical study and clinical trial materials; and
- facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

We expense research and development costs as incurred.

We typically use our employee and infrastructure resources across our development programs. We track outsourced development costs by product candidate or development program, but we do not allocate personnel costs, license payments made under our licensing arrangements or other internal costs to specific development programs or product candidates. These costs are included in other research and development expenses in the table below.

The following table summarizes our research and development expenses by product candidate or development program:

	For the Years Ended December 31,		
(in thousands)	2020	2019	Change
HMI-102 external development costs	$ 36,409	$ 32,753	$ 3,656
Other development-stage programs' external development costs	23,625	12,632	10,993
Employee-related costs	38,373	28,532	9,841
Other research and development costs	1,985	15,481	(13,496)
Total research and development expenses	$ 100,392	$ 89,398	$ 10,994

Research and development activities are central to our business model. We expect that our research and development expenses will continue to increase substantially for the foreseeable future as we advance clinical trials of HMI-102, for the treatment of PKU, including our Phase 1/2 pheNIX clinical trial, continue to advance HMI-103, HMI-203, and HMI-202 through IND-enabling studies and into clinical trials and continue to discover and develop additional product candidates.

We cannot determine with certainty the duration and costs of future clinical trials of HMI-102 and IND-enabling studies and future clinical trials of our other product candidates in development or any other future product candidate we may develop or if, when, or to what extent we will generate revenue from the commercialization and sale of any product candidate for which we obtain marketing approval. We may never succeed in obtaining marketing approval for any product candidate. The duration, costs and timing of clinical trials and development of HMI-102, our other product candidates in development and any other future product candidate we may develop will depend on a variety of factors, including:

- the scope, rate of progress, expense and results of clinical trials of HMI-102, HMI-103, HMI-202, and HMI-203 as well as of any future clinical trials of other product candidates and other research and development activities that we may conduct;
- uncertainties in clinical trial design and patient enrollment rates;
- any delays in clinical trials as a result of the COVID-19 pandemic;
- the actual probability of success for our product candidates, including the safety and efficacy results, early clinical data, competition, manufacturing capability and commercial viability;
- significant and changing government regulation and regulatory guidance;
- the timing and receipt of any marketing approvals; and
- the expense of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA or another regulatory authority were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in our clinical trials due to patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in our executive, finance, human resources, business development and administrative functions. General and administrative expenses also include legal fees relating to intellectual property and corporate matters; professional fees for accounting, auditing, tax and consulting services; insurance costs; travel expenses; and facility-related expenses, which include direct depreciation costs, rent expense, maintenance of facilities and other operating costs.

We expect that our general and administrative expenses will increase in the future as we increase our personnel headcount to support increased research and development activities relating to HMI-102, HMI-103, HMI-202, HMI-203 and any other product candidates we may develop. We also have incurred and expect to continue to incur increased expenses associated with being a public company, including costs of accounting, audit, compliance with the Sarbanes-Oxley Act of 2002, legal, regulatory and tax-related services associated with maintaining compliance with Nasdaq and SEC requirements; director and officer insurance costs; and investor and public relations costs.

Interest Income

Interest income consists of interest income earned on our cash, cash equivalents and short-term investments. Our interest income has decreased due to lower yields on invested funds as well as lower invested balances during the year ended December 31, 2020 as compared to the same period in 2019. Market volatility resulting from the COVID-19 pandemic has and may continue to adversely impact our interest income.

Income Taxes

Since our inception in 2015, we have not recorded any U.S. federal or state income tax benefits for the net losses we have incurred in any year or for our earned research and development tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2020, we had federal and state net operating loss carryforwards of $265.1 million and $271.5 million, respectively, that expire at various dates through 2040. As of December 31, 2020, we also had federal and state research and development tax credit carryforwards of $34.2 million and $7.2 million, respectively, that expire at various dates through 2040. Included in the $34.2 million of federal research and development credit carryforwards is $29.0 million of orphan drug credit carryforwards.

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of our consolidated financial statements and related disclosures requires us to make estimates, assumptions and judgements that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our financial statements.

Revenue Recognition—In May 2014, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2014-09, Revenue (Topic 606): *Revenue from Contracts with Customers* ("ASU 2014-09"), which amends the guidance for accounting for revenue from contracts with customers. ASU 2014-09 supersedes the revenue recognition requirements in FASB ASC Topic 605, *Revenue Recognition* ("ASC 605"), and creates a new Topic 606, *Revenue from Contracts with Customers* ("ASC 606"). On January 1, 2019, we adopted ASC 606 using the full retrospective transition method.

Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine the appropriate amount of revenue to be recognized for arrangements determined to be within the scope of ASC 606, we perform the following five steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. We only apply the five-step model to contracts when it is probable that we will collect consideration we are entitled to in exchange for the goods or services we transfer to the customer.

We estimate the transaction price based on the amount expected to be received for transferring the promised goods or services in the contract. The consideration may include fixed consideration and variable consideration. At the inception of each

arrangement that includes variable consideration, we evaluate the amount of consideration to which we expect to be entitled to. We utilize either the most likely amount method or expected value method to estimate the amount expected to be received based on which method best predicts the amount expected to be received. The amount of variable consideration that is included in the transaction price may be constrained and is included in the transaction price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period.

Our contracts may include development and regulatory milestone payments that are assessed under the most likely amount method and constrained until it is probable that a significant revenue reversal would not occur. Milestone payments that are not within our control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, we re-evaluate the probability of achievement of such development and clinical milestones and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue in the period of adjustment.

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). We allocate the transaction price based on the estimated standalone selling price of each performance obligation. We develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. We utilize key assumptions to determine the stand-alone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction and the estimated costs. Variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated are consistent with the amounts we would expect to receive for the satisfaction of each performance obligation.

The consideration allocated to each performance obligation is recognized as revenue when control is transferred for the related goods or services. For performance obligations which consist of licenses and other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress. We evaluate the measure of progress for our over-time arrangements at each reporting period and, if necessary, adjust the measure of performance and related revenue recognition and, if necessary, update the measure or progress and revenue recognized.

Accrued Research and Development Expenses—As part of the process of preparing our financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contract and purchase orders, communicating with our personnel and vendors to identify services that have been performed on our behalf and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- CROs and other third parties in connection with performing research activities on our behalf and conducting preclinical studies and clinical trials on our behalf and CMOs in connection with producing product for our clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to product manufacturing and development and distribution of preclinical supplies.

We base our expenses related to preclinical and clinical studies on our estimates of the services received and efforts expended pursuant to quotes and contracts with CROs that conduct and manage preclinical studies and clinical trials and CMOs that manufacture product for our research and development activities on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. In accruing fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or amount of prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low in any particular period. To date, we have not made any material adjustments to our prior estimates of accrued research and development expenses.

Stock-Based Compensation—We account for stock-based compensation transactions using a grant-date fair-value-based method under FASB Codification Topic 718, *Compensation—Stock Compensation*.

We measure stock options and other stock-based awards granted to employees, directors, consultants or advisors of the company or its affiliates based on their fair value on the date of the grant and recognize compensation expense of those awards, over the requisite service period, which is generally the vesting period of the respective award. We apply the straight-line method of expense recognition to all awards with only service-based vesting conditions and apply the graded-vesting method to all awards with performance-based vesting conditions or to awards with both service-based and performance-based vesting conditions.

We estimate the fair value of each stock option grant on the date of grant using the Black-Scholes option-pricing model, which uses as inputs the fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield.

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012, or the JOBS Act, permits an "emerging growth company," which we are, to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected to take advantage of this extended transition period.

Recent Accounting Pronouncements

In February 2016, the FASB issued new leasing standards to increase transparency and comparability among organizations related to their leasing activities. For additional information regarding our adoption of the new leasing standards, please refer to Notes 2 and 8 to our consolidated financial statements.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments - Credit Losses (Topic 326)*: Measurement of Credit Losses on Financial Instruments ("ASU 2016-13") to improve financial reporting by requiring more timely recording of credit losses on loans and other financial instruments held by financial institutions and other organizations. ASU 2016-13 requires the measurement of all expected credit losses for financial assets held at the reporting date based on historical experience, current conditions and reasonable and supportable forecasts. ASU 2016-13 also requires enhanced disclosures to help investors and other financial statement users better understand significant estimates and judgments used in estimating credit losses, as well as the credit quality and underwriting standards of an organization's portfolio. ASU 2016-13 is effective for us beginning January 1, 2023, with early application permitted. We are currently evaluating the impact the adoption of this standard will have on our consolidated financial statements.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation—Stock Compensation (Topic 718)*: Improvements to Nonemployee Share-Based Payment Accounting ("ASU 2018-07"), which changes certain aspects of the accounting for share-based payments granted to nonemployees. Under ASU 2018-07, most of the guidance on such payments to nonemployees would be aligned with the requirements for share-based payments granted to employees. We adopted ASU 2018-07 on January 1, 2020. The adoption of ASU 2018-07 did not have a material impact on our consolidated financial statements and related disclosures.

In October 2020, the FASB issued ASU 2020-10, *Codification Improvements*, which updates various codification topics by clarifying or improving disclosure requirements to align with the SEC's regulations. We will adopt ASU 2020-10 as of the reporting period beginning January 1, 2021. The adoption of this update is not expected to have a material impact on our consolidated financial statements.

Results of Operations

Comparison of Years Ended December 31, 2020 and 2019

The following table summarizes our results of operations for the years ended December 31, 2020 and 2019:

(in thousands)	For the Years Ended December 31, 2020	2019	Change
Collaboration revenue	$ 2,702	$ 1,666	$ 1,036
Operating expenses:			
Research and development	100,392	89,398	10,994
General and administrative	32,573	22,211	10,362
Total operating expenses	132,965	111,609	21,356
Loss from operations	$ (130,263)	$ (109,943)	$ (20,320)
Other income:			
Interest income	1,569	6,027	(4,458)
Total other income	1,569	6,027	(4,458)
Net loss	$ (128,694)	$ (103,916)	$ (24,778)

Collaboration Revenue

Collaboration revenue for the year ended December 31, 2020 was $2.7 million, compared to $1.7 million for the year ended December 31, 2019. For the year ended December 31, 2020, collaboration revenue consisted primarily of revenue recognized under our collaboration agreement with Novartis. We recognize such revenues consistent with the pattern of performance of our research and development activities under the collaboration, taking into consideration all upfront payments and research funding payments under this arrangement together as a single performance obligation. Collaboration revenue recognized under the collaboration in a given period is based on actual costs incurred during that period as a percentage of total estimated costs to complete the single performance obligation under the arrangement.

Research and Development Expenses

(in thousands)	For the Years Ended December 31, 2020	2019	Change
HMI-102 external development costs	$ 36,409	$ 32,753	$ 3,656
Other development-stage programs' external development costs	23,625	12,632	10,993
Employee-related costs	38,373	28,532	9,841
Other research and development costs	1,985	15,481	(13,496)
Total research and development expenses	$ 100,392	$ 89,398	$ 10,994

Research and development expenses for the year ended December 31, 2020 were $100.4 million, compared to $89.4 million for the year ended December 31, 2019. The increase of $11.0 million was due to an increase of $3.7 million in direct research expenses for HMI-102 including costs incurred with our CRO to conduct and manage our Phase 1/2 pheNIX clinical trial, as well as costs related to manufacturing clinical trial materials. Additionally, there was a $11.0 million increase in direct research expenses related to our other development-stage programs, including our newly announced HMI-203 program for Hunter syndrome, as well as a $9.8 million increase in employee-related costs due to additional employee headcount to support our ongoing development programs, research initiatives, technology platform and manufacturing capabilities resulting in increases in salaries, payroll taxes, stock-based compensation expense and recruiting costs. Partially offsetting these increases was a $13.5 million decrease in research and development costs related to laboratory supplies and research materials for our early-stage research programs.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2020 were $32.6 million, compared to $22.2 million for the year ended December 31, 2019. The increase of $10.4 million was due to an increase in employee-related

expenses of $5.2 million, which included $3.4 million of increased stock-based compensation expense, an increase in facility costs of $1.4 million, an increase in legal costs and other professional fees of $0.9 million, an increase in insurance and taxes of $0.8 million, an increase in software expense of $0.7 million, an increase in consulting expense of $0.6 million, an increase in recruiting fees of $0.4 million and an increase in market research of $0.4 million .

Interest Income

Interest income for the year ended December 31, 2020 was $1.6 million, compared to $6.0 million for the year ended December 31, 2019. The decrease was the result of lower invested balances in cash, cash equivalents and short-term investments for the year ended December 31, 2020 compared to the year ended December 31, 2019, as well as significantly lower yields on invested funds.

Net Loss

Net loss for the year ended December 31, 2020 was $128.7 million, compared to $103.9 million for the year ended December 31, 2019. The increase in net loss was primarily due to the increases in research and development and general and administrative expenses discussed above.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. We expect to incur significant expenses and operating losses for the foreseeable future as we advance the preclinical and clinical development of our product candidates. We expect that our research and development and general and administrative costs and our capital expenditures will increase in connection with conducting preclinical studies and clinical trials for our product candidates, contracting with CMOs producing material in our internal manufacturing facility to support preclinical studies and clinical trials, expanding our research and development laboratories and manufacturing facility, expanding our intellectual property portfolio, and providing general and administrative support for our operations. As a result, we will need additional capital to fund our operations, which we may obtain from additional equity or debt financings, collaborations, licensing arrangements, or other sources.

We do not currently have any approved products and have never generated any revenue from product sales. To date, we have financed our operations primarily through the sale of common stock, the sale of preferred stock and through an up-front payment from a collaboration partner. Since our inception in 2015, we have raised approximately $539 million in aggregate net proceeds through our IPO in April 2018, a follow-on public offering of common stock in April 2019, proceeds from the sale of common stock under an “at-the-market” sales agreement, equity investments and preferred stock financings. Included in our net proceeds is $50.0 million from a former collaboration partner, comprised of an up-front payment of $35.0 million and a $15.0 million equity investment and a $60.0 million equity investment from Pfizer through a private placement transaction.

In March 2020, we entered into a sales agreement, or the Sales Agreement, with Cowen and Company, LLC, or Cowen, as sales agent, pursuant to which we may, from time to time, issue and sell common stock with an aggregate value of up to $150.0 million in "at-the-market" offerings, or the ATM, under our Registration Statement on Form S-3 (File No. 333-237131) filed with the SEC on March 12, 2020. Sales of common stock, if any, pursuant to the Sales Agreement, may be made in sales deemed to be an “at the market offering” as defined in Rule 415(a) of the Securities Act, including sales made directly through the Nasdaq Global Market or on any other existing trading market for our common stock. No securities were issued pursuant to the Sales Agreement during the year ended December 31, 2020. As of December 31, 2020, there was $150.0 million of common stock remaining available for sale under the ATM. Simultaneous with the filing of the registration statement in March 2020, our previous Registration Statement on Form S-3 (File No. 333-230664) filed with the SEC on April 1, 2019 and our prior sales agreement with Cowen providing for the offering, issuance and sale of up to an aggregate $100.0 million of our common stock from time to time in “at-the-market” offerings were terminated.

Strategic Collaborations and Investments

On November 9, 2020, we entered into the Stock Purchase Agreement with Pfizer, pursuant to which Pfizer purchased 5,000,000 shares of our common stock through a private placement transaction at a purchase price of $12.00 per share, for an aggregate purchase price of $60.0 million. Under the Stock Purchase Agreement, Pfizer was granted an exclusive right of first refusal, or ROFR, for a 30-month period beginning on the date of the closing of the private placement to negotiate a potential collaboration on the development and commercialization of HMI-102 and HMI-103. Pfizer may exercise its right of first refusal under the ROFR one time for each of HMI-102 and HMI-103 during the ROFR period. In addition to the ROFR, the Stock Purchase Agreement provided for an information sharing committee comprised of representatives of each company which will serve as a forum for sharing information regarding the development of HMI-102 and HMI-103 during the ROFR

period. Additionally, Pfizer has designated a member to join our Scientific Advisory Board to participate in matters related to the development of these programs.

See Part I, Item 1. "Strategic Collaborations—Collaboration and License Agreement with the Novartis Institutes for BioMedical Research, Inc." for additional information about our collaboration and license agreement with Novartis.

Cash Flows

Our cash, cash equivalents and short-term investments totaled $217.4 million and $262.4 million as of December 31, 2020 and 2019, respectively. We had no indebtedness as of December 31, 2020 and 2019.

The following table summarizes our sources and uses of cash for the period presented:

	For the Years Ended December 31,	
(in thousands)	**2020**	**2019**
Net cash used in operating activities	$ (94,332)	$ (91,358)
Net cash provided by (used in) investing activities	204,896	(51,799)
Net cash provided by financing activities	53,093	158,213
Net change in cash and cash equivalents	$ 163,657	$ 15,056

Cash Flows for the year ended December 31, 2020

Operating Activities

Net cash used in operating activities for the year ended December 31, 2020 was $94.3 million, driven primarily by our net loss of $128.7 million as we incurred expenses associated with research and development activities on HMI-102, HMI-103, HMI-203, and HMI-202, including the Phase 1/2 pheNIX trial for our HMI-102 program, and research activities on other applications for our technology, and a decrease in operating lease liabilities of $2.3 million. These items were partially offset by net non-cash expenses of $22.8 million, which includes $13.2 million of stock-based compensation expense and $8.0 million of depreciation expense, and a decrease in working capital of $13.8 million.

Investing Activities

Net cash provided by investing activities for the year ended December 31, 2020 was $204.9 million, attributable to maturities of short-term investments of $228.6 million, partially offset by purchases of short-term investments of $20.0 million and purchases of property and equipment of $3.7 million.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2020 was $53.1 million, primarily due to $52.0 million of net proceeds allocated to the issuance of common stock in a private placement transaction with Pfizer in November 2020.

Cash Flows for the year ended December 31, 2019

Operating Activities

Net cash used in operating activities for the year ended December 31, 2019 was $91.4 million, driven primarily by our net loss of $103.9 million as we incurred expenses associated with research and development activities on HMI-102, HMI-103 and HMI-202, including the Phase 1/2 pheNIX trial for our HMI-102 program, and research activities on other applications for our technology. The funding of our net loss was partially offset by net non-cash expenses of $12.1 million, including $7.6 million of stock compensation expense and $6.3 million of depreciation expense. Changes to working capital were mostly offsetting, with $4.5 million in decreased accounts payable and $0.6 million in decreased deferred revenue netting against $2.8 million in decreased prepaid expenses and other current assets and $2.3 million in increased accrued expenses and other liabilities.

Investing Activities

Net cash used in investing activities for the year ended December 31, 2019 was $51.8 million, attributable to $286.4 million in purchases of short-term investments and $21.8 million in purchases of property and equipment, partially offset by maturities of short-term investments of $256.4 million.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2019 was $158.2 million, primarily due to $134.5 million of net proceeds from the issuance of common stock in a public offering in April 2019 and $22.5 million of net proceeds from the issuance of common stock under an "at-the-market" sales agreement in December 2019.

Funding Requirements

Our operating expenses increased substantially in 2020 and are expected to increase in future years in connection with our ongoing activities, particularly as we advance our Phase 1/2 pheNIX clinical trial with HMI-102 and our preclinical activities including IND-enabling studies and expected Phase 1/2 clinical trials, continue to scale-up our manufacturing processes, engage with CMOs, manufacture materials for preclinical and clinical activities in our internal manufacturing facility and initiate additional human clinical trials. In addition, we have incurred and expect to continue to incur additional costs associated with operating as a public company. We also expect our capital expenditures to increase as we expand our operations.

Specifically, our expenses will increase as we:

- pursue the preclinical and clinical development of HMI-102, including the ongoing pheNIX Phase 1/2 clinical trial, HMI-103, HMI-203 and HMI-202;
- pursue the preclinical and clinical development of other product candidates based on our gene therapy and gene editing technology;
- further scale up our internal manufacturing processes and capabilities, manufacture materials in our internal manufacturing facility and contract with CMOs to support our preclinical studies and clinical trials of our product candidates;
- further expand our manufacturing capacity;
- operate our business in our facility with expanded research and development labs and manufacturing suites and purchase additional equipment for our operations;
- in-license or acquire the rights to other products, product candidates or technologies;
- maintain, expand and protect our intellectual property portfolio;
- hire additional personnel in research, manufacturing and regulatory and clinical development as well as management personnel; and
- expand our operational, financial and management systems and increase personnel, including personnel to support our operations as a public company.

We believe that our existing cash and cash equivalents will enable us to fund our current projected operating expenses and capital expenditure requirements into the third quarter of 2022, including, subject to the impact of the COVID-19 pandemic on our business, additional development activities related to our Phase 1/2 pheNIX clinical trial with HMI-102, the advancement of HMI-103, our lead gene editing product candidate for PKU, through IND-enabling studies and into a Phase 1/2 clinical trial, HMI-203, our lead CNS/PNS gene therapy product candidate for Hunter syndrome, through IND-enabling studies and into a Phase 1/2 clinical trial, and HMI-202, a CNS gene therapy product candidate for MLD, through additional preclinical studies as we focus on optimizing the program's vector, the continued scale-up of our manufacturing processes and the expansion of our intellectual property portfolio. We have based these estimates on assumptions that may prove to be imprecise, and we may use our available capital resources sooner than we currently expect.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical drugs, it is difficult to estimate with certainty the amount of our working capital requirements. Our future funding requirements will depend on many factors, including:

- the progress, costs and results of our preclinical development and initial clinical trials for HMI-102, including the pheNIX Phase 1/2 clinical trial, HMI-103, HMI-203, and HMI-202;

- the progress, costs and results of our additional research and preclinical development programs in gene therapy and gene editing;
- the costs, scope and timing of internal process development and manufacturing scale-up activities, the production of materials in our internal manufacturing facility, and outsourcing activities with CMOs associated with our lead product development programs and other programs we advance through preclinical and clinical development;
- our ability to establish and maintain strategic collaborations, licensing or other agreements and the financial terms of such agreements;
- the scope, progress, results and costs of any product candidates that we may derive from our platform technology or any other product candidates that we may develop;
- the extent to which we in-license or acquire rights to other products, product candidates or technologies; and
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against any intellectual property-related claims.

In addition, the magnitude and duration of the COVID-19 pandemic and its impact on our liquidity and future funding requirements is uncertain as of the filing date of this Annual Report on Form 10-K, as the pandemic continues to evolve globally. See "Impact of the COVID-19 Pandemic" above and "Risk Factors— The COVID-19 pandemic caused by the novel strain of coronavirus could adversely impact our business, including our preclinical studies and clinical trials." in Item 1A of this Annual Report on Form 10-K for a further discussion of the possible impact of the COVID-19 pandemic on our business.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaboration agreements, other third-party funding, strategic alliances, licensing arrangements and marketing and distribution arrangements.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our shareholders as common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through other third-party funding, collaboration agreements, strategic alliances, licensing arrangements or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations

The following is a summary of our significant contractual obligations as of December 31, 2020:

	Payments Due by Period				
Contractual Obligation	Total	Less Than 1 Year	More Than 1 Year and Less Than 3	More Than 3 years and Less Than 5	More Than 5 years
	(in thousands)				
Operating lease obligation (1)	$ 19,403	$ 2,973	$ 6,064	$ 6,433	$ 3,933
License obligations (2)	$ 655	$ 45	$ 90	$ 90	$ 430

(1) Represents future minimum lease payments under our operating leases for office and lab space in Bedford, Massachusetts that expire in October 2021 and February 2027. Future minimum lease payments are net of anticipated sublease payments of approximately $0.9 million in 2021.

(2) Represents minimum annual license fees under our license agreements with Caltech and COH. These amounts do not include any potential contingent payments upon the achievement by us of specified clinical, regulatory and commercial events, as applicable, or patent prosecution or royalty payments we may be required to make under these license agreements. We have excluded these potential payments in the contractual obligations table because the timing and likelihood of these contingent payments are not currently known and would be difficult to predict or estimate. See Part I, Item 1. "Strategic Collaborations" for additional information about these license agreements, including with respect to potential payments thereunder.

We enter into contracts in the normal course of business with CROs and CMOs for clinical trials, preclinical research studies and testing, manufacturing and other services and products for operating purposes. These contracts do not contain any minimum purchase commitments and are cancelable by us upon prior notice of 30 days and, as a result, are not included in the table of contractual obligations above.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements and do not have any holdings in variable interest entities.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risks in the ordinary course of our business. These risks primarily include interest rate sensitivities. Our interest-earning assets consist of cash, cash equivalents, and short-term investments of $217.4 million, or 82.4% of our total assets at December 31, 2020, and $262.4 million, or 84.5% of our total assets at December 31, 2019. Interest income earned on these assets was $1.6 million in 2020 and $6.0 million in 2019. Our interest income is sensitive to changes in the general level of interest rates, primarily U.S. interest rates. If a 10% change in interest rates were to have immediately occurred on December 31, 2020, this change would not have had a material effect on the fair value of our investment portfolio as of that date. At December 31, 2020, our cash equivalents consisted of bank deposits and money market funds. Such interest-earning instruments carry a degree of interest rate risk; however, historical fluctuations in interest income have not been significant for us. We had no debt outstanding as of December 31, 2020 and 2019.

Item 8. Financial Statements and Supplementary Data.

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15 of Part IV of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Limitations on effectiveness of controls and procedures

In designing and evaluating our disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Evaluation of disclosure controls and procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, has evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act). Based on such evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2020.

Management's annual report on internal control over financial reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting, as such term is defined in Rule 13a-15(f) under the Exchange Act. Our management conducted an assessment of the effectiveness of our internal control over financial reporting based on the criteria set forth in "Internal Control - Integrated Framework (2013)" issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this assessment, our management concluded that, as of December 31, 2020, our internal control over financial reporting was effective.

Attestation report of the registered public accounting firm

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm due to an exemption established by the JOBS Act for "emerging growth companies."

Changes in internal control over financial reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2020 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Directors and Executive Officers

The following table sets forth the name, age and position of each of our executive officers and directors.

Name	Age	Position
Executive Officers:		
Arthur O. Tzianabos, Ph.D.	57	President and Chief Executive Officer and Director
W. Bradford Smith	65	Chief Financial Officer, Treasurer and Secretary
Albert Seymour, Ph.D.	53	Chief Scientific Officer
Tim Kelly	52	Chief Technical Operations Officer
Gabriel M. Cohn, M.D.	62	Chief Medical Officer
Directors:		
Steven Gillis, Ph.D. (3)	67	Director
Richard J. Gregory, Ph.D. (2)	63	Director
Kush M. Parmar, M.D., Ph.D. (2)	40	Chairman of the Board
Matthew R. Patterson (1)	49	Director
Jeffrey V. Poulton (1)	53	Director
Alise S. Reicin, M.D. (3)	60	Director
Mary Thistle (1)	61	Director

(1) Member of the audit committee.
(2) Member of the compensation committee.
(3) Member of the nominating and corporate governance committee.

Arthur O. Tzianabos, Ph.D. has served as our President, Chief Executive Officer and member of our board of directors since April 2016. Dr. Tzianabos joined Homology from OvaScience, Inc., a biotechnology company (which has since merged with and into Millendo Therapeutics, Inc.), where he served as President and Chief Scientific Officer from September 2013 to March 2016. Prior to OvaScience, Dr. Tzianabos spent eight years at Shire plc, a biotechnology company, where he served in positions of increasing responsibility, including Senior Director, Discovery Research, Vice President, Program Management and Senior Vice President and Head, Research and Early Development. From 1992 to 2005, Dr. Tzianabos was a faculty member at Harvard Medical School and maintained laboratories at the Channing Laboratory, Brigham and Women's Hospital and the Department of Microbiology and Molecular Genetics at Harvard Medical School. Dr. Tzianabos currently serves as a director of Stoke Therapeutics, Inc. and is Chairman of the board of directors of Akouos, Inc. Dr. Tzianabos previously served as a director of BIND Therapeutics, Inc. Dr. Tzianabos holds a B.S. in Biology from Boston College and a Ph.D. in Microbiology from the University of New Hampshire. We believe Dr. Tzianabos' extensive academic and clinical experience, as well as his knowledge of the industry, qualifies him to serve on our board of directors.

W. Bradford Smith has served as our Chief Financial Officer and Treasurer since April 2017 and our Secretary since July 2017. From March 2014 to April 2017, Mr. Smith was Chief Financial Officer of Ocular Therapeutix, Inc., a biopharmaceutical platform company. Prior to joining Ocular Therapeutix, Inc., Mr. Smith served as the Chief Financial Officer of OmniGuide, Inc., a medical device company, from July 2008 to March 2014. Mr. Smith holds a B.S. in Biology from Tufts University and an M.B.A. from the Whittemore School of Business and Economics at the University of New Hampshire.

Albert Seymour, Ph.D. has served as our Chief Scientific Officer since April 2016. Prior to joining Homology, Dr. Seymour was Senior Vice President, Head of Global Research and Nonclinical Development at Shire plc, a biotechnology company, from 2011 to 2016. Dr. Seymour received his B.A. in Biology from the University of Delaware, an M.S. from Johns Hopkins University School of Medicine and his Ph.D. in Human Genetics from the University of Pittsburgh.

Tim Kelly has served as our Chief Technical Operations Officer since April 2018, and prior to that, he served as our Senior Vice President of Technical Operations from May 2017 to April 2018. From January 2017 to May 2017, Mr. Kelly served as Head of Technical Operations at Sarepta Therapeutics, Inc., a biopharmaceutical company. Prior to that, Mr. Kelly spent eight years, from 2009 to 2017, at Shire plc, a biotechnology company, where he served most recently as Senior Vice President and Head of Biologics Operating Unit from May 2016 to January 2017, and prior to that served in roles of increasing responsibility, including Interim Head of Technical Operations from August 2015 to April 2016 and Head of Product Strategy

& Planning from 2014 to July 2015. He was previously the Head of Technical Operations at UCB S.A. in Belgium. Mr. Kelly also held roles of increasing responsibility at Biogen Idec, including Senior Director of International Operations. Mr. Kelly holds a B.S. with emphasis in Engineering Mechanics from the United States Air Force Academy and an M.B.A. from Troy University.

Gabriel M. Cohn, M.D. has served as our Chief Medical Officer since December 2019. Prior to joining Homology, Dr. Cohn was Vice President, Clinical Development Lead at AVROBIO, Inc., a clinical-stage gene therapy company, from November 2017 to November 2019. Prior to AVROBIO, Dr. Cohn served as Vice President and Head of Global Clinical and Medical Affairs at OvaScience, Inc., a biotechnology company, from 2015 to July 2017. Prior to that, Dr. Cohn spent seven years at Shire plc, a biotechnology company, including Shire Human Genetic Therapies (HGT), where he most recently held the position of Senior Medical Director, Clinical Sciences from 2012 to 2015, and prior to that served in roles of increasing responsibility including Interim Global Franchise Medical Lead, Gaucher Disease in 2011 and Medical Director, North America from 2008 to 2011. Prior to joining the biotechnology industry, Dr. Cohn served as the Chief, Division of Clinical and Reproductive Genetics and Medical Director, Genetic Services at Baystate Medical Center and as Assistant Professor at Tufts University School of Medicine. He began his academic career as the Director, Reproductive Genetics at SUNY Health Science Center (HSC) at Syracuse (now Upstate). Dr. Cohn has a B.S. in Biology from Brooklyn College, an M.D. from SUNY HSC at Syracuse School of Medicine and an M.B.A. from University of Massachusetts Amherst.

Directors

Steven Gillis, Ph.D. has served as a member of our board of directors since 2016. Since 2005, Dr. Gillis has been a managing director at ARCH Venture Partners, a venture capital firm. From 1994 to 2005, Dr. Gillis served as Chief Executive Officer and chairman of the board of directors of Corixa Corporation, which he co-founded in October 1994. Previously, Dr. Gillis served as Director, Head of Research and Development, Chief Scientific Officer and acting Chief Executive Officer of Immunex Corporation, which he co-founded, from 1981 until his departure in 1994. As a former director and chairman of Trubion Pharmaceuticals, Inc., Dr. Gillis led its acquisition by Emergent BioSolutions in the fall 2010. Dr. Gillis currently serves as a director of Takeda Pharmaceutical Company Limited (and as director of Shire plc prior to its acquisition by Takeda), and serves as a director and chairman of VBI Vaccines Inc. Dr. Gillis also currently serves as a director of several private companies. Dr. Gillis previously served as a director at and Pulmatrix, Inc. from 2008 to 2020, at PhaseRx, Inc. from 2008 to 2018 and at bluebird bio, Inc. from 2011 to 2015. Dr. Gillis received his B.A. in Biology and English from Williams College and his Ph.D. in Biological Science from Dartmouth College. We believe that Dr. Gillis's knowledge of immunology and experience in the venture capital industry, particularly with biotechnology and pharmaceutical companies, qualifies him to serve as a member of our board of directors.

Richard J. Gregory, Ph.D. has served as a member of our board of directors since 2015. Prior to his retirement, Dr. Gregory served as Executive Vice President and Chief Scientific Officer of ImmunoGen, Inc., a biotechnology company, from 2015 until August 2019. Prior to joining ImmunoGen, Inc., he spent 25 years at Genzyme Corporation, a biotechnology company, in roles of increasing responsibility, including Senior Vice President and Head of Research from 2003 until Genzyme Corporation's acquisition by Sanofi in 2011, and Head of Research and Development for Genzyme from 2011 through 2014. Dr. Gregory serves as a director of ProMIS Neurosciences, Inc. Dr. Gregory received his B.A. in Science from Virginia Tech and holds a Ph.D. from the University of Massachusetts, Amherst, and completed his post-doctoral work at the Worcester Foundation for Experimental Biology. We believe that Dr. Gregory's knowledge of immunology qualifies him to serve as a member of our board of directors.

Kush M. Parmar, M.D., Ph.D. has served as a member of our board of directors since 2015 and as Chairman of the Board since March 2018. Dr. Parmar is a Managing Partner at 5AM Venture Management LLC, an early stage venture capital firm focused on the life sciences, where he has been since 2010. Before joining 5AM, from 2002 to 2010, he was at Harvard Medical School, where he was an NIH-sponsored M.D./Ph.D. physician scientist fellow in the joint Harvard-MIT Health Sciences and Technology Program. Dr. Parmar currently serves on the boards of 5:01 Acquisition Corp. and Akouos, Inc., as well as the boards of numerous private companies. He previously served as a board member or observer for Arvinas, Inc., Achaogen, Inc., Audentes Therapeutics, Inc. (acquired by Astellas Pharma Inc.), Pulmatrix, Inc. and scPharmaceuticals Inc. He is a member of the scientific advisory boards of Penn Medicine, Princeton University's Department of Molecular Biology, and the Grace Science Foundation, and is a fellow of the Society of Kauffman Fellows. Before joining 5AM, Dr. Parmar completed clinical clerkships at the Massachusetts General & Brigham and Women's Hospitals, attended courses at Harvard Business School and consulted for an oncology startup. He also founded a non-profit international development organization, the Cruz Blanca Initiative. He holds an A.B. in Molecular Biology and Medieval Studies from Princeton University, a Ph.D. in Experimental Pathology from Harvard University, and an M.D. from Harvard Medical School. We believe that Dr. Parmar's experience in the life sciences industry, his experience as a venture capitalist and senior executive, as well as his service on the boards of directors of numerous companies provide him with the qualifications to serve as a director of our company.

Matthew R. Patterson has served as a member of our board of directors since 2018. Mr. Patterson is the co-founder of Audentes Therapeutics, Inc., a biotechnology company, and has served in the role of Strategic Advisor since January 2020. Previously, he served as its Chief Executive Officer from November 2012 until Audentes' acquisition by Astellas Pharma Inc. in January 2020. Mr. Patterson also served as Audentes' Chairman of the board of directors and formerly served as President until May 2018. Prior to that, Mr. Patterson was the Entrepreneur-In-Residence at OrbiMed Advisors LLC. Prior to OrbiMed, Mr. Patterson served in roles at Amicus Therapeutics, Inc., BioMarin Pharmaceutical Inc. and Genzyme Corporation. Mr. Patterson serves as a director of Vor Biopharma, Inc. and 5:01 Acquisition Corp., and also serves as a director of several private companies. Mr. Patterson holds a B.A. from Bowdoin College. We believe that Mr. Patterson's experience in the biotechnology and biopharmaceutical industries, as well as his service on the board of directors of a public company provide him with the qualifications to serve as a director of our company.

Jeffrey V. Poulton has served as a member of our board of directors since July 2020. Mr. Poulton has served as Executive Vice President and Chief Financial Officer at Alnylam Pharmaceuticals, Inc., a biopharmaceutical company, since August 2019. Prior to joining Alnylam, Mr. Poulton served as Chief Financial Officer of Indigo Agriculture, a plant microbiome company, from January 2018 to April 2019, where he supported the initial commercial scale-up of the business, including expansion outside the U.S. Between 2003 and December 2017, Mr. Poulton held various roles of increasing responsibility at Shire plc, most recently as Chief Financial Officer and a member of Shire's Executive Committee and Board of Directors from January 2015 to December 2017. During his tenure at Shire, Mr. Poulton also led Shire's rare disease U.S., LATAM and Asia Pacific commercial operations, as well as Shire's global rare disease business unit. Prior to Shire, Mr. Poulton led corporate finance and business development initiatives in both the gas and electric utilities industry and the materials manufacturing sector, serving in financial leadership positions at Cinergy Corp. and PPG Industries. Mr. Poulton also served in the United States Navy as a Commissioned Officer. Mr. Poulton holds a B.A. in Economics from Duke University and an M.B.A. from Indiana University. We believe that Mr. Poulton is qualified to serve on our board of directors due to his finance background and industry experience.

Alise Reicin, M.D. has served as a member of our board of directors since July 2019. Dr. Reicin has served as Chief Executive Officer of Tectonic Therapeutic, Inc., a biotechnology company, since August 2020. Prior to Tectonic. Dr. Reicin served as President, Global Clinical Development at Celgene Corporation, a pharmaceutical company, from November 2018 to December 2019. Prior to Celgene, she served as Head of Global Clinical Development at EMD Serono, a pharmaceutical company, from May 2015 through October 2018. Prior to EMD Serono, Dr. Reicin served as VP, Program Leadership Oncology at Merck and Co., a pharmaceutical company. She holds a B.A. in Biochemistry from Barnard College of Columbia University and an M.D. from Harvard Medical School. We believe that Dr. Reicin's clinical expertise and leadership roles in the biotechnology and biopharmaceutical industries provide her with the qualifications to serve as a director of our company.

Mary Thistle has served as a member of our board of directors since 2018. Ms. Thistle has served as Special Advisor to the Bill & Melinda Gates Medical Research Institute, a non-profit biotech organization, since the fall of 2020, and previously served as the organization's Chief of Staff from January 2018 until assuming her current role. Prior to that, she held senior leadership positions at Dimension Therapeutics, Inc., a gene therapy company, including Chief Operating Officer from 2016 to 2017 and Chief Business Officer from 2015 to 2016. Prior to joining Dimension Therapeutics, Inc., she spent six years at Cubist Pharmaceuticals, Inc., a biopharmaceutical company, where she held various leadership positions, including Senior Vice President, Business Development from 2014 to 2015, Vice President, Business Development from 2012 to 2013 and Senior Director, Business Development from 2009 to 2012. Prior to that, she held various positions at ViaCell, Inc. and PerkinElmer Inc. Ms. Thistle currently serves on the board of directors of Ziopharm Oncology, Inc., as well as the boards of several private companies. Ms. Thistle holds a B.S. in Accounting from the University of Massachusetts, Boston. We believe that Ms. Thistle is qualified to serve on our board of directors due to her finance background and industry experience.

Delinquent Section 16(a) Reports

Section 16(a) of the Exchange Act requires our directors, executive officers and stockholders who beneficially own more than 10% of any class of our equity securities registered pursuant to Section 12 of the Exchange Act (collectively, the "Reporting Persons") to file initial statements of beneficial ownership of securities and statements of changes in beneficial ownership of securities with respect to our equity securities with the SEC. Based on our review of the copies of such forms filed with the SEC and upon any written representations of the Reporting Persons received by us, we believe that there has been compliance with all Section 16(a) filing requirements applicable to such Reporting Persons with respect to the year ended December 31, 2020.

Code of Ethics

We have a written Code of Business Conduct and Ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of the code on our website at www.homologymedicines.com in the "Investors" section under "Corporate Governance." In addition, we intend to post on our website all disclosures that are required by law or the listing standards of The Nasdaq Stock Market LLC ("Nasdaq") concerning any amendments to, or waivers from, any provision of the code. The information contained on our website is not incorporated by reference into this Annual Report on Form 10-K.

Audit Committee and Audit Committee Financial Expert

We have a separately-designated standing audit committee ("Audit Committee"). The members of the Audit Committee are Matthew R. Patterson, Jeffrey V. Poulton and Mary Thistle. Ms. Thistle serves as the Chairperson of the Audit Committee. The members of our Audit Committee meet the requirements for financial literacy under the applicable rules of the SEC and Nasdaq. Our board of directors has determined that Ms. Thistle is an "audit committee financial expert" as defined by Item 407(d)(5)(ii) of Regulation S-K.

Item 11. Executive Compensation.

This section discusses the material components of our 2020 compensation program for our principal executive officer and next three most highly compensated executive officers who are named in the 2020 Summary Compensation Table below. These "named executive officers" and their positions are:

- Arthur O. Tzianabos, Ph.D., President and Chief Executive Officer;
- Albert Seymour, Ph.D., Chief Scientific Officer; and
- W. Bradford Smith, Chief Financial Officer.

2020 Summary Compensation Table

The following table sets forth information concerning the compensation of our named executive officers for the years ended December 31, 2019 and 2020:

Name and principal position	Fiscal Year	Salary $	Bonus $	Option Awards $ (1)	Non-Equity Incentive Plan Compensation $	All Other Compensation $ (2)	Total $
Arthur O. Tzianabos, Ph.D.	2020	563,200	—	—	309,760	13,000	885,960
President and Chief Executive Officer	2019	537,600	—	4,217,097	295,680	12,500	5,062,877
Albert Seymour, Ph.D.	2020	426,800	—	—	170,720	10,057	607,577
Chief Scientific Officer	2019	405,600	—	1,295,756	162,240	13,231	1,876,827
W. Bradford Smith	2020	406,700	—	—	162,680	13,000	582,380
Chief Financial Officer, Treasurer and Secretary	2019	384,200	—	1,307,536	153,680	14,880	1,860,296

(1) Amounts reflect the full grant date fair value of stock options granted during the applicable year computed in accordance with ASC Topic 718, rather than the amounts paid to or realized by the named individual. We provide information regarding the assumptions used to calculate the value of all option awards in Note 12 to our consolidated financial statements included in this Annual Report on Form 10-K.

(2) Amount shown represents 401(k) matching contributions. For additional information, refer to the discussion below under the heading "Narrative Disclosure to Summary Compensation Table —Retirement Plans."

Narrative Disclosure to Summary Compensation Table

The primary elements of compensation for our named executive officers are base salary, annual performance bonuses and long-term equity-based compensation awards. The named executive officers also generally participate in employee benefit plans and programs that we offer to our other full-time employees on the same basis.

2020 Salaries

The named executive officers receive a base salary to provide a fixed component of compensation reflecting the executive's skill set, experience, role and responsibilities. The following table shows the annual base salaries for 2020 and 2021 of our named executive officers. The 2021 annual base salaries became effective January 1, 2021.

Name	2020 Annual Base Salary ($)	2021 Annual Base Salary ($)
Arthur O. Tzianabos, Ph.D.	563,200	583,100
Albert Seymour, Ph.D.	426,800	450,000
W. Bradford Smith	406,700	445,300

2020 Bonuses

We offer our named executive officers the opportunity to earn annual cash bonuses to compensate them for attaining short-term company and individual goals as approved by our board of directors. For 2020, bonuses were based on attaining corporate goals relating to product development, manufacturing processes, and raising equity capital and individual goals related to each named executive officer's area of responsibility within the Company. The 2020 target bonus amounts, expressed as a percentage of annual base salary, of our named executive officers were 55% for Dr. Tzianabos, 40% for Dr. Seymour and 40% for Mr. Smith.

In December 2020, our board of directors met to review performance against the 2020 bonus goals and, based on its determination that the corporate and individual goals had been achieved at 100% of target level, approved cash bonuses for the named executive officers in the amounts set forth in the Non-Equity Incentive Plan Compensation column of the 2020 "Summary Compensation Table" above.

In December 2020, our board of directors approved maintaining the same target bonus amounts for each of our named executive officers for 2021.

Equity Compensation

We did not make any grants of equity awards to our named executive officers in 2020. However, we typically offer stock options to our employees, including our named executive officers, as the long-term incentive component of our compensation program. Stock options allow our employees to purchase shares of our common stock at a price equal to the fair market value of our common stock on the date of grant, as determined by the board of directors. Initial stock option grants to newly hired employees generally vest as to 25% of the underlying shares on either the first anniversary of the date of grant or a specified vesting commencement date and in equal monthly installments over the following 36 months, subject to the holder's continued service with us. Since 2017, stock options granted from time to time as periodic awards to existing employees generally vest in 48 equal monthly installments on the first day of each calendar month following the vesting commencement date, subject to the holder's continued service with us through the applicable vesting dates. Historically, our stock options have been intended to qualify as "incentive stock options" to the extent permitted under Internal Revenue Code of 1986, as amended, and, prior to the completion of our initial public offering, allowed "early exercise" of an unvested option in exchange for shares of restricted stock subject to the same vesting schedule as the underlying stock option.

We maintain the 2018 Incentive Award Plan to facilitate the grant of cash and equity incentives to directors, employees (including our named executive officers) and consultants of our company and to enable our company to obtain and retain services of these individuals.

Please refer to our Outstanding Equity Awards at 2020 Fiscal Year End table below for additional information regarding the stock options held by our named executive officers.

Retirement Plans

We maintain a 401(k) retirement savings plan for our employees, including our named executive officers, who satisfy certain eligibility requirements. Our named executive officers are eligible to participate in the 401(k) Plan on the same terms as other full-time employees. We provide matching contributions under the plan of 50% of the first 6% of each participant's eligible compensation contributed. Employee contributions are allocated to each participant's individual account and are then invested in selected investment alternatives according to the participants' directions. Employees are immediately and fully

vested in their own contributions. Employer contributions vest over three years according to the employees' years of service. We believe that providing a vehicle for tax deferred retirement savings though our 401(k) Plan adds to the overall desirability of our executive compensation package and further incentivizes our employees, including our named executive officers, in accordance with our compensation policies.

Employee Benefits

Our named executive officers are eligible to participate in our employee benefit plans and programs, which include medical, dental, and vision benefits, health spending accounts, and short- and long-term disability, accidental death and dismemberment, and life insurance, to the same extent as our other full-time employees generally, subject to the terms and eligibility requirements of those plans.

Outstanding Equity Awards at 2020 Fiscal Year-End

The following table summarizes the number of shares of common stock underlying outstanding equity incentive plan awards for each named executive officer as of December 31, 2020.

	Option Awards					
Name	Vesting Commencement Date	Number of Securities Underlying Unexercised Options (#) Exercisable	(1)	Number of Securities Underlying Unexercised Options (#) Unexercisable	(1)	Per Share Option Exercise Price ($)	Option Expiration Date
Arthur O. Tzianabos, Ph.D.	4/1/2016	462,135	(2)	—	(2)	0.47	4/22/2026
	1/1/2018	375,242		139,411		6.63	12/7/2027
	3/27/2018	63,492		28,884		16.00	3/27/2028
	1/1/2019	97,270		105,730		24.28	12/14/2028
	1/1/2020	82,041		275,959		19.92	12/11/2029
Albert Seymour, Ph.D.	1/1/2018	55,702		20,715		6.63	12/7/2027
	3/27/2018	-		4,176		16.00	3/27/2028
	1/1/2019	35,458		38,542		24.28	12/14/2028
	1/1/2020	25,208		84,792		19.92	12/11/2029
W. Bradford Smith	4/5/2017	89,786	(2)	13,618	(2)	0.63	4/6/2027
	1/1/2018	46,283		17,213		6.63	12/7/2027
	3/27/2018	34,155		15,556		16.00	3/27/2028
	1/1/2019	42,166		45,834		24.28	12/14/2028
	1/1/2020	25,437		85,563		19.92	12/11/2029

(1) Except as otherwise described below, stock options have a term of ten years from the grant date and vest and become exercisable in 48 equal monthly installments based upon the executive's completion of each full month of service following the vesting commencement date, subject to the named executive officer's continued employment with the Company through each applicable vesting date and potential accelerated vesting as described under the heading "Employment Agreements" below. In addition, stock options granted to our named executive officers prior to 2018 permitted early exercise in exchange for restricted stock. As a result, all of such options were exercisable as of December 31, 2020. The number of shares for which each such option is shown as being exercisable and unexercisable represents, respectively, the number of shares for which each such option was vested and unvested as of December 31, 2020.

(2) Awards vest as to 25% of the underlying shares on the first anniversary of the specified vesting commencement date and in equal monthly installments over the following 36 months, subject to the named executive officer's continued employment with the Company through each applicable vesting date and potential accelerated vesting as described under the heading "Employment Agreements" below.

Employment Agreements

We have entered into employment agreements with each of our named executive officers. The employment agreements are for unspecified terms. Under their respective employment agreements, if we terminate Dr. Tzianabos, Dr. Seymour or Mr. Smith without "cause" or he resigns for "good reason," subject to his timely executing a release of claims and continued compliance with a separate restrictive covenant agreement, he is entitled to receive (i) base salary continuation for a period of nine months (or, for Dr. Tzianabos, 12 months), (ii) payment of all bonuses earned but unpaid as of the date of termination and (iii) direct payment of or reimbursement for continued medical, dental or vision coverage pursuant to COBRA for up to nine

months (or, for Dr. Tzianabos, 12 months), less the amount he would have had to pay to receive such coverage as an active employee based on the cost sharing levels in effect on his termination date.

If we terminate Dr. Tzianabos, Dr. Seymour or Mr. Smith without "cause" or he resigns for "good reason," in either case, on or within 12 months following a change in control, then, in lieu of the severance benefits described above, subject to his timely executing a release of claims, he is entitled to receive (i) an amount in cash equal to 1.0 times (or, for Dr. Tzianabos, 1.5 times) the sum of his base salary plus target annual bonus for the year of termination, (ii) payment of all bonuses earned but unpaid as of the date of termination, (iii) direct payment of or reimbursement for continued medical, dental or vision coverage pursuant to COBRA for up to 12 months (or, for Dr. Tzianabos, 18 months), less the amount he would have had to pay to receive such coverage as an active employee based on the cost sharing levels in effect on his termination date, and (iv) accelerated vesting of all unvested equity or equity-based awards that vest solely based on the passage of time, with any such awards that vest based on the attainment of performance-vesting conditions being governed by the terms of the applicable award agreement.

Each of our named executive officers has agreed to refrain from competing with us or soliciting our employees, in each case, while employed and following his termination of employment for any reason for a period of 12 months.

For purposes of the employment agreements, "cause" generally means the named executive officer's refusal to substantially perform the duties associated with his position with our company or to carry out the reasonable and lawful instructions of the board of directors concerning duties or actions consistent with his position, his breach of a material provision of the employment agreement which remains uncured (to the extent capable of cure) for a period of 30 days following written notice from our company, his conviction, plea of no contest or nolo contendere or imposition of unadjudicated probation for any felony or crime involving moral turpitude, his unlawful use (including being under the influence) or possession of illegal drugs on our premises or while performing his duties and responsibilities under the employment agreement, or his commission of any act of fraud, embezzlement, misappropriation, willful misconduct, or breach of fiduciary duty against us.

For purposes of the employment agreements, "good reason" generally means, subject to certain cure rights, the named executive officer's termination of employment due to a reduction in salary or target bonus, a material decrease in authority or areas of responsibility, our company's breach of any one or more of the material provisions of the employment agreement, or a relocation by our company of the named executive officer's primary office to a location more than 25 miles from the named executive officer's primary office on the date of the agreement.

Non-Employee Director Compensation

The following table sets forth in summary form information concerning the compensation that was earned by or paid to each of our non-employee directors during the year ended December 31, 2020. Dr. Tzianabos, our Chief Executive Officer, received no compensation for his service as a director during the year ended December 31, 2020.

2020 Director Compensation Table

Name	Fees Earned or Paid in Cash ($)	Option Awards ($)(1)		Total ($)
Steven Gillis, Ph.D.	48,000	164,759	(2)	212,759
Richard J. Gregory, Ph.D.	48,750	164,759	(2)	213,509
Kush M. Parmar, M.D., Ph.D.	85,000	164,759	(2)	249,759
Matthew R. Patterson	47,500	164,759	(2)	212,259
Jeffrey V. Poulton (3)	23,750	342,900	(4)	366,650
Alise S. Reicin, M.D.	44,000	164,759	(2)	208,759
Mary Thistle	55,000	164,759	(2)	219,759

(1) Amounts reflect the grant date fair value of stock options granted during the applicable year computed in accordance with ASC Topic 718, rather than the amounts paid to or realized by the named individual. We provide information regarding the assumptions used to calculate the value of all option awards in Note 12 to our consolidated financial statements included in this Annual Report on Form 10-K.

(2) Represents the grant date fair value of an option to purchase 18,000 shares of our common stock granted to each then-current non-employee director on June 10, 2020 with an exercise price of $16.32 per share.

(3) Mr. Poulton was appointed to our board of directors on July 21, 2020. Mr. Poulton's fees for his board and committee service were prorated as if he had served during the entire second half of 2020.

(4) Represents the grant date fair value of an initial grant of an option to purchase 36,000 shares of our common stock with an exercise price of $16.48 per share granted to Mr. Poulton upon his appointment as a director on July 21, 2020.

The table below shows the aggregate numbers of shares subject to option awards held as of December 31, 2020 by each non-employee director. None of our non-employee directors held any other outstanding equity awards as of December 31, 2020.

	Options Outstanding		
Name	**Exercisable**	**Unexercisable**	**Total**
Steven Gillis, Ph.D.	36,145	28,595	64,740
Richard J. Gregory, Ph.D.	36,145	28,595	64,740
Kush M. Parmar, M.D., Ph.D.	36,145	28,595	64,740
Matthew R. Patterson	38,411	27,279	65,690
Jeffrey V. Poulton (3)	—	36,000	36,000
Alise S. Reicin, M.D.	10,282	38,878	49,160
Mary Thistle	36,145	28,595	64,740

We maintain a compensation program for our non-employee directors under which each non-employee director receives the following amounts for their service on our board of directors. As amended effective January 1, 2020, our non-employee director compensation program provides for the following:

- an option to purchase 36,000 shares of our common stock upon the director's initial election or appointment to our board of directors (the "Initial Award"),
- if the director has served on our board of directors for at least six months as of the date of an annual meeting of stockholders, an option to purchase 18,000 shares of our common stock on the date of the annual meeting (the "Annual Award"),
- an annual director fee of $40,000, and
- if the director serves on a committee of our board of directors or in the other capacities stated below, an additional annual fee as follows:
    - chairman of the board or lead independent director, $35,000,
    - chairman of the audit committee, $15,000,
    - audit committee member other than the chairman, $7,500,
    - chairman of the compensation committee, $10,000,
    - compensation committee member other than the chairman, $5,000,
    - chairman of the nominating and corporate governance committee, $8,000, and
    - nominating and corporate governance committee member other than the chairman, $4,000.

Stock options granted to our non-employee directors under the program have an exercise price equal to the fair market value of our common stock on the date of grant and expire not later than ten years after the date of grant. Stock options granted upon a director's initial election or appointment vest in three equal installments on each of the first three anniversaries of the date of grant. Stock options granted annually to directors vest in a single installment on the earlier of the day before the next annual meeting or the first anniversary of the date of grant. In addition, all unvested stock options vest in full upon the occurrence of a change in control.

Director fees under the program are payable in arrears in four equal quarterly installments not later than the fifteenth day following the final day of each calendar quarter, provided that the amount of each payment is prorated for any portion of a quarter that a director is not serving on our board.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

Equity Compensation Plan Information

The following table provides information on our equity compensation plans as of December 31, 2020.

Plan Category	Number of Securities to be Issued Upon Exercise of Outstanding Options, Warrants and Rights	Weighted-Average Exercise Price of Outstanding Options, Warrants and Rights	Number of Securities Remaining Available for Future Issuance Under Equity Compensation Plans(4)
Equity compensation plans approved by security holders (1)	5,840,824 (2)	$ 15.18 (3)	3,437,197
Equity compensation plans not approved by security holders	—	—	—
Total	5,840,824	$ 15.18	3,437,197

(1) Consists of the 2015 Stock Incentive Plan, as amended (the "2015 Plan"), the 2018 Incentive Award Plan (the "2018 Plan") and the 2018 Employee Stock Purchase Plan (the "2018 ESPP").

(2) Includes 1,661,468 outstanding options to purchase stock under the 2015 Plan and 4,179,356 outstanding options to purchase stock under the 2018 Plan.

(3) As of December 31, 2020, the weighted-average exercise price of outstanding options under the 2015 Plan was $3.95 and the weighted-average exercise price of outstanding options under the 2018 Plan was $19.65.

(4) Includes 2,397,547 shares available for future issuance under the 2018 Plan and 1,039,650 shares available for issuance under the 2018 ESPP (of which 48,792 shares were issued with respect to the purchase period in effect as of December 31, 2020, which purchase period ended on February 26, 2021). As of March 26, 2018, in connection with our initial public offering, no further grants are made under the 2015 Plan. The 2018 Plan provides for an annual increase on the first day of each calendar year beginning on January 1, 2019 and ending on and including January 1, 2028, by an amount equal to the lesser of (i) 4% of the aggregate number of shares of common stock outstanding on the final day of the immediately preceding calendar year and (ii) such smaller number of shares of common stock as determined by our board of directors (but no more than 20,887,347 shares may be issued upon the exercise of incentive stock options), plus any shares that were subject to awards outstanding under the 2015 Plan as of the effective date of the 2018 Plan which are forfeited, expire, lapse for any reason or are settled for cash without the issuance of shares. The 2018 ESPP provides for an annual increase on the first day of each calendar year beginning on January 1, 2019 and ending on and including January 1, 2028, by an amount equal to the lesser of (i) 1% of the aggregate number of shares of common stock outstanding on the final day of the immediately preceding calendar year and (ii) such smaller number of shares of common stock as is determined by our board of directors, provided that no more than 4,778,738 shares of our common stock may be issued under the 2018 ESPP.

Security Ownership of Certain Beneficial Owners and Management

The following table sets forth certain information with respect to holdings of our common stock by (i) stockholders who beneficially owned more than 5% of the outstanding shares of our common stock, and (ii) each of our directors (which includes all nominees), each of our named executive officers and all directors and executive officers as a group as of March 1, 2021, unless otherwise indicated. The number of shares beneficially owned by each stockholder is determined under rules issued by the SEC. Under these rules, beneficial ownership includes any shares as to which a person has sole or shared voting power or investment power. Applicable percentage ownership is based on 50,482,124 shares of common stock outstanding as of March 1, 2021. In computing the number of shares beneficially owned by a person and the percentage ownership of that person, shares of common stock subject to options, warrants or other rights held by such person that are currently exercisable or will become exercisable within 60 days of March 1, 2021 are considered outstanding, although these shares are not considered outstanding for purposes of computing the percentage ownership of any other person.

Unless otherwise indicated, the address of each beneficial owner listed below is One Patriots Park, Bedford, MA 01730. We believe, based on information provided to us that each of the stockholders listed below has sole voting and investment power with respect to the shares beneficially owned by the stockholder unless noted otherwise, subject to community property laws where applicable.

Name of Beneficial Owner	Number of Shares Beneficially Owned	Percentage
5% or Greater Stockholders		
Entities affiliated with ARCH Venture Fund (1)	5,768,694	11.4%
Pfizer Inc. (2)	5,000,000	9.9%
Entities affiliated with 5AM Ventures (3)	4,535,919	9.0%
JPMorgan Chase & Co. (4)	3,441,712	6.8%
TLS Beta Pte. Ltd. (5)	3,220,293	6.4%
BlackRock, Inc. (6)	2,763,142	5.5%
Named Executive Officers and Directors		
Arthur O. Tzianabos, Ph.D. (7)	1,255,023	2.4%
Albert Seymour, Ph.D. (8)	318,335	*
W. Bradford Smith (9)	263,965	*
Steven Gillis, Ph.D. (1)(10)	5,815,434	11.5%
Richard J. Gregory, Ph.D. (11)	57,546	*
Kush M. Parmar, M.D., Ph.D. (3)(12)	4,582,659	9.1%
Matthew R. Patterson (13)	43,234	*
Jeffrey V. Poulton	—	*
Alise S. Reicin, M.D. (14)	10,282	*
Mary Thistle (15)	46,740	*
All executive officers and directors as a group (12 persons) (16)	**12,650,058**	**24.0%**

*Less than 1%

(1) Based on a Schedule 13G filed with the SEC on February 13, 2020 and the Company's records. Consists of 4,631,031 shares of common stock held by ARCH Venture Fund VIII, L.P. (“ARCH Fund VIII”) and 1,137,663 shares of common stock held by ARCH Venture Fund VIII Overage, L.P. (“ARCH Fund Overage”). The sole general partner of ARCH Fund VIII is ARCH Venture Partners VIII, L.P. (“ARCH Partners VIII”), which may be deemed to beneficially own the shares held by ARCH Fund VIII. The sole general partner of ARCH Partners VIII and ARCH Fund Overage is ARCH Venture Partners VIII, LLC (“ARCH VIII LLC”), which has shared voting and dispositive power over the shares of common stock held by each of ARCH Fund VIII and ARCH Fund Overage. ARCH Partners VIII and ARCH VIII LLC disclaim beneficial ownership of such shares, except to the extent of any pecuniary interest therein. The managing directors of ARCH VIII LLC are Keith L. Crandell, Clinton Bybee and Robert Nelsen, and they may be deemed to have shared voting and dispositive power over the shares of common stock held by ARCH Fund VIII and ARCH Fund Overage. Messrs. Crandell, Bybee and Nelsen disclaim beneficial ownership of such shares, except to the extent of any pecuniary interest therein. Steven Gillis, M.D., Ph.D., one of our directors, is a managing director at ARCH Venture Partners. Director Steven Gillis owns an interest in ARCH Partners VIII but does not have voting or investment control over the shares held by ARCH Fund VIII, and disclaims beneficial ownership of such shares, except to the extent of any pecuniary interest therein. The address of ARCH Fund VIII and ARCH Fund Overage is 8755 West Higgins Road, Suite 1025, Chicago, Illinois 60631.

(2) Based on a Schedule 13G filed with the SEC on November 19, 2020, Pfizer Inc. has sole voting and dispositive power over all 5,000,000 shares. The address of Pfizer Inc. is 235 East 42nd Street, New York, NY 10017.

(3) Based on a Schedule 13G filed with the SEC on February 16, 2021 and the Company's records. Consists of 4,354,484 shares of common stock held by 5AM Ventures IV, L.P. (“Ventures IV”), as to which Ventures IV has shared voting and dispositive power, and 181,435 shares of common stock held by 5AM Co-Investors IV, L.P. (“Co-Investors IV”), as to which Co-Investors IV has shared voting and dispositive power. 5AM Partners IV, LLC (“Partners IV”) is the sole general partner of Ventures IV and Co-Investors IV. Dr. John Diekman, Andrew J. Schwab and Dr. Scott M. Rocklage, are the managing members of Partners IV and, along with Partners IV, have shared voting and investment power over the shares beneficially owned by Ventures IV and Co-Investors IV. Kush M. Parmar, M.D., Ph.D., one of our directors, is an

affiliate of Ventures IV. Each of Partners IV, Dr. Diekman, Mr. Schwab and Dr. Rocklage disclaim beneficial ownership of such shares except to the extent of its or their recurring interest therein. The address of all entities affiliated with 5AM Ventures is 501 2nd Street, Suite 350, San Francisco, CA 94107.

(4) Based solely on a Schedule 13G filed with the SEC on January 25, 2021, JPMorgan Chase & Co. has sole voting power over 3,054,192 shares and sole dispositive power over 3,441,712 shares. The address of Blackrock, Inc. is 383 Madison Avenue, New York, NY 10179.

(5) Based solely on a Schedule 13G filed with the SEC on April 11, 2018, Temasek Holdings (Private) Limited, Fullerton Management Pte Ltd and Temasek Life Sciences Private Limited each has shared voting and dispositive power over 3,220,293 shares of common stock, V-Sciences Investments Pte Ltd has shared voting and dispositive power over 625,000 shares of common stock, and TLS Beta Pte. Ltd. has shared voting and dispositive power over 2,595,293 shares of common stock. The principal business address of Temasek Holdings (Private) Limited, Fullerton Management Pte Ltd, Temasek Life Sciences Private Limited, V-Sciences Investments Pte Ltd and TLS Beta Pte. Ltd. is 60B Orchard Road #06-18 Tower 2, The Atrium@Orchard, Singapore 238891.

(6) Based solely on a Schedule 13G filed with the SEC on February 2, 2021, Blackrock, Inc. has sole voting power over 2,724,076 shares and sole dispositive power over 2,763,142 shares. The address of Blackrock, Inc. is 55 East 52nd Street, New York, NY 10055.

(7) Includes options to purchase 1,177,518 shares of common stock that are or will be immediately exercisable by Dr. Tzianabos within 60 days of March 1, 2021.

(8) Includes options to purchase 189,318 shares of common stock that are or will be immediately exercisable by Dr. Seymour within 60 days of March 1, 2021.

(9) Consists of options to purchase 263,965 shares of common stock that are or will be immediately exercisable by Mr. Smith within 60 days of March 1, 2021.

(10) Includes options to purchase 46,740 shares of common stock that are or will be immediately exercisable by Dr. Gillis within 60 days of March 1, 2021.

(11) Includes options to purchase 46,740 shares of common stock that are or will be immediately exercisable by Dr. Gregory within 60 days of March 1, 2021.

(12) Includes options to purchase 46,740 shares of common stock that are or will be immediately exercisable by Dr. Parmar within 60 days of March 1, 2021.

(13) Consists of options to purchase 43,234 shares of common stock that are or will be immediately exercisable by Mr. Patterson within 60 days of March 1, 2021.

(14) Consists of options to purchase 10,282 shares of common stock that are or will be immediately exercisable by Ms. Reicin within 60 days of March 1, 2021.

(15) Consists of options to purchase 46,740 shares of common stock that are or will be immediately exercisable by Ms. Thistle within 60 days of March 1, 2021.

(16) Includes options to purchase 12,650,058 shares of common stock that are or will be immediately exercisable within 60 days of March 1, 2021.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

Policies and Procedures for Related Person Transactions

Our board of directors has adopted a written Related Person Transaction Policy, setting forth the policies and procedures for the review and approval or ratification of related person transactions. Under the policy, our finance department is primarily responsible for developing and implementing processes and procedures to obtain information regarding related persons with respect to potential related person transactions and then determining, based on the facts and circumstances, whether such potential related person transactions do, in fact, constitute related person transactions requiring compliance with the policy. If

our finance department determines that a transaction or relationship is a related person transaction requiring compliance with the policy, our Chief Financial Officer is required to present to the audit committee all relevant facts and circumstances relating to the related person transaction. Our audit committee must review the relevant facts and circumstances of each related person transaction, including if the transaction is on terms comparable to those that could be obtained in arm's length dealings with an unrelated third party and the extent of the related person's interest in the transaction, take into account the conflicts of interest and corporate opportunity provisions of our code of business conduct and ethics, and either approve or disapprove the related person transaction. If advance audit committee approval of a related person transaction requiring the audit committee's approval is not feasible, then the transaction may be preliminarily entered into by management upon prior approval of the transaction by the chair of the audit committee subject to ratification of the transaction by the audit committee at the audit committee's next regularly scheduled meeting; provided, that if ratification is not forthcoming, management will make all reasonable efforts to cancel or annul the transaction. If a transaction was not initially recognized as a related person, then upon such recognition the transaction will be presented to the audit committee for ratification at the audit committee's next regularly scheduled meeting; provided, that if ratification is not forthcoming, management will make all reasonable efforts to cancel or annul the transaction. Our management will update the audit committee as to any material changes to any approved or ratified related person transaction and will provide a status report at least annually of all then current related person transactions. No director may participate in approval of a related person transaction for which he or she is a related person.

The following are certain transactions, arrangements and relationships with our directors, executive officers and stockholders owning 5% or more of our outstanding common stock since January 1, 2019.

Stock Purchase Agreement with Pfizer

On November 9, 2020, we entered into a stock purchase agreement, or the Stock Purchase Agreement, with Pfizer Inc., or Pfizer, which holds approximately 9.9% of our common stock as of March 1, 2021, pursuant to which Pfizer purchased 5,000,000 shares of our common stock through a private placement transaction at a purchase price of $12.00 per share, for an aggregate purchase price of $60.0 million. Under the Stock Purchase Agreement, Pfizer was granted an exclusive right of first refusal, or ROFR, for a 30-month period beginning on the date of the closing of the private placement to negotiate a potential collaboration on the development and commercialization of HMI-102 and HMI-103. Pfizer may exercise its right of first refusal under the ROFR one time for each of HMI-102 and HMI-103 during the ROFR period. Additionally, Pfizer has designated a member to join our Scientific Advisory Board to participate in matters related to the development of these programs. For more information regarding Pfizer and its equity holdings, see Part III, Item 12. “Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters—Security Ownership of Certain Beneficial Owners and Management.”

2019 Follow-On Offering

In April 2019, we completed a registered public offering pursuant to which we issued and sold an aggregate of 6,388,889 shares of our common stock (including 833,333 shares sold pursuant to the underwriters’ full exercise of their option to purchase additional shares) at a public offering price of $22.50 per share for aggregate net proceeds to us of approximately $134.5 million. The following table sets forth the number of shares of common stock purchased in our registered public offering by certain former holders of more than 5% of our common stock:

Name	Shares of Common Stock Purchased		Total Purchase Price
Entities affiliated with Deerfield (affiliate of Cameron Wheeler, Ph.D., who resigned from our board of directors in July 2019)	533,333	$	11,999,993
Entities affiliated with T. Rowe Price Group, Inc.	719,464	$	16,187,940

Employment Agreements

We have entered into employment agreements with our named executive officers. For more information regarding these agreements, see Item 11. “Executive Compensation—Narrative Disclosure to Compensation Tables—Employment Agreements.”

Indemnification Agreements

We have entered into indemnification agreements with each of our directors and executive officers. These agreements, among other things, require us or will require us to indemnify each director (and in certain cases their related venture capital funds) and executive officer to the fullest extent permitted by Delaware law, including indemnification of expenses such as

attorneys' fees, judgments, fines and settlement amounts incurred by the director or executive 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 executive officer.

Director Independence

Steven Gillis, Ph.D., Richard J. Gregory, Ph.D., Kush M. Parmar, M.D., Ph.D., Matthew R. Patterson, Alise S. Reicin, M.D., Jeffrey V. Poulton and Mary Thistle each qualify as "independent" in accordance with the listing requirements of Nasdaq. The Nasdaq independence definition includes a series of objective tests, including that the director is not, and has not been for at least three years, one of our employees and that neither the director nor any of his family members has engaged in various types of business dealings with us. In addition, as required by Nasdaq rules, our board of directors has made a subjective determination as to each independent director that no relationships exist, which, in the opinion of our board of directors, would interfere with the exercise of independent judgment in carrying out the responsibilities of a director. In making these determinations, our board of directors reviewed and discussed information provided by the directors and us with regard to each director's business and personal activities and relationships as they may relate to us and our management, including that Dr. Gillis and Dr. Parmar are affiliated with certain of our significant stockholders. Arthur O. Tzianabos, Ph.D. is not independent because he is the President and Chief Executive Officer of Homology. There are no family relationships among any of our directors or executive officers.

Item 14. Principal Accountant Fees and Services.

The following table summarizes the fees of Deloitte & Touche LLP, our independent registered public accounting firm, billed to us in each of the last two fiscal years for audit services and billed to us in each of the last two fiscal years for other services:

Fee Category	2020	2019
	(in thousands)	
Audit Fees	$ 598	$ 602
Tax Fees	20	13
All Other Fees	2	28
Total	$ 620	$ 643

Audit Fees

Audit fees consist of fees for the audit of our consolidated financial statements, the review of the unaudited interim financial statements included in our quarterly reports on Form 10-Q and other professional services provided in connection with statutory and regulatory filings or engagements and services associated with the issuance of comfort letters and the issuance of consents on registration statements.

Tax Fees

Tax fees consist of fees for tax compliance, tax advice, and tax planning services.

All Other Fees

All other fees consist of an annual license fee for use of accounting research software and in 2019, fees for services performed related to the adoption the Financial Accounting Standards Board issued Accounting Standards Update Topic 606, *Revenue from Contracts with Customers*.

Audit Committee Pre-Approval Policy and Procedures

The Audit Committee has adopted a policy (the "Pre-Approval Policy") that sets forth the procedures and conditions pursuant to which audit and non-audit services proposed to be performed by the independent auditor may be pre-approved. The Pre-Approval Policy generally provides that we will not engage Deloitte & Touche LLP to render any audit, audit-related, tax or permissible non-audit service unless the service is either (i) explicitly approved by the Audit Committee ("specific pre-approval") or (ii) entered into pursuant to the pre-approval policies and procedures described in the Pre-Approval Policy ("general pre-approval"). Unless a type of service to be provided by Deloitte & Touche LLP has received general pre-approval under the Pre-Approval Policy, it requires specific pre-approval by the Audit Committee or by a designated member of the Audit Committee to whom the committee has delegated the authority to grant pre-approvals. Any proposed services exceeding pre-approved cost levels or budgeted amounts will also require specific pre-approval. For both types of pre-approval, the Audit Committee will consider whether such services are consistent with the SEC's rules on auditor independence. The Audit Committee will also consider whether the independent auditor is best positioned to provide the most effective and efficient service, for reasons such as its familiarity with the Company's business, people, culture, accounting systems, risk profile and other factors, and whether the service might enhance the Company's ability to manage or control risk or improve audit quality. All such factors will be considered as a whole, and no one factor should necessarily be determinative. On an annual basis, the Audit Committee reviews and generally pre-approves the services (and related fee levels or budgeted amounts) that may be provided by Deloitte & Touche LLP without first obtaining specific pre-approval from the Audit Committee. The Audit Committee may revise the list of general pre-approved services from time to time, based on subsequent determinations.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Financial Statements.

The following documents are included on pages F-1 through F-26 attached hereto and are filed as part of this Annual Report on Form 10-K.

Index to Consolidated Financial Statements

(a)(2) Financial Statement Schedules.

All financial statement schedules have been omitted because they are not applicable, not required or the information required is shown in the financial statements or the notes thereto.

(a)(3) Exhibits.

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

		Incorporated by Reference				
Exhibit Number	Description of Exhibit	Form	File No.	Exhibit	Filing date	Filed Herewith
3.1	Restated Certificate of Incorporation of Homology Medicines, Inc.	8-K	001-38433	3.1	4/3/18	
3.2	Amended and Restated Bylaws of Homology Medicines, Inc.	8-K	001-38433	3.1	12/18/20	
4.1	Amended and Restated Investors' Rights Agreement, dated July 28, 2017, by and among Homology Medicines, Inc. and the investors named therein, as amended	10-Q	001-38433	4.1	11/09/20	
4.2	Specimen Stock Certificate evidencing the shares of common stock	S-1/A	333-223409	4.2	3/19/18	
4.3	Form of Indenture	S-3	333-230664	4.3	4/1/19	
4.4	Description of Securities					*
10.1#	2015 Stock Incentive Plan, as amended, and forms of agreements thereunder	S-1/A	333-223409	10.1	3/19/18	
10.2#	2018 Incentive Award Plan, and forms of awards thereunder					*
10.3#	2018 Employee Stock Purchase Plan	S-1/A	333-223409	10.3	3/19/18	
10.4#	2018 Employee Stock Purchase Plan – Offering Document	10-Q	001-38433	10.1	11/13/18	
10.5#	Non-Employee Director Compensation Program	10-K	001-38433	10.5	3/12/20	
10.6#	Form of Indemnification Agreement for Directors and Officers	S-1/A	333-223409	10.5	3/19/18	
10.7	Lease Agreement, dated August 31, 2016, between Homology Medicines, Inc. and ARE-MA Region No. 24, LLC	S-1	333-223409	10.5	3/2/18	
10.8	Lease Agreement, dated December 21, 2017, between Homology Medicines, Inc. and Bedford Patriots Park, LLC	S-1	333-223409	10.6	3/2/18	

10.9#	Employment Agreement, November 12, 2019, by and between Homology Medicines, Inc. and Gabriel M. Cohn, M.D.	10-K	001-38433	10.9	3/12/20	
10.10#	Employment Agreement, dated March 18, 2018, by and between Homology Medicines, Inc. and Albert Seymour	S-1/A	333-223409	10.12	3/19/18	
10.11#	Employment Agreement, dated March 18, 2018, by and between Homology Medicines, Inc. and Bradford Smith	S-1/A	333-223409	10.13	3/19/18	
10.12#	Employment Agreement, dated March 18, 2018, by and between Homology Medicines, Inc. and Arthur Tzianabos, Ph.D.	S-1/A	333-223409	10.14	3/19/18	
10.13#	Employment Agreement, dated April 2, 2018, by and between Homology Medicines, Inc. and Tim Kelly	10-K	001-38433	10.13	3/12/19	
10.14.1†	Collaboration and License Agreement, dated November 6, 2017, between Homology Medicines, Inc. and Novartis Institutes for BioMedical Research, Inc.	S-1/A	333-223409	10.15	3/23/18	
10.14.2†	Amendment to Collaboration and License Agreement, dated December 17, 2018, between Homology Medicines, Inc. and Novartis Institutes for BioMedical Research, Inc.	10-Q	001-38433	10.1	08/10/20	
10.14.3†	Second Amendment to Collaboration and License Agreement, dated October 30, 2020, between Homology Medicines, Inc. and Novartis Institutes for BioMedical Research, Inc.	10-Q	001-38433	10.1	11/09/20	
10.15†	Exclusive License Agreement, dated April 28, 2016, between Homology Medicines, Inc. and City of Hope	S-1/A	333-223409	10.16	3/19/18	
10.16.1†	License Agreement, dated September 14, 2016, between Homology Medicines, Inc. and California Institute of Technology	S-1/A	333-223409	10.17.1	3/19/18	
10.16.2†	First Amendment to License Agreement, dated May 16, 2017, between Homology Medicines, Inc. and California Institute of Technology	S-1	333-223409	10.16.2	3/2/18	
10.16.3†	Letter Agreement, dated November 14, 2017, between Homology Medicines, Inc. and California Institute of Technology	S-1	333-223409	10.16.3	3/2/18	
10.17†	Stock Purchase Agreement, dated November 9, 2020, by and between Homology Medicines, Inc. and Pfizer Inc.	8-K	001-38433	10.1	11/09/20	
21.1	Subsidiaries of Homology Medicines, Inc.	S-1	333-223409	21.1	3/2/18	
23.1	Consent of Deloitte & Touche LLP, independent registered public accountant					*
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002					*
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002					*
32.1	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					**
32.2	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					**
101.INS	Inline XBRL Instance Document – the Instance Document does not appear in the interactive data file because its XBRL tags are embedded within the Inline XBRL document					*
101.SCH	Inline XBRL Taxonomy Extension Schema Document					*
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					*
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					*

101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document	*
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document	*
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)	*

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* Filed herewith

** Furnished herewith

# Indicates management contract or compensatory plan.

† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment.

Item 16. Form 10-K Summary.

None.

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**.**

Homology Medicines, Inc.

Date: March 11, 2021

By: /s/ Arthur O. Tzianabos, Ph.D.
Arthur O. Tzianabos, Ph.D.
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Arthur O. Tzianabos, Ph.D. **Arthur O. Tzianabos, Ph.D.**	President, Chief Executive Officer and Director *(principal executive officer)*	March 11, 2021
/s/ W. Bradford Smith **W. Bradford Smith**	Chief Financial Officer, Treasurer and Secretary *(principal financial and accounting officer)*	March 11, 2021
/s/ Kush M. Parmar, M.D., Ph.D. **Kush M. Parmar, M.D., Ph.D.**	Chairman of the Board of Directors	March 11, 2021
/s/ Steven Gillis, Ph.D. **Steven Gillis, Ph.D.**	Director	March 11, 2021
/s/ Richard J. Gregory, Ph.D. **Richard J. Gregory, Ph.D.**	Director	March 11, 2021
/s/ Matthew R. Patterson **Matthew R. Patterson**	Director	March 11, 2021
/s/ Jeffrey V. Poulton **Jeffrey V. Poulton**	Director	March 11, 2021
/s/ Alise S. Reicin, M.D. **Alise S. Reicin, M.D.**	Director	March 11, 2021
/s/ Mary Thistle **Mary Thistle**	Director	March 11, 2021

HOMOLOGY MEDICINES, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the stockholders and the Board of Directors of Homology Medicines, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Homology Medicines, Inc. and its subsidiary (the "Company") as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows, for the years then ended, 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 2019, and the results of its operations and its cash flows for the years then ended, in conformity with accounting principles generally accepted in the United States of America.

Change in Accounting Principle

As discussed in Note 2 to the financial statements, the Company changed its method of accounting for leases in 2020 due to the adoption of Accounting Standards update No. 2016-02, *Leases* (Topic 842), as amended, using the modified retrospective approach.

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 audits. 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 audits 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 audits, 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 audits 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 audits provide a reasonable basis for our opinion.

/s/ Deloitte & Touche LLP

Boston, Massachusetts
March 11, 2021

We have served as the Company's auditor since 2017.

HOMOLOGY MEDICINES, INC.

CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share amounts)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 217,431	$ 53,774
Short-term investments	—	208,614
Prepaid expenses and other current assets	2,133	4,189
Total current assets	219,564	266,577
Property and equipment, net	37,002	42,716
Right-of-use assets	5,897	—
Restricted cash	1,274	1,274
Total assets	$ 263,737	$ 310,567
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,722	$ 2,608
Accrued expenses and other liabilities	9,803	7,644
Operating lease liabilities	2,501	—
Deferred rent	—	1,313
Deferred revenue	5,632	809
Total current liabilities	22,658	12,374
Non-current liabilities:		
Operating lease liabilities, net of current portion	12,941	—
Deferred rent, net of current portion	—	9,544
Deferred revenue, net of current portion	32,143	30,142
Total liabilities	67,742	52,060
Stockholders' equity:		
Preferred stock, $0.0001 par value, 10,000,000 shares authorized as of December 31, 2020 and 2019, respectively; no shares issued and outstanding at December 31, 2020 and 2019, respectively	—	—
Common stock, $0.0001 par value; 200,000,000 shares authorized as of December 31, 2020 and 2019, respectively; 50,268,666 and 45,138,408 shares issued as of December 31, 2020 and 2019, respectively; and 50,265,575 and 45,116,742 shares outstanding as of December 31, 2020 and 2019, respectively	5	4
Additional paid-in capital	524,358	457,994
Accumulated other comprehensive gain	—	183
Accumulated deficit	(328,368)	(199,674)
Total stockholders' equity	195,995	258,507
Total liabilities and stockholders' equity	$ 263,737	$ 310,567

See notes to consolidated financial statements.

HOMOLOGY MEDICINES, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except share and per share amounts)

	For the Years Ended December 31,	
	2020	2019
Collaboration revenue	$ 2,702	$ 1,666
Operating expenses:		
Research and development	100,392	89,398
General and administrative	32,573	22,211
Total operating expenses	132,965	111,609
Loss from operations	(130,263)	(109,943)
Other income:		
Interest income	1,569	6,027
Total other income	1,569	6,027
Net loss	$ (128,694)	$ (103,916)
Net loss per share-basic and diluted	$ (2.80)	$ (2.47)
Weighted average common shares outstanding-basic and diluted	45,910,787	42,117,690

See notes to consolidated financial statements.

HOMOLOGY MEDICINES, INC.

CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)

	For the Years Ended December 31,	
	2020	2019
Net loss	$ (128,694)	$ (103,916)
Other comprehensive gain (loss):		
Change in unrealized gain (loss) on available for sale securities, net	(183)	260
Total other comprehensive gain (loss)	(183)	260
Comprehensive loss	$ (128,877)	$ (103,656)

See notes to consolidated financial statements.

HOMOLOGY MEDICINES, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands, except share and per share amounts)

	Common Stock $0.0001 Par Value		Additional Paid-in Capital	Accumulated Other Comprehensive Gain (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at January 1, 2019	37,358,526	$ 3	$ 292,187	$ (77)	$ (95,758)	$ 196,355
Issuance of common stock in follow-on offering, net of discounts and issuance costs	6,388,889	1	134,523	—	—	134,524
Issuance of common stock pursuant to ATM financing, net of discounts and issuance costs	1,105,000	—	22,409	—	—	22,409
Issuance of common stock pursuant to employee stock purchase plan	55,234	—	829	—	—	829
Vesting of common stock from option exercises	94,816	—	60	—	—	60
Issuance of common stock from option exercises	114,277	—	351	—	—	351
Stock-based compensation	—	—	7,635	—	—	7,635
Other comprehensive gain	—	—	—	260	—	260
Net loss	—	—	—	—	(103,916)	(103,916)
Balance at December 31, 2019	45,116,742	$ 4	$ 457,994	$ 183	$ (199,674)	$ 258,507
Vesting of common stock from option exercises	18,575	—	24	—	—	24
Issuance of common stock from option exercises	46,410	—	176	—	—	176
Issuance of common stock pursuant to employee stock purchase plan	83,848	—	938	—	—	938
Issuance of common stock pursuant to private placement	5,000,000	1	51,978	—	—	51,979
Stock-based compensation	—	—	13,248	—	—	13,248
Other comprehensive loss	—	—	—	(183)	—	(183)
Net loss	—	—	—	—	(128,694)	(128,694)
Balance at December 31, 2020	50,265,575	$ 5	$ 524,358	$ —	$ (328,368)	$ 195,995

See notes to consolidated financial statements.

HOMOLOGY MEDICINES, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	For the Years Ended December 31,	
	2020	**2019**
Cash flows from operating activities:		
Net loss	$ (128,694)	$ (103,916)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	7,965	6,318
Noncash lease expense	939	—
Stock-based compensation expense	13,248	7,635
Accretion of short-term investments	(198)	(1,871)
Loss on disposal of property and equipment	888	13
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	2,056	2,759
Accounts payable	2,459	(4,452)
Accrued expenses and other liabilities	2,432	2,315
Deferred revenue	6,824	(569)
Deferred rent	—	410
Operating lease liabilities	(2,251)	—
Net cash used in operating activities	(94,332)	(91,358)
Cash flows from investing activities:		
Purchases of short-term investments	(19,991)	(286,391)
Maturities of short-term investments	228,620	256,425
Purchases of property and equipment	(3,733)	(21,833)
Net cash provided by (used in) investing activities	204,896	(51,799)
Cash flows from financing activities:		
Proceeds from issuance of common stock in private placement	51,979	—
Proceeds from issuance of common stock in follow-on public offering, net of discounts and issuance costs	—	134,524
Proceeds from issuance of common stock pursuant to ATM financing, net of discounts and issuance costs	—	22,509
Proceeds from issuance of common stock from option exercises	176	351
Proceeds from issuance of common stock pursuant to employee stock purchase plan	938	829
Net cash provided by financing activities	53,093	158,213
Net change in cash, cash equivalents and restricted cash	163,657	15,056
Cash, cash equivalents and restricted cash, beginning of period	55,048	39,992
Cash, cash equivalents and restricted cash, end of period	$ 218,705	$ 55,048
Supplemental disclosures of noncash investing and financing activities:		
Reclassification of liability for common stock vested	$ 24	$ 60
Property and equipment additions included in accounts payable	$ 110	$ 455
Property and equipment additions included in accrued expenses and other liabilities	$ —	$ 249
Unrealized (loss) gain on available for sale securities, net	$ (183)	$ 260
Offering costs included in accrued expenses and other liabilities	$ —	$ 100

See notes to consolidated financial statements.

1. NATURE OF BUSINESS AND BASIS OF PRESENTATION

Nature of Business—Homology Medicines, Inc. (the "Company") is a clinical-stage genetic medicines company dedicated to translating proprietary gene therapy and gene editing technology into novel treatments for patients with rare genetic diseases with significant unmet medical needs by curing the underlying cause of the disease. The Company was founded in March 2015 as a Delaware corporation. Its principal offices are in Bedford, Massachusetts.

Since its inception, the Company has devoted substantially all of its resources to recruiting personnel, developing its technology platform and advancing its pipeline of product candidates, developing and implementing manufacturing processes, building out internal manufacturing and research and development space, and maintaining and building its intellectual property portfolio. The Company is subject to a number of risks similar to those of other companies conducting high-risk, early-stage research and development of product candidates. Principal among these risks are dependency on key individuals and intellectual property, competition from other products and companies, and the technical risks associated with the successful research, development and manufacturing of its product candidates. The Company's success is dependent upon its ability to continue to raise additional capital in order to fund ongoing research and development, conduct clinical trials, obtain regulatory approval of its products, further expand its manufacturing capacity, successfully commercialize its products, generate revenue, meet its obligations, and, ultimately, attain profitable operations.

On April 2, 2018, the Company completed its initial public offering ("IPO") with the sale of 10,350,000 shares of its common stock, including shares issued upon the exercise in full of the underwriters' over-allotment option, at a public offering price of $16.00 per share, resulting in net proceeds of $150.8 million, after deducting underwriting discounts and commissions and offering expenses. Upon the closing of the IPO, all of the Company's outstanding shares of convertible preferred stock automatically converted into 24,168,656 shares of common stock at the applicable conversion ratio then in effect.

On April 12, 2019, the Company completed a follow-on public offering of its common stock. The Company sold 5,555,556 shares of its common stock at a public offering price of $22.50 per share and received net proceeds of $116.9 million, after deducting underwriting discounts and commissions and offering expenses. In addition, on April 26, 2019 and May 7, 2019, in connection with the exercise in full of the underwriters' option to purchase additional shares, the Company issued an aggregate of 833,333 shares of its common stock at a public offering price of $22.50 per share and received net proceeds of $17.6 million, after deducting underwriting discounts and commissions.

On March 12, 2020, the Company filed a Registration Statement on Form S-3 (File No. 333-237131) (the "Shelf") with the Securities and Exchange Commission ("SEC") in relation to the registration of common stock, preferred stock, debt securities, warrants and/or units of any combination thereof for a period up to three years from the date of the filing. The Shelf became effective on March 12, 2020. The Company also simultaneously entered into a sales agreement with Cowen and Company, LLC ("Cowen"), as sales agent, providing for the offering, issuance and sale by the Company of up to an aggregate $150.0 million of its common stock from time to time in "at-the-market" offerings under the Shelf (the "ATM"). The Company did not sell any shares of common stock pursuant to the ATM during the year ended December 31, 2020. At December 31, 2020, there remained $150.0 million of common stock available for sale under the ATM. Simultaneous with the filing of the Shelf, the previous Registration Statement on Form S-3 (File No. 333-230664) filed with the SEC on April 1, 2019, and a prior sales agreement with Cowen providing for the offering, issuance and sale by the Company of up to an aggregate $100.0 million of its common stock from time to time in "at-the-market" offerings, with $76.8 million of remaining capacity, were terminated.

On November 9, 2020, the Company entered into a common stock purchase agreement (the "Stock Purchase Agreement") with Pfizer Inc. ("Pfizer"), pursuant to which the Company agreed to issue and sell to Pfizer 5,000,000 shares of the Company's common stock through a private placement transaction (the "Private Placement") at a purchase price of $12.00 per share, for an aggregate purchase price of $60.0 million (see Note 16).

To date, the Company has not generated any revenue from product sales and does not expect to generate any revenue from the sale of product in the foreseeable future. Through December 31, 2020, the Company has financed its operations primarily through public offerings of its common stock, the issuance of convertible preferred stock, and with proceeds from its collaboration and license agreement with Novartis Institutes of BioMedical Research, Inc. ("Novartis") (see Note 15) and its private placement with Pfizer. During the year ended December 31, 2020, the Company incurred a net loss of $128.7 million and as of December 31, 2020, had $328.4 million in accumulated deficit. The Company expects to incur additional operating losses and negative operating cash flows for the foreseeable future.

Based on current projections, management believes that existing cash and cash equivalents will enable the Company to continue its operations into the third quarter of 2022. In the absence of a significant source of recurring revenue, the continued viability of the Company beyond that point is dependent on its ability to continue to raise additional capital to finance its operations. There can be no assurance that the Company will be able to obtain sufficient capital to cover its costs on acceptable terms, if at all.

Basis of Presentation—The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("U.S. GAAP") and have been prepared on a going concern basis, which contemplates the realization of assets and the satisfaction of liabilities in the normal course of business.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Principles of Consolidation—The Company's consolidated financial statements include the accounts of the Company and its subsidiary, Homology Medicines Securities Corporation, a wholly owned Massachusetts corporation, for the sole purpose of buying, selling, and holding securities on the Company's behalf. All intercompany balances and transactions have been eliminated in the consolidated financial statements.

Use of Estimates—The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue, and expenses, and the disclosure of contingent assets and liabilities as of and during the reporting period. The Company bases its estimates and assumptions on historical experience when available and on various factors that it believes to be reasonable under the circumstances. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, revenue recognition, accrued research and development expenses and useful lives assigned to property and equipment. The Company assesses estimates on an ongoing basis; however, actual results could materially differ from those estimates.

Comprehensive Income (Loss) —Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. The Company's only element of other comprehensive income (loss) is unrealized gains and losses on available-for-sale investments.

Cash and Cash Equivalents and Restricted Cash—Cash and cash equivalents consist of standard checking accounts, money market accounts and certain investments. The Company considers all highly liquid investments with original or remaining maturities at the time of purchase of 90 days or less to be cash equivalents. Restricted cash consists of cash serving as collateral for letters of credit issued for security deposits for the Company's facility leases in Bedford, Massachusetts.

The following table provides a reconciliation of cash, cash equivalents and restricted cash to amounts shown in the consolidated statements of cash flows:

	December 31,	
	2020	2019
	(in thousands)	
Cash and cash equivalents	$ 217,431	$ 53,774
Restricted cash	1,274	1,274
Total cash, cash equivalents and restricted cash	$ 218,705	$ 55,048

Short-Term Investments—Short-term investments represent holdings of available-for-sale marketable securities in accordance with the Company's investment policy and cash management strategy. Short-term investments have maturities of greater than 90 days at the time of purchase and mature within one-year from the balance sheet date. Investments in marketable securities are recorded at fair value, with any unrealized gains and losses, reported within accumulated other comprehensive income as a separate component of stockholders' equity until realized or until a determination is made that an other-than-temporary decline in market value has occurred. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense over the life of the underlying security. Such amortization and accretion, together with interest on securities, are included in interest income in the Company's consolidated statements of operations. The cost of marketable securities sold is determined based on the specific identification method and any realized gains or losses on the sale of investments are reflected as a component of other income.

Concentrations of Credit Risk—Financial instruments that potentially subject the Company to significant concentration of credit risk consist primarily of cash, cash equivalents and short-term investments. Periodically, the Company may maintain deposits in financial institutions in excess of government insured limits. We believe that we are not exposed to significant credit risk as our deposits are held at financial institutions that management believes to be of high credit quality and the Company has not experienced any losses on these deposits. We regularly invest excess cash with major financial institutions in money market funds, U.S. government and corporate debt securities and commercial paper, all of which can be readily purchased and sold using established markets. As of December 31, 2020, the Company's cash and cash equivalents were held with two financial institutions. We believe that the market risk arising from our holdings of these financial instruments is mitigated based on the fact that many of these securities are either government-backed or of high credit rating.

Offering Costs—The Company capitalizes incremental legal, professional accounting and other third-party fees that are directly associated with equity financings as other current assets until the transactions are completed. After equity financings are complete, these costs are recorded in stockholders' equity as a reduction of additional paid-in capital generated as a result of the offering.

Leases— In February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2016-02, *Leases* (Topic 842) ("ASU 2016-02"), which eliminated the tests for lease classification under prior U.S. GAAP and requires lessees to recognize right-of-use assets and related lease liabilities on the balance sheet. The FASB subsequently issued the following amendments to ASU 2016-02 that have the same effective date and transition date: ASU No. 2018-01 – *Leases* (Topic 842): *Land Easement Practical Expedient for Transition to Topic 842*, ASU No. 2018-10 – *Codification Improvements to Topic* 842*, Leases*, ASU No. 2018-11 – *Leases* (Topic 842): *Targeted Improvements*, ASU No. 2018-20 – *Leases* (Topic 842): *Narrow-Scope Improvements for Lessors*, and ASU No. 2019-01 – *Leases* (Topic 842): *Codification Improvements*. The Company adopted these amendments with ASU 2016-02 (collectively, the new leasing standards) effective January 1, 2020.

The Company adopted the new leasing standards using the modified retrospective approach, as of January 1, 2020, with no restatement of prior periods or cumulative adjustments to accumulated deficit. The Company elected the package of practical expedients permitted under the transition guidance within the new standard, which, among other things, allows the Company to carry forward the historical lease classification. In addition, the Company elected the practical expedient not to apply the recognition requirements in the leasing standards to short-term leases (a lease that at commencement date has a lease term of 12 months or less and does not contain a purchase option that it is reasonably certain to exercise) and the practical expedient that permits lessees to make an accounting policy election (by class of underlying asset) to not separate lease components of a contract from non-lease components.

The Company determines if an arrangement is a lease at contract inception. The Company's contracts are determined to contain a lease when all of the following criteria based on the specific circumstances of the arrangement are met: (1) there is an identified asset for which there are no substantive substitution rights; (2) the Company has the right to obtain substantially all of the economic benefits from the identified asset; and (3) the Company has the right to direct the use of the identified asset.

At the commencement date, operating lease liabilities and their corresponding right-of-use assets are recorded based on the present value of future lease payments over the expected lease term. The Company's lease agreements do not provide an implicit rate. As a result, the Company utilizes an estimated incremental borrowing rate to discount lease payments, which is based on the rate of interest the Company would have to pay to borrow a similar amount on a collateralized basis over a similar term. Certain adjustments to the right-of-use asset may be required for items such as initial direct costs paid or lease incentives received. Operating lease cost is recognized over the expected term on a straight-line basis. Variable lease cost is recognized as incurred.

The Company acts as sublessor related to a sublease of the Company's former headquarters. Fixed sublease payments received are recognized on a straight-line basis over the sublease term. Right-of-use assets are periodically evaluated for impairment.

The expected lease term for those leases commencing prior to January 1, 2020 did not change with the adoption of the new leasing standards. The expected lease term for leases commencing after the adoption of the new leasing standards includes noncancelable lease periods and, when applicable, periods covered by an option to extend the lease if the Company is reasonably certain to exercise that option, as well as periods covered by an option to terminate the lease if the Company is reasonably certain not to exercise that option.

As a result of the adoption of the new leasing standards, on January 1, 2020, the Company recorded non-cash transactions to recognize a right-of-use asset of $6.8 million, operating lease liabilities of $17.7 million and the derecognition of deferred rent of $10.9 million originally accounted for under legacy guidance. The adoption did not have a material impact on the condensed consolidated statement of operations. For additional information on the adoption of the new leasing standards, refer to Note 8.

	January 1, 2020 (in thousands)		
	Prior to adoption of new leasing standards	Adjustment for adoption of new leasing standards	As Adjusted
Right-of-use assets (1)(2)	$ —	$ 6,835	$ 6,835
Deferred rent (2)	$ 1,313	$ (1,313)	$ —
Deferred rent, net of current portion (2)	$ 9,544	$ (9,544)	$ —
Operating lease liabilities (3)	$ —	$ 2,251	$ 2,251
Operating lease liabilities, net of current portion (3)	$ —	$ 15,441	$ 15,441

(1) Represents capitalization of operating right-of-use assets
(2) Represents reclassification of deferred rent and incentives as a reduction to operating right-of-use assets
(3) Represents recognition of operating lease liabilities

Guarantees and Indemnifications—As permitted under Delaware law, the Company indemnifies its officers, directors, consultants and employees for certain events or occurrences that happen by reason of the relationship with, or position held at, the Company. Through December 31, 2020, the Company had not experienced any losses related to these indemnification obligations, and no claims were outstanding. The Company does not expect significant claims related to these indemnification obligations and, consequently, concluded that the fair value of these obligations is negligible, and no related liabilities have been established.

Property and Equipment—Property and equipment are recorded at cost. Expenditures for repairs and maintenance are expensed as incurred. When assets are retired or disposed of, the assets and related accumulated depreciation are derecognized from the accounts, and any resulting gain or loss is included in the determination of net loss. Depreciation is provided using the straight-line method over the estimated useful lives of the related assets. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.

Computer equipment and software	3 years
Laboratory equipment and office furniture	5 years
Manufacturing equipment	5 - 7 years
Leasehold improvements	Shorter of the lease term or estimated useful life

Impairment of Long-Lived Assets—The Company evaluates its long-lived assets, which consist primarily of property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the carrying amount of the asset exceeds the fair value of the asset. To date, no impairments have been recognized for these assets.

Research and Development Costs—Research and development costs are charged to expense as incurred. Research and development expense consists of expenses incurred in performing research and development activities, including salaries and benefits, materials and supplies, preclinical and clinical expenses, stock-based compensation expense, depreciation of equipment, contract services, and other outside expenses.

Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information provided to the Company by its vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the consolidated financial statements as prepaid expense or accrued research and development expense.

Income Taxes—The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the Company's consolidated financial statements and tax returns. Deferred tax assets and liabilities are determined based upon the differences between the financial statement carrying amounts and the tax bases of existing assets and liabilities and for loss and credit carryforwards, using enacted tax rates expected to be in effect in the year in which the differences are expected to reverse. Deferred tax assets are reduced by a valuation allowance if it is more likely than not that these assets may not be realized. The Company determines whether it is more likely than not that a tax position will be sustained upon examination. The tax benefit to be recognized for any tax position that meets the more-likely-than-not recognition threshold is calculated as the largest amount of benefit that is greater than 50% likely of being realized upon ultimate settlement. If it is not more likely than not that a position will be sustained, none of the benefit attributable to the position is recognized. The Company accounts for interest and penalties related to uncertain tax positions as part of its provision for income taxes. Since inception, the Company has provided a valuation allowance for the full amount of the net deferred tax assets as the realization of the net deferred tax assets has not been determined to be more likely than not.

Segment Information—Operating segments are identified as components of an enterprise about which separate discrete financial information is made available for evaluation by the chief operating decision maker ("CODM") in making decisions regarding resource allocation and assessing performance. The CODM is the Company's Chief Executive Officer. The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company's singular focus is dedicated to translating proprietary gene editing and gene therapy technology into novel treatments for patients with rare genetic diseases. All of the Company's tangible assets are held in the United States.

Revenue Recognition— Revenue is recognized in accordance with FASB Accounting Standards Codification ("ASC") Topic 606, *Revenue from Contracts with Customers* ("ASC 606"). On January 1, 2019, the Company adopted ASC 606 using the full retrospective transition method.

Under ASC 606, the Company recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine the appropriate amount of revenue to be recognized for arrangements determined to be within the scope of ASC 606, the Company performs the following five steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect consideration it is entitled to in exchange for the goods or services it transfers to the customer.

The promised goods or services in the Company's arrangements would likely consist of a license, rights to the Company's intellectual property or research, development and manufacturing services. Performance obligations are promised goods or services in a contract to transfer a distinct good or service to the customer and are considered distinct when (i) the customer can benefit from the good or service on its own or together with other readily available resources and (ii) the promised good or service is separately identifiable from other promises in the contract. In assessing whether promised goods or services are distinct, the Company considers factors such as the stage of development of the underlying intellectual property, the capabilities of the customer to develop the intellectual property on its own or whether the required expertise is readily available and whether the goods or services are integral or dependent to other goods or services in the contract.

The Company estimates the transaction price based on the amount expected to be received for transferring the promised goods or services in the contract. The consideration may include fixed consideration and variable consideration. At the inception of each arrangement that includes variable consideration, the Company evaluates the amount of consideration to which the Company expects to be entitled to. The Company utilizes either the most likely amount method or expected value method to estimate the amount expected to be received based on which method best predicts the amount expected to be received. The amount of variable consideration that is included in the transaction price may be constrained and is included in the transaction price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period.

The Company's contracts may include development and regulatory milestone payments that are assessed under the most likely amount method and constrained until it is probable that a significant revenue reversal would not occur. Milestone payments that are not within the Company's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, the Company re-evaluates the probability of achievement of such development and regulatory milestones and any related constraint, and if necessary, adjust its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue in the period of adjustment.

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from the Company's collaboration arrangement.

The Company allocates the transaction price based on the estimated standalone selling price of each performance obligation. The Company must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. The Company utilizes key assumptions to determine the stand-alone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction and the estimated costs. Variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated are consistent with the amounts the Company would expect to receive for the satisfaction of each performance obligation.

The consideration allocated to each performance obligation is recognized as revenue when control is transferred for the related goods or services. For performance obligations which consist of licenses and other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress. The Company evaluates the measure of progress for its over-time arrangements at each reporting period and, if necessary, updates the measure of progress and revenue recognized.

Stock-based Compensation—The Company recognizes compensation expense for awards to employees based on the grant date fair value of stock-based awards on a straight-line basis over the period during which an award holder provides service in exchange for the award. The fair value of options on the date of grant is calculated using the Black-Scholes option pricing model based on key assumptions such as stock price, expected volatility and expected term. The Company's estimates of these assumptions are primarily based on the trading price of the Company's stock, historical data, peer company data and judgment regarding future trends and factors. Stock-based awards granted to nonemployees are initially recorded at fair value and are re-measured at each reporting period as the awards vest and expense is recognized over the period the services are provided.

The purchase price of common stock under the Company's employee stock purchase plan ("ESPP") is equal to 85% of the lesser of (i) the fair market value per share of the common stock on the first business day of an offering period and (ii) the fair market value per share of the common stock on the purchase date. The fair value of the look-back provision under the ESPP is calculated using the Black-Scholes option pricing model. The fair value of the look-back provision plus the 15% discount is recognized as compensation expense over the 180-day purchase period.

Fair Value Measurements—Certain assets and liabilities are reported on a recurring basis at fair value. Fair value is defined 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 must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices (unadjusted) in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

Net Loss per Share—Basic net loss per share is computed by dividing net loss by the weighted-average number of common shares outstanding during the period. Diluted net loss per share is computed using the weighted-average number of common shares outstanding during the period and, if dilutive, the weighted-average number of potential shares of common stock. The weighted-average number of common shares included in the computation of diluted net loss gives effect to all potentially dilutive common equivalent shares, including outstanding stock options and unvested shares of common stock.

Common stock equivalent shares are excluded from the computation of diluted net loss per share if their effect is antidilutive. In periods in which the Company reports a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders is generally the same as basic net loss per share attributable to common stockholders since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

Recent Accounting Pronouncements—The Jumpstart Our Business Startups Act of 2012 permits an emerging growth company to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. As an emerging growth company, the Company has elected to take advantage of this extended transition period.

In February 2016, the FASB issued new leasing standards to increase transparency and comparability among organization related to their leasing activities. For additional information on the adoption of the new leasing standards, please refer to section titled "Leases" above, and Note 8.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13") to improve financial reporting by requiring more timely recording of credit losses on loans and other financial instruments held by financial institutions and other organizations. ASU 2016-13 requires the measurement of all expected credit losses for financial assets held at the reporting date based on historical experience, current conditions and reasonable and supportable forecasts. ASU 2016-13 also requires enhanced disclosures to help investors and other financial statement users better understand significant estimates and judgments used in estimating credit losses, as well as the credit quality and underwriting standards of an organization's portfolio. ASU 2016-13 is effective for the Company beginning January 1, 2023, with early application permitted. The Company is currently evaluating the impact the adoption of this standard will have on its consolidated financial statements.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"), which changes certain aspects of the accounting for share-based payments granted to nonemployees. Under ASU 2018-07, most of the guidance on such payments to nonemployees would be aligned with the requirements for share-based payments granted to employees. The Company adopted ASU 2018-07 on January 1, 2020. The adoption of ASU 2018-07 did not have a material impact on the Company's consolidated financial statements and related disclosures.

In October 2020, the FASB issued ASU 2020-10, *Codification Improvements*, which updates various codification topics by clarifying or improving disclosure requirements to align with the SEC's regulations. The Company will adopt ASU 2020-10 as of the reporting period beginning January 1, 2021. The adoption of this update is not expected to have a material effect on the Company's consolidated financial statements.

3. CASH AND CASH EQUIVALENTS

From time to time, the Company may have cash balances in financial institutions in excess of federal deposit insurance limits. The Company has never experienced any losses related to these balances. The Company considers only those investments that are highly liquid, readily convertible to cash, and that mature within three months from date of purchase to be cash equivalents.

The following table summarizes the Company's cash and cash equivalents:

	December 31,	
	2020	2019
	(in thousands)	
Cash	$ 250	$ 250
Repurchase agreements	—	14,000
Money market funds	217,181	39,524
Total cash and cash equivalents	$ 217,431	$ 53,774

4. SHORT-TERM INVESTMENTS

The Company may invest its excess cash in fixed income instruments denominated and payable in U.S. dollars including U.S. treasury securities, commercial paper, corporate debt securities and asset-backed securities in accordance with the Company's investment policy that primarily seeks to maintain adequate liquidity and preserve capital.

The Company has designated all investments as available-for-sale and therefore such investments are reported at fair value and classified as short-term investments on the Company's consolidated balance sheets. Unrealized gains or losses on investments are recorded in accumulated other comprehensive income or loss, a component of stockholders' equity, on the Company's consolidated balance sheets. The Company had no short-term investments as of December 31, 2020.

The following table summarizes the Company's short-term investments as of December 31, 2019:

As of December 31, 2019	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
		(in thousands)		
Asset-backed securities	$ 14,866	$ 10	$ —	$ 14,876
Commercial paper	41,259	—	—	41,259
U.S. Treasury securities	59,926	45	—	59,971
Corporate debt securities	92,380	128	—	92,508
Total short-term investments	$ 208,431	$ 183	$ —	$ 208,614

The Company utilizes the specific identification method in computing realized gains and losses. The Company had no realized gains and losses on its short-term investments for the years ended December 31, 2020 and 2019. The contractual maturity dates of all of the Company's investments are less than one year.

5. FAIR VALUE MEASUREMENTS

The Company's financial instruments consist of cash and cash equivalents, short-term investments, restricted cash and accounts payable. The carrying amount of cash, restricted cash and accounts payable are each considered a reasonable estimate of fair value due to the short-term maturity.

Assets measured at fair value on a recurring basis were as follows:

Description	December 31, 2020	Quoted Prices (Unadjusted) in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
		(in thousands)		
Cash equivalents:				
Money market mutual funds	$ 217,181	$ 217,181	$ —	$ —
Total financial assets	$ 217,181	$ 217,181	$ —	$ —

Description	December 31, 2019	Quoted Prices (Unadjusted) in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
		(in thousands)		
Cash equivalents:				
Money market mutual funds	$ 39,524	$ 39,524	$ —	$ —
Repurchase agreements	14,000	—	14,000	—
Total cash equivalents	$ 53,524	$ 39,524	$ 14,000	$ —
Short-term investments:				
Asset-backed securities	$ 14,876	$ —	$ 14,876	$ —
Commercial paper	41,259	—	41,259	—
U.S. Treasury securities	59,971	—	59,971	—
Corporate debt securities	92,508	—	92,508	—
Total short-term investments	$ 208,614	$ —	$ 208,614	$ —
Total financial assets	$ 262,138	$ 39,524	$ 222,614	$ —

Short-term securities are valued using models or other valuation methodologies that use Level 2 inputs. These models are primarily industry-standard models that consider various assumptions, including time value, yield curve, volatility factors,

default rates, current market and contractual prices for the underlying financial instruments, as well as other relevant economic measures. Substantially all of these assumptions are observable in the marketplace, can be derived from observable data or are supported by observable levels at which transactions are executed in the marketplace.

There were no transfers between fair value measure levels during the years ended December 31, 2020 and 2019.

6. PROPERTY AND EQUIPMENT

Property and equipment, net consists of the following:

	December 31,	
	2020	2019
	(in thousands)	
Laboratory equipment	$ 12,703	$ 10,837
Manufacturing equipment	7,754	4,911
Computers and purchased software	1,596	640
Furniture and fixtures	1,363	1,363
Leasehold improvements	29,961	30,862
Assets not yet in service	—	2,513
Property and equipment, at cost	53,377	51,126
Less accumulated depreciation and amortization	(16,375)	(8,410)
Property and equipment, net	$ 37,002	$ 42,716

Depreciation expense for the years ended December 31, 2020 and 2019 was approximately $8.0 million and $6.3 million, respectively. The Company disposed of $0.9 million and less than $0.1 million of property and equipment, net during the years ended December 31, 2020 and 2019, respectively.

7. ACCRUED EXPENSES AND OTHER LIABILITIES

Accrued expenses and other liabilities consist of the following:

	December 31,	
	2020	2019
	(in thousands)	
Accrued compensation and benefits	$ 6,902	$ 4,551
Accrued research and development expenses	2,393	2,258
Accrued professional fees	291	542
Accrued unvested common stock subject to repurchase	13	37
Accrued other	204	256
Total accrued expenses and other liabilities	$ 9,803	$ 7,644

8. COMMITMENTS AND CONTINGENCIES

Operating Leases—In September 2016, the Company entered into a noncancelable operating lease beginning in November 2016 for office, laboratory and manufacturing space in Bedford, Massachusetts, that expires in October 2021, with an option for an additional three-year term. In 2018, the Company entered into a sublease agreement for the entire leased premises. The rent commencement date of the sublease was December 2018, and the sublease will terminate on the scheduled termination date of the original lease. Under the terms of the sublease, the subtenant is obligated to pay the Company aggregate base rent of approximately $2.7 million over the term of the sublease, based on the same level of rent the Company is obligated to pay the landlord, in addition to a passthrough of operating expenses and real estate taxes charged by the landlord.

In December 2017, the Company entered into a noncancelable operating lease for approximately 67,000 square feet of research and development, manufacturing and general office space in Bedford, Massachusetts. The lease expires in February 2027 with an option for an additional five-year term. Rent became due under the lease in two phases; rent on the first 46,000 square feet started in September 2018 and rent on the remaining 21,000 square feet started in March 2019. The initial annual base rent was $39.50 per square foot and increases by three percent annually. The Company is obligated to pay, on a pro-rata

basis, real estate taxes and operating costs related to the premises. The lease agreement entered into in December 2017 allowed for a tenant improvement allowance not to exceed $10.9 million, which the Company received in full, to be applied to the total cost of tenant improvements to the leased premises. The unamortized balance of the tenant improvement allowance was included in deferred rent incentives and has been recorded as a reduction to operating right-of-use asset upon adoption of the new leasing standards.

The Company maintains letters of credit, secured by restricted cash, for security deposits totaling $1.3 million as of December 31, 2020 and 2019, respectively, in conjunction with its current leases.

The following table summarizes operating lease costs and variable lease costs, as well as sublease income for the year ended December 31, 2020:

Year ended December 31, 2020	Amount (in thousands)
Operating lease costs	$ 2,492
Variable lease costs	2,355
Sublease income	(913)
Net lease cost	$ 3,934

Rent expense for the year ended December 31, 2019 was $1.4 million.

The maturities of our operating lease liabilities as of December 31, 2020 were as follows:

For the Years Ending December 31,	Amount (in thousands)
2021	$ 3,834
2022	2,987
2023	3,077
2024	3,169
Thereafter	7,197
Total undiscounted lease payments	$ 20,264
Less: imputed interest	(4,822)
Present value of operating lease liabilities	$ 15,442

The following table summarizes the lease term and discount rate as of December 31, 2020:

	As of December 31, 2020
Weighted-average remaining lease term (years)	
Operating leases	5.9
Weighted-average discount rate	
Operating leases	9.9%

The following table summarizes the supplemental cash flow information related to the Company's operating leases for the year ended December 31, 2020.

	Year ended December 31, 2020 (in thousands)
Cash paid for amounts included in the measurement of lease liabilities	$ 3,804

9. LICENSE AGREEMENTS

City of Hope

In April 2016, the Company entered into a license agreement with City of Hope ("COH"), an academic research and medical center. The license term extends until the last to expire patent, unless terminated earlier by either party under certain provisions. The Company is required to pay an annual license fee of $25,000, reimburse COH for patent costs incurred, pay amounts up to $3.2 million upon the achievement of certain development and commercialization milestones for each product under the license, pay royalties on future sales in the low single-digits and royalties on sublicense revenue in the low double-digits, if any. During the year ended December 31, 2019, the Company paid $50,000 to COH upon dosing the first patient in the pheNIX Phase 1/2 clinical trial. During the year ended December 31, 2020, the Company paid $75,000 plus interest to COH in connection with achievement of a milestone event.

As a result of the execution of the Collaboration Agreement with Novartis (see Note 15), the Company paid $4.5 million to COH in December 2017, under the terms of the license agreement.

In May 2015, the Company entered into a sponsored research agreement with COH with a goal to identify potential treatments for diseases in humans. Under this agreement, the Company recorded $0.1 million in research and development expense for the year ended December 31, 2019. The agreement terminated in September 2019 in accordance with its terms.

California Institute of Technology

In September 2016, the Company entered into a co-exclusive license agreement with the California Institute of Technology ("Caltech"), an academic research institute. The license term extends until the expiration, revocation, invalidation or unenforceability of the licensed patent rights. The Company is required to pay an annual minimal royalty fee of $20,000, reimburse for patent costs incurred, pay an amount up to $7.2 million upon the achievement of certain development and regulatory milestones and pay royalties on future sales in the low single-digits and royalties on sublicense revenue in the mid to high single-digits, if any.

10. INCOME TAXES

A reconciliation between the U.S. federal statutory tax rate and the Company's effective tax rate is summarized as follows:

	For the Years Ended December 31,	
	2020	2019
Federal statutory rate	21.0%	21.0%
Tax credits	10.6%	13.4%
State taxes, net of federal tax benefit	8.0%	6.1%
Non-deductible expenses	(1.8%)	(1.0%)
Change in valuation allowance	(37.8%)	(39.5%)
Effective income tax rate	—%	—%

The principal components of the Company's deferred tax assets and liabilities consist of the following:

	December 31,	
	2020	2019
	(in thousands)	
Deferred tax assets:		
Net operating losses	$ 72,838	$ 41,589
R&D credits	39,888	25,328
Deferred revenue	8,251	8,456
Deferred rent	4,219	2,966
Capitalized R&D costs	1,039	1,207
Equity compensation	1,368	883
Accrued expense and other	1,914	108
Total deferred tax assets	129,517	80,537
Deferred tax liabilities:		
Depreciation	(3,726)	(2,744)
Other	(757)	—
Total deferred tax liabilities	(4,483)	(2,744)
Valuation allowance	(125,034)	(77,793)
Net deferred taxes	$ —	$ —

The Company has no income tax expense due to the operating loss incurred for the years ended December 31, 2020 and 2019. The Company has provided a valuation allowance for the full amount of the net deferred tax assets as the realization of the net deferred tax assets is not determined to be more likely than not.

At December 31, 2020, the Company had $265.1 million and $271.5 million of federal and state net operating loss carryforwards, respectively, that expire at various dates through 2040. Included in the federal net operating loss carryforwards of $265.1 million is $233.6 million that can be carried forward indefinitely. At December 31, 2020, the Company had $34.2 million and $7.2 million of federal and state research and development credit carryforwards, respectively, that expire at various dates through 2040. Included in the $34.2 million of federal research and development credit carryforwards is $29.0 million of orphan drug credit carryforwards. The valuation allowance increased in 2020 and 2019 by $47.2 million and $40.2 million, respectively, due to the increase in the deferred tax assets by the same amounts, primarily due to the net operating loss carryforwards and research and development tax credits not utilized.

For all years through December 31, 2020, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards. Since a full valuation allowance has been provided against the Company's research and development credits, any reduction in the gross deferred tax asset established for the research and development credit carryforwards would not result in any net impact to the Company's consolidated financial statements.

Realization of the future tax benefits is dependent on many factors, including the Company's ability to generate taxable income within the net operating loss carryforward period. Under the provisions of the Internal Revenue Code, certain substantial changes in the Company's ownership, including a sale of the Company or significant changes in ownership due to sales of equity, may have limited, or may limit in the future, the amount of net operating loss carryforwards that could be used annually to offset future taxable income. The Company has not completed a study to assess whether a change of control has occurred or whether there have been multiple changes of control since the Company's formation due to the significant complexity and cost associated with such study and because there could be additional changes in control in the future. As a result, the Company is not able to estimate the effect a change in control would have, if any, on the Company's ability to utilize its net operating loss and research and development credit carryforwards in the future.

The Company files tax returns in the United States and Massachusetts. All tax years since inception remain open to examination by the major taxing jurisdictions to which the Company is subject, as carryforward attributes generated in years past may still be adjusted upon examination by the Internal Revenue Service ("IRS") or other authorities if they have or will be used in a future period. The Company is not currently under examination by the IRS or any other jurisdictions for any tax years.

As of December 31, 2020, the Company had no uncertain tax positions. The Company has elected to recognize interest and penalties related to income tax matters as a component of income tax expense, of which no interest or penalties were recorded for the years ended December 31, 2020 and 2019.

11. STOCKHOLDERS' EQUITY

Common Stock—Voting, dividend and liquidation rights of the holders of the common stock are subject to and qualified by the rights, powers and preferences of the holders of the preferred stock.

Voting—Each holder of outstanding shares of common stock are entitled to one vote in respect of each share. The holders of outstanding shares of common stock, voting together as a single class, shall be entitled to elect one director. The number of authorized shares of common stock may be increased or decreased by the affirmative vote of a majority of the outstanding shares of common stock and preferred stock voting together as a single class.

Dividends—Subject to the payment in full of any preferential dividends to which the holders of preferred stock are entitled, the holders of common stock shall be entitled to receive dividends out of funds legally available therefore at such times and in such amounts as the Board of Directors may determine in its sole discretion.

Liquidation Rights—In the event of any voluntary or involuntary liquidation, dissolution or winding-up of the Company, after the payment or provision for payment of all debts and liabilities of the Company and any preferential amounts to which the holders of preferred stock are entitled with respect to the distribution of assets in liquidation, the holders of common stock shall be entitled to share ratably in the remaining assets of the Company available for distribution.

There were 50,265,575 and 45,116,742 shares of common stock outstanding at December 31, 2020 and 2019, respectively.

Preferred Stock—As of December 31, 2020 and 2019, there were no shares of preferred stock issued and outstanding.

12. STOCK INCENTIVE PLANS

2015 Stock Incentive Plan

In December 2015, the Company's Board of Directors adopted the 2015 Stock Incentive Plan (the "2015 Plan"), which provided for the grant of qualified incentive and nonqualified stock options or restricted stock awards to the Company's employees, officers, directors, advisors, and outside consultants. Stock options generally vest over a four-year period and expire ten years from the date of grant. Certain options provide for accelerated vesting if there is a change in control, as defined in the 2015 Plan. At December 31, 2020, there were no additional shares available for future grant under the 2015 Plan.

2018 Incentive Award Plan

In March 2018, the Company's Board of Directors adopted and the Company's stockholders approved the Homology Medicines, Inc. 2018 Incentive Award Plan (the "2018 Plan" and, together with the 2015 Plan, the "Plans"), which became effective on the day prior to the first public trading date of the Company's common stock. Upon effectiveness of the 2018 Plan, the Company ceased granting new awards under the 2015 Plan.

The 2018 Plan provides for the grant of incentive stock options, nonqualified stock options, restricted stock awards, restricted stock units, stock appreciation rights and other stock or cash-based awards to employees and consultants of the Company and certain affiliates and directors of the Company. The number of shares of common stock initially available for issuance under the 2018 Plan was 3,186,205 shares of common stock plus the number of shares subject to awards outstanding under the 2015 Plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by the Company on or after the effective date of the 2018 Plan. In addition, the number of shares of common stock available for issuance under the 2018 Plan is subject to an annual increase on the first day of each calendar year beginning on January 1, 2019 and ending on and including January 1, 2028 equal to the lesser of (i) 4% of the Company's outstanding shares of common stock on the final day of the immediately preceding calendar year and (ii) such smaller number of shares of common stock as determined by the Company's Board of Directors, provided that not more than 20,887,347 shares of common stock may be issued under the 2018 Plan upon the exercise of incentive stock options (the "Evergreen Provision"). As of December 31, 2020, there were 2,397,547 shares available for future grant under the 2018 Plan. On January 1, 2021, pursuant to the Evergreen Provision, an additional 2,010,623 shares were added to the 2018 Plan, representing 4% of total common shares outstanding at December 31, 2020.

2018 Employee Stock Purchase Plan

In March 2018, the Company's Board of Directors adopted, and the Company's stockholders approved, the Homology Medicines, Inc. 2018 Employee Stock Purchase Plan (the "2018 ESPP"). The 2018 ESPP allows employees to buy Company stock through after-tax payroll deductions at a discount from market value. The 2018 ESPP is intended to qualify as an "employee stock purchase plan" under Section 423 of the Internal Revenue Code. The number of shares of common stock initially available for issuance under the 2018 ESPP was 353,980 shares of common stock plus an annual increase on the first day of each calendar year beginning on January 1, 2019 and ending on and including January 1, 2028 equal to the lesser of (i) 1% of the Company's outstanding shares of common stock on the final day of the immediately preceding calendar year and (ii) such smaller number of shares of common stock as determined by the Company's Board of Directors, provided that not more than 4,778,738 shares of common stock may be issued under the 2018 ESPP (the "ESPP Evergreen Provision"). At December 31, 2020, there were 1,039,650 shares available for future issuance under the 2018 ESPP. On January 1, 2021, pursuant to the ESPP Evergreen Provision, an additional 502,655 shares were added to the 2018 ESPP, representing 1% of total common shares outstanding at December 31, 2020.

Under the 2018 ESPP, employees may purchase common stock through after-tax payroll deductions at a price equal to 85% of the lower of the fair market value on the first trading day of an offering period or the last trading day of an offering period. The 2018 ESPP generally provides for offering periods of six months in duration that end on the final trading day of each February and August. In accordance with the Internal Revenue Code, no employee will be permitted to accrue the right to purchase stock under the 2018 ESPP at a rate in excess of $25,000 worth of shares during any calendar year during which such a purchase right is outstanding (based on the fair market value per share of the Company's common stock as of the first day of the offering period).

During the year ended December 31, 2020, 83,848 shares were issued under the 2018 ESPP for aggregate proceeds to the Company of $0.9 million. During the year ended December 31, 2019, 55,234 shares were issued under the 2018 ESPP for aggregate proceeds to the Company of $0.8 million. Pursuant to the 2018 ESPP, the Company recorded stock-based compensation of $0.2 million and $0.2 million for the years ended December 31, 2020 and 2019, respectively.

Stock-based compensation expense

The Company recognizes compensation expense for awards to employees based on the grant date fair value of stock-based awards on a straight-line basis over the period during which an award holder provides service in exchange for the award, which is generally the vesting period. The fair value of each option award is estimated on the date of grant using the Black-Scholes option-pricing model, with the assumptions noted in the table below. Expected volatility for the Company's common stock was determined based on an average of the historical volatility of a peer group of publicly traded companies that are similar to the Company. The expected term of options granted to employees was calculated using the simplified method, which represents the average of the contractual term of the option and the weighted-average vesting period of the option. The Company uses the simplified method because it does not have sufficient historical option exercise data to provide a reasonable basis upon which to estimate expected term. The contractual life of the options was used for the expected term of options granted to non-employees. The assumed dividend yield is based upon the Company's expectation of not paying dividends in the foreseeable future. The risk-free rate is based on the U.S. Treasury yield curve in effect at the time of grant for periods commensurate with the expected term of the award. The Company recognizes forfeitures as they occur.

The assumptions used in the Black-Scholes option pricing model are as follows:

	For the Years Ended December 31,	
	2020	2019
Expected volatility	63.2% — 66.3%	62.4% — 64.7%
Weighted-average risk-free interest rate	0.31% — 1.73%	1.36% — 2.60%
Expected dividend yield	— %	— %
Expected term (in years)	5.5 - 6.25	6.25
Underlying common stock fair value	$9.82 - $21.75	$12.73 — $30.34

The Company recorded stock-based compensation expense related to stock options and shares purchased under the 2018 ESPP as follows:

	For the Years Ended December 31,	
	2020	2019
	(in thousands)	
Research and development	$ 6,390	$ 4,164
General and administrative	6,858	3,471
	$ 13,248	$ 7,635

As of December 31, 2020, there was $29.2 million of unrecognized compensation expense related to unvested employee and non-employee share-based compensation arrangements granted under the Plans. The unrecognized compensation expense is estimated to be recognized over a period of 2.4 years at December 31, 2020.

A summary of option activity under the Plans during the year ended December 31, 2020 is as follows:

	Number of Options	Weighted-Average Exercise Price per Share	Weighted-Average Remaining Contractual Term (in Years)	Aggregate Intrinsic Value
				(in thousands)
Outstanding at January 1, 2020	4,843,018	$ 14.78	8.5	$ 33,809
Granted	1,311,200	$ 17.82		
Exercised	(46,410)	$ 3.79		
Cancelled/Forfeited	(266,984)	$ 22.75		
Outstanding at December 31, 2020	5,840,824	$ 15.18	7.8	$ 12,278
Vested and expected to vest at December 31, 2020	5,840,824	$ 15.18	7.8	$ 12,278
Exercisable at December 31, 2020	2,869,589	$ 12.18	7.0	$ 10,803

The total intrinsic value of options exercised during the year ended December 31, 2020 and 2019 was $0.6 million and $1.9 million, respectively. The weighted-average grant date fair value of options granted during the years ended December 31, 2020 and 2019 was $10.39 and $12.90, respectively.

Stock options granted pursuant to the 2015 Plan permit option holders to elect to exercise unvested options in exchange for unvested common stock. Options granted under the 2015 Plan that are exercised prior to vesting will continue to vest according to the respective option agreement, and such unvested shares are subject to repurchase by the Company at the optionee's original exercise price in the event the optionee's service with the Company voluntarily or involuntarily terminates.

A summary of the Company's unvested common stock from early exercises that is subject to repurchase by the Company is as follows:

	Shares
Unvested shares—January 1, 2020	21,666
Vested	(18,575)
Issued	—
Repurchased	—
Unvested shares—December 31, 2020	3,091

As of December 31, 2020 and 2019, 3,091 shares and 21,666 shares, respectively, remained subject to a repurchase right by the Company, with a related liability included in accrued expenses and other liabilities in the consolidated balance sheets of less than $0.1 million as of each date.

13. NET LOSS PER SHARE

The Company's potential dilutive securities, which include unvested common stock from the early-exercise of stock options and outstanding common stock options, have been excluded from the computation of diluted net loss per share as the

effect would be to reduce the net loss per share. Therefore, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The Company excluded the following potential common shares, presented based on amounts outstanding at December 31, 2020 and 2019, from the computation of diluted net loss per share attributable to common stockholders because including them would have had an anti-dilutive effect:

	As of December 31,	
	2020	2019
Unvested common stock from early exercise of options	3,091	21,666
Stock options to purchase common stock	5,840,824	4,843,018
Total	5,843,915	4,864,684

14. DEFINED CONTRIBUTION PLAN

The Company has a 401(k) defined contribution plan (the "401(k) Plan") for all of its employees. Eligible employees may make pretax contributions to the 401(k) Plan up to statutory limits, while the Company contributes to the plan at the discretion of the Board of Directors. The Company's discretionary match made under the 401(k) Plan for the years ended December 31, 2020 and 2019 was $0.7 million and $0.5 million, respectively.

15. COLLABORATION AND LICENSE AGREEMENT

Summary of Agreement

In November 2017, the Company entered into a collaboration and license agreement with Novartis (as amended, the "Collaboration Agreement") for the research, development, manufacturing and commercialization of products using the Company's gene-editing technology for the treatment of certain ophthalmic targets and sickle cell disease. In February 2019, Novartis elected to discontinue the sickle cell disease program under the Collaboration Agreement effective in August 2019. In May 2020, Novartis confirmed an ophthalmic target for a therapeutic editing program. Additionally, in accordance with the terms of the Collaboration Agreement, Novartis' right to substitute other ophthalmic targets expired. For additional information on the Collaboration Agreement, please refer to Note 17.

Under the terms of the Collaboration Agreement, the Company granted Novartis a research license, a development and commercialization license, and a manufacturing license, under certain of its intellectual property rights to research, develop, manufacture and commercialize ophthalmic targets. Upon entering into the Collaboration Agreement in November 2017, the Company received an upfront, nonrefundable payment of $35.0 million and issued additional shares of its Series B preferred stock to Novartis for consideration of $10.0 million, in addition to the $5.0 million of Series B preferred stock Novartis had purchased in July 2017. The Company recorded the November 2017 issuance of Series B preferred stock at its estimated fair value of $11.7 million, including $1.7 million of the upfront payment, and allocated the remaining $33.3 million of the upfront payment to the Collaboration Agreement.

The Collaboration Agreement consists of a research term, where the Company and Novartis were collaborating to perform research and conduct preclinical development to identify candidates that modulate ophthalmic targets. The Collaboration Agreement also includes exploratory work on the applicability of the gene editing technology with respect to other gene targets. The Company's obligation to perform such exploratory research was extended pursuant an amendment to the Collaboration Agreement was set to conclude in May 2021. The Company was responsible for the manufacturing of proprietary research grade human hematopoietic stem cell derived adeno-associated virus vectors ("AAVHSCs") during the research term. Novartis agreed to reimburse research activities performed by the Company at a full-time equivalent rate ("FTE") and manufacturing activities at cost, up to a maximum of $17.0 million during the research term, as specified and defined in the Collaboration Agreement. Novartis agreed to pay the Company a target fee of $5.0 million if the target meets certain success criteria during the research term (the "target fee trigger date"). The research term was to continue for five years from the effective date of the Collaboration Agreement. Pursuant to the Collaboration Agreement, the Company also agreed to participate on a joint steering committee and a joint manufacturing subcommittee, with equal representation from both the Company and Novartis.

Novartis had the exclusive right to develop and commercialize one ophthalmic candidate or product arising from the research activities. Subject to certain limitations pursuant to the terms of the Collaboration Agreement, Novartis agreed to fund all development and commercialization costs. The Company was responsible for manufacturing candidates and products for Novartis during the development and commercialization terms. The Company's manufacturing activities were to be reimbursed at cost during the development term and at cost plus a margin during the commercialization term, as defined in the Collaboration Agreement. If the Company was not able to manufacture candidates or products that met the quality or quantity requirements of Novartis, then Novartis would have had the right to designate a third-party contract manufacturer or manufacture such candidates or products itself.

In accordance with the Collaboration Agreement, taking into consideration Novartis' election to discontinue the sickle cell disease program, and the expiration of Novartis' rights to make substitutions of an ophthalmic target, the Company was also eligible to receive up to a total of $265.0 million in milestone payments, including up to $90.0 million in development milestone payments, up to $85.0 million in regulatory milestone payments and up to $90.0 million in commercial milestone payments, with respect to the licensed products. The Company was also eligible to earn tiered royalties on net sales of licensed products by Novartis, its affiliates or sublicensees, ranging from mid-single-digit, to sub-teen double-digit percentages, and such royalties were potentially subject to various reductions and offsets. If any of the exploratory research efforts were advanced into formal research and development programs, the parties agreed to negotiate the economics including potential milestone payments for such programs at that time.

Revenue Recognition

The Company determined that the (1) research, development and commercialization and manufacturing licenses, (2) the research activities performed by the Company (3) service on the joint committees and (4) manufacturing during the research and development terms represented a single performance obligation under the Collaboration Agreement. Since the option for Novartis to obtain manufacturing during the commercialization term from the Company is at a price that would reflect the standalone selling price, the option does not provide Novartis with a material right and is therefore not a performance obligation under the contract.

The Company has concluded that the research, development and commercialization and manufacturing licenses are not distinct from the research activities and manufacturing during the research and development term as Novartis cannot benefit from the licenses without the Company performing the research and manufacturing services. These services are so specialized and rely on the Company's expertise in gene editing technologies not available in the marketplace. As a result, these licenses have been combined with the research activities, service on the joint committees and the manufacturing during the research and development terms as a single performance obligation.

The transaction price consists of the $33.3 million non-refundable upfront payment, net of amounts classified as equity, and projected reimbursable research and manufacturing activities, which have been estimated using the expected value method. None of the target fees or development and regulatory milestone payments have been included in the transaction price, as all are fully constrained. As part of the evaluation of the constraint, the Company considered numerous factors, including the fact that achievement of the milestones is outside of the Company's control and is contingent upon the success of the Company's preclinical studies, clinical trials, Novartis' efforts and the receipt of regulatory approval. In addition, the Company has determined that the commercial milestones and sales-based royalties will be recognized when the related sales occur as they were determined to relate predominately to the licenses transferred to Novartis, and therefore have also been excluded from the transaction price. The Company will re-evaluate the transaction price, including estimated variable consideration included in the transaction price and all constrained amounts, in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

The Company identified only one performance obligation in the Collaboration Agreement. Therefore, the Company allocated the transaction price at the onset of the contract to the single performance obligation.

The Company recognizes revenue over time using a cost-to-cost method, which it believes best depicts the transfer of control to the customer. Under the cost-to-cost method, the extent of progress towards completion is measured based on the ratio of actual costs incurred to the total estimated costs expected upon satisfying the identified performance obligation. Under this method, revenue is recorded over the performance period as a percentage of the estimated transaction price based on the extent of progress towards completion. As of December 31, 2020, the aggregate amount of the transaction price related to the unsatisfied portion of the performance obligation is $30.2 million, and the Company will recognize this revenue as the research and manufacturing activities are performed, which was expected to occur over a period of time that was estimated to conclude in 2027.

In estimating the total costs to satisfy its single performance obligation pursuant to the Novartis agreement, the Company is required to make significant estimates including the expected time it will take to fulfill the performance obligation, which, as of December 31, 2020, was expected to be approximately ten years from the date the Collaboration Agreement was entered into, and the expected costs associated with manufacturing during the research and development terms for a novel manufacturing process as well as the probability of success of a target to move into the development phase. The Company has made estimates of such costs utilizing its experience with similar product candidates, however not identical to those in the Collaboration Agreement. In making such estimates, significant judgment is required to evaluate those key assumptions related to cost estimates. The cumulative effect of revisions to the total estimated costs to complete the Company's single performance obligation will be recorded in the period in which the changes are identified and amounts can be reasonably estimated. While such revisions will have no impact on the Company's reported cash flows, a significant change in these assumptions and estimates could have a material impact on the timing and amount of revenue recognized in future periods.

During the years ended December 31, 2020 and 2019, the Company recognized revenue under the Collaboration Agreement of $2.3 million and $1.7 million, respectively, of which $0.8 million and $0.6 million was included in deferred revenue at the beginning of each such period. As of December 31, 2020 and 2019, there was approximately $30.2 million and $31.0 million of deferred revenue related to the Collaboration Agreement, respectively. In addition, as of December 31, 2020 and 2019, the Company has recorded accounts receivable of $0.4 million, related to reimbursable research and development costs under the Collaboration Agreement, which are included in prepaid expenses and other current assets on the consolidated balance sheets.

16. PFIZER STOCK PURCHASE AGREEMENT

On November 9, 2020, the Company entered into a common stock purchase agreement (the "Stock Purchase Agreement") with Pfizer Inc. ("Pfizer"), pursuant to which the Company agreed to issue and sell to Pfizer 5,000,000 shares of the Company's common stock through a private placement transaction (the "Private Placement") at a purchase price of $12.00 per share, for an aggregate purchase price of $60.0 million. The shares of common stock sold to Pfizer are subject to a one-year lock-up from closing, during which time Pfizer is prohibited from selling or otherwise disposing of such shares.

Under the Stock Purchase Agreement, Pfizer was granted an exclusive right of first refusal (the "ROFR") for a 30-month period (the "ROFR Period") beginning on the date of the closing of the Private Placement (collectively, the "ROFR Provision"), to negotiate a potential collaboration on the development and commercialization of HMI-102 and HMI-103. Pfizer may exercise its right of first refusal under the ROFR Provision one time for each of HMI-102 and HMI-103 during the ROFR period. In addition to the ROFR, the Stock Purchase Agreement provides for an information sharing committee (the "Information Committee"), comprised of representatives of each company which will serve as a forum for sharing information regarding the development of HMI-102 and HMI-103 during the ROFR Period.

The Company recorded the issuance of common stock at its estimated fair value of $52.0 million, which reflects a discount for the lack of marketability of the shares. The remaining $8.0 million of aggregate purchase price was allocated to the other elements of the Stock Purchase Agreement, which represent a contract with a customer. The Company concluded that the Information Committee represents the only performance obligation under the contract. The ROFR does not provide Pfizer with a material right and is therefore not a performance obligation. As such, the Company allocated the $8.0 million to the Information Committee obligation.

The Company will recognize revenue over time as the measure of progress which it believes best depicts the transfer of control to Pfizer. The Information Committee will meet regularly over the ROFR Period to share information which results in recognition of the transaction price over the 30-month ROFR Period.

During the year ended December 31, 2020, the Company recognized collaboration of $0.4 million, and as of December 31, 2020, there was approximately $7.6 million of deferred revenue related to the Company's obligation to Pfizer.

17. SUBSEQUENT EVENT

On February 26, 2021, Homology received notice from Novartis that they had elected to terminate the Collaboration Agreement with the Company, with respect to the remaining ophthalmic target under the Collaboration Agreement. Accordingly, the notice served as notice of Novartis' termination of the Collaboration Agreement in its entirety, which will be effective on August 26, 2021. As a result of the termination of the Collaboration Agreement, Homology regained worldwide exclusive rights from Novartis to research, develop, manufacture and commercialize Homology's proprietary nuclease-free gene editing technology platform for an ophthalmic target (see Note 15). Homology announced its plans to continue to advance the program toward naming a development candidate. The Company and Novartis believe that results of studies conducted

under the Collaboration Agreement provide early proof-of-principle and support a nuclease-independent approach to editing of relevant cell types in the eye after sub-retinal injection, and are the subject of a planned presentation at an upcoming scientific meeting.

* * * * *

HOMOLOGY™
Medicines, Inc.

EXECUTIVE OFFICERS AND SENIOR LEADERSHIP

Arthur Tzianabos, Ph.D.
President, Chief Executive Officer and Director

Albert Seymour, Ph.D.
Chief Scientific Officer

W. Bradford Smith
Chief Financial Officer and Treasurer

Tim Kelly
Chief Operating Officer

Gabriel M. Cohn, M.D., M.B.A.
Chief Medical Officer

Theresa McNeely
Chief Communications Officer and Patient Advocate

Michael Blum, M.B.A.
Senior Vice President, Commercial

Paul Alloway, Ph.D., J.D.
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Melissa Gelormini
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Mary Thistle
Special Advisor, Bill & Melinda Gates Medical Research Institute

Arthur Tzianabos, Ph.D.
President and Chief Executive Officer, Homology Medicines

2021 ANNUAL SHAREHOLDER MEETING

June 17, 2021, 9:00 a.m. ET
Virtual

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FORM 10-K

Copies of our Annual Report on Form 10-K for the year ended December 31, 2020 are available by request without charge by:

Visiting investors.homologymedicines.com/financial-information/sec-filings

Writing to IR@homologymedicines.com or to Homology Medicines, ATTN: Investor Relations, One Patriots Park, Bedford, MA 01730

Filings we make with the Securities and Exchange Commission may also be accessed free of charge on the Securities and Exchange Commission's publicly available website at www.sec.gov.

FORWARD-LOOKING STATEMENTS

This Annual Report contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this Annual Report that do not relate to matters of historical fact should be considered forward-looking statements, including statements regarding the potential, safety, efficacy, and regulatory and clinical progress of our product candidates; plans and timing for the release of clinical data; advancing our novel platform and pipeline; our goal of delivering potential cures to patients; beliefs about preclinical data; and expectations for 2021, including planned clinical trials and development programs. These statements are neither promises nor guarantees, but 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, including, but not limited to, the following: the impact of the COVID-19 pandemic on our business and operations, including our preclinical studies and clinical trials, and on general economic conditions; the fact that we have and expect to continue to incur significant losses; our need for additional funding, which may not be available; failure to identify additional product candidates and develop marketable products; the early stage of our development efforts; our failure or the failure of our collaborators to successfully develop and commercialize drug candidates; potential unforeseen events during clinical trials could cause delays or other adverse consequences; risks relating to the regulatory approval process; our product candidates may cause serious adverse side effects; inability to maintain our collaborations, or the failure of these collaborations; our reliance on third parties; the inability to obtain orphan drug exclusivity; failure to obtain international marketing approval; failure to obtain U.S. marketing approval; ongoing regulatory obligations; effects of significant competition; failure to attract, retain and motivate qualified personnel; the possibility of system failures or security breaches; risks relating to intellectual property; the price of our common stock may be volatile; significant costs as a result of operating as a public company; and any securities class action litigation. These and other important factors discussed under the caption "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2020 and our other filings with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this Annual Report. Any such forward-looking statements represent management's estimates as of the date of this Annual Report. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change.

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