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: 001-37526

Zynerba Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**26-0389433**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)
80 W. Lancaster Avenue, Suite 300, Devon, PA	**19333**
(Address of principal executive offices)	(Zip Code)

(484) 581-7505
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, par value $0.001 per share	ZYNE	**The Nasdaq Global 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 and posted 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 and post 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 ☐
	Smaller reporting company ☒
Non-accelerated filer ☒	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 Act). ☐ Yes ☒ No

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of the last business day of the registrant's second fiscal quarter, was approximately $96.4 million, based upon the closing price on the Nasdaq Global Market reported for June 30, 2020. The market value of voting stock and non-voting common equity by non-affiliates excludes the value of those shares held by executive officers and directors of the registrant (such exclusion shall not be deemed to constitute an admission that any such person is an "affiliate" of the Registrant.)

As of March 5, 2021, the registrant had 41,251,537 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates certain information by reference from the registrant's proxy statement for the 2021 annual meeting of stockholders to be filed no later than 120 days after the end of the registrant's fiscal year ended December 31, 2020.

TABLE OF CONTENTS

FORWARD-LOOKING STATEMENTS

Statements made in this Annual Report on Form 10-K, or this Report, that are not statements of historical or current facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements discuss our current expectations and projections relating to our financial condition, results of operations, plans, objectives, future performance and business. These statements may be preceded by, followed by or include the words "aim," "anticipate," "believe," "estimate," "expect," "forecast," "intend," "outlook," "plan," "potential," "project," "projection," "seek," "may," "could," "would," "will," "should," "can," "can have," "likely," the negatives thereof and other words and terms of similar meaning.

Forward-looking statements are inherently subject to risks, uncertainties and assumptions; they are not guarantees of performance. You should not place undue reliance on these statements. We have based these forward-looking statements on our current expectations and projections about future events. Although we believe that our assumptions made in connection with the forward-looking statements are reasonable, we cannot assure you that the assumptions and expectations will prove to be correct.

You should understand that the following important factors could affect our future results and could cause those results or other outcomes to differ materially from those expressed or implied in our forward-looking statements:

- our expectations, projections and estimates regarding expenses, future revenue, capital requirements, incentive and other tax credit eligibility, collectability and timing and availability of and the need for additional financing;
- the results, cost and timing of our preclinical studies and clinical trials, including any delays to such clinical trials relating to enrollment or site initiation, as well as the number of required trials for regulatory approval and the criteria for success in such trials;
- our dependence on third parties in the conduct of our preclinical studies and clinical trials;
- legal and regulatory developments in the United States and foreign countries, including any actions or advice that may affect the design, initiation, timing, continuation, progress or outcome of clinical trials or result in the need for additional clinical trials;
- the results of our preclinical studies and earlier clinical trials of our product candidates may not be predictive of future results and we may not have favorable results in our ongoing or planned clinical trials;
- the difficulties and expenses associated with obtaining and maintaining regulatory approval of our product candidates, and the indication and labeling under any such approval;
- our plans and ability to develop and commercialize our product candidates;
- the successful development of our commercialization capabilities, including sales and marketing capabilities, whether alone or with potential future collaborators;
- the size and growth of the potential markets for our product candidates, the rate and degree of market acceptance of our product candidates and our ability to serve those markets;
- the coverage and reimbursement status for our product candidates from third-party payors;
- the success of competing therapies and products that are or become available;
- our ability to limit our exposure under product liability lawsuits, shareholder class action lawsuits or other litigation;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- legislative changes and recently proposed changes regarding the healthcare system, including changes and proposed changes to the Patient Protection and Affordable Care Act;
- our ability to obtain and maintain third-party manufacturing for our product candidates on commercially reasonable terms;
- delays, interruptions or failures in the manufacture and supply of our product candidates;
- the performance of third parties upon which we depend, including third-party contract research organizations, or CROs, contract manufacturing organizations, or CMOs, contractor laboratories and independent contractors;
- our ability to recruit or retain key scientific, commercial or management personnel or to retain our executive officers;

- the timing and outcome of current and future legal proceedings;
- our ability to maintain proper functionality and security of our internal computer and information systems and prevent or avoid cyberattacks, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption;
- the timing and outcome of the Australian Taxation Office's, or ATO, review regarding our eligibility to receive certain tax credits; and
- the extent to which health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic, could disrupt our operations or materially and adversely affect our business and financial conditions.

See Item 1A, "Risk Factors," in this Report for a more complete discussion of these risks and uncertainties and for other risks and uncertainties. Those factors and the other risk factors described therein are not necessarily all of the important factors that could cause actual results or developments to differ materially from those expressed in any of our forward-looking statements. Consequently, there can be no assurance that actual results or developments anticipated by us will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, us. Given these uncertainties, you are cautioned not to place undue reliance on such forward-looking statements. We undertake no obligation, and specifically decline any obligation, to publicly update or revise any forward-looking statements, even if experience or future developments make it clear that projected results expressed or implied in such statements will not be realized, except as may be required by law.

PART I

Item 1. Business

Unless the context indicates otherwise, the terms “Zynerba,” “Zynerba Pharmaceuticals,” “we,” “us,” “our,” “our company” and “our business” refer to Zynerba Pharmaceuticals, Inc.

Company Overview

Zynerba Pharmaceuticals is the leader in pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders. We are committed to improving the lives of patients and their families living with severe, chronic health conditions including Fragile X syndrome, or FXS, autism spectrum disorder, or ASD, 22q11.2 deletion syndrome, or 22q, and a heterogeneous group of rare and ultra-rare epilepsies known as developmental and epileptic encephalopathies, or DEE.

Cannabinoids are a class of compounds derived from *Cannabis* plants. The two primary cannabinoids contained in *Cannabis* are cannabidiol and tetrahydrocannabinol, or THC. Clinical and preclinical data suggest that cannabidiol has positive effects on treating behavioral symptoms of FXS, ASD, 22q and seizures in patients with epilepsy.

We are currently developing Zygel, the first and only pharmaceutically-produced cannabidiol formulated as a permeation-enhanced gel for transdermal delivery, which is patent protected through 2030. Five additional patents expiring in 2038 are directed to methods of use relating to Zygel, including methods of treating FXS and ASD.

In preclinical animal studies, Zygel’s permeation enhancer increased delivery of cannabidiol through the layers of the skin and into the circulatory system. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism of cannabidiol when delivered transdermally. In addition, an *in vitro* study published in *Cannabis and Cannabinoid Research* in April 2016 demonstrated that cannabidiol is degraded to THC (the major psychoactive cannabinoid in *Cannabis)* in an acidic environment such as the stomach. As a result, we believe such degradation may lead to increased psychoactive effects if cannabidiol is delivered orally. These effects may be avoided with the transdermal delivery of Zygel, which maintains cannabidiol in a neutral pH. Zygel is being developed as a clear gel with once- or twice-daily dosing and is targeting treatment of behavioral symptoms of FXS, ASD and 22q and the reduction of seizures in patients with DEE syndromes. We have been granted orphan drug designations from United States Food and Drug Administration, or FDA, for the use of cannabidiol for the treatment of FXS and for the treatment of 22q. In May 2019, we received Fast Track designation from the FDA for treatment of behavioral symptoms associated with FXS. The FDA’s Fast Track program is designed to facilitate the development of drugs intended to treat serious conditions and fill unmet medical needs and can lead to expedited review by the FDA in order to get new important drugs to the patient earlier.

Our clinical program for Zygel includes clinical trials evaluating Zygel in the treatment of behavioral symptoms of FXS, ASD and 22q and the reduction of seizures and the treatment of associated symptoms in patients with DEE syndromes. As of March 2021, the Zygel safety database across all clinical studies conducted by us includes data from 906 volunteers and patients. Across these clinical studies, Zygel has been well tolerated and consistent with previously reported data.

CONNECT-FX Trial (FXS)

In June 2020 we announced results of our pivotal CONNECT-FX clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study designed to assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the *FMR1* gene. While Zygel did not achieve statistical significance versus placebo in the primary endpoint of improvement in the Social Avoidance subscale of the Aberrant Behavior Checklist – Community FXS, or ABC-C_{FXS}, a pre-planned ad hoc analysis of the most severely impacted patients in the trial, as defined by patients having at least 90% methylation (“highly methylated”) of the impacted *FMR1* gene, demonstrated that those patients receiving Zygel achieved statistical significance compared to placebo in the

primary endpoint of improvement in the Social Avoidance subscale of the ABC-C_{FXS} at 12 weeks of treatment. Following discussions with the FDA regarding the CONNECT-FX trial and the regulatory path forward for Zygel, we plan to conduct a double-blind, placebo-controlled pivotal trial, testing Zygel in pediatric and adolescent patients with FXS who have a highly methylated *FMR1* gene to confirm the positive results observed in the CONNECT-FX trial. We plan to review the trial design and protocol for the new trial through a Type C meeting with the FDA in the first half of 2021 and expect to initiate the pivotal trial before the end of 2021.

Phase 2 BRIGHT Trial (ASD)

In May 2020, we reported positive top-line results of the Phase 2 BRIGHT clinical trial, a 14- week open label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for the treatment of pediatric and adolescent patients with ASD. Patients treated with Zygel demonstrated statistically significant improvement at week 14 compared to baseline for each ABC-C subscale (Irritability, Inappropriate Speech, Stereotypy, Social Withdrawal, and Hyperactivity). The results of the other efficacy assessments were consistent with the results demonstrated in the ABC-C. We expect to discuss a path forward with the FDA in the first half of 2021.

Phase 2 INSPIRE Trial (22q)

In May 2019, we initiated the open-label Phase 2 INSPIRE clinical trial, a 14-week open label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for treatment of behavioral symptoms of 22q. We expect to enroll approximately 20 male and female patients (ages six through 17 years). Recruitment into the INSPIRE trial has been delayed due to the impact of COVID-19 and resulting significant travel restrictions in Australia. Once these restrictions are lifted and enrollment is complete, we will provide a timeframe for disclosing top line results of this trial. In September 2020, we were granted orphan drug designation from the FDA for the use of cannabidiol for the treatment of 22q.

Phase 2 BELIEVE Trial (DEE)

In September 2019, we reported top-line results from the Phase 2 BELIEVE clinical trial, a six-month, open-label, multi-dose clinical trial designed to evaluate the efficacy and safety of Zygel in children and adolescents (ages three through 17 years) with DEE. Following discussions with the FDA regarding the clinical pathway for Zygel in DEE, we plan to pursue individual syndromes. We are evaluating potential target indications and expect to finalize target syndrome selection for one or more DEE syndromes in 2021.

Zygel Clinical Development Timelines

We are closely monitoring the progression of the COVID-19 pandemic, including its potential impact on our clinical development plans and timelines going forward. In response to COVID-19, for our current clinical development programs, we implemented multiple measures consistent with the FDA's guidance on the conduct of clinical trials of medical products during the COVID-19 pandemic, including remote site monitoring and patient visits using telemedicine where needed, direct to patient drug shipment from investigator sites, and local study-related clinical laboratory collection. Except with respect to our Phase 2 open-label INSPIRE trial, timelines for delivery of top-line results for our clinical trials were not adversely impacted by COVID-19 and we intend to implement similar measures, as necessary, for our planned clinical trials in 2021.

Cannabidiol Science Overview

The endocannabinoid system includes the endocannabinoids, primarily 2-arachidonoylglycerol, or 2-AG, and anandamide or AEA, and the cannabinoid receptors CB_1 and CB_2. The disruption of the endocannabinoid system may play a core role in the underlying pathophysiology of FXS, ASD, and epilepsy.

Cannabidiol modulates the endocannabinoid system by inhibiting the metabolism (breakdown) of 2-AG and AEA. This inhibition is thought to result in increased 2-AG AEA availability, greater CB_1 and CB_2 activation, reduced excitatory

signaling, increased synaptic plasticity. Cannabidiol may restore homeostatic mechanisms in patients with endocannabinoid system dysfunction. The effect of cannabidiol on the endocannabinoid system is the scientific basis for the use of cannabidiol in the treatment of FXS, ASD and 22q.

Cannabidiol may also treat the neuropsychiatric symptoms of these conditions due to its activity as an agonist at 5-HT_{1A} and an antagonist at GPR55 receptors.

The effects of cannabidiol modulation of the nucleoside transporter, antagonism of GPR55 receptors and regulation of intercellular calcium are known to decrease neuronal excitability and are the scientific basis of the antiepileptic potential of cannabidiol.

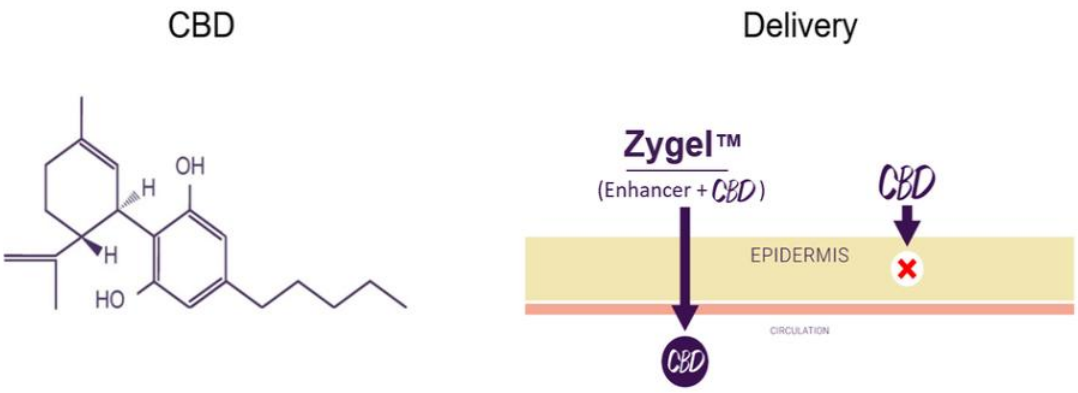
Clinical and preclinical data suggest that cannabidiol has positive effects on treating FXS, ASD and epilepsy. Patients with FXS, ASD, 22q and epilepsy share several of the same behavioral symptoms, which may be treatable with cannabidiol. Clinical data also suggest that cannabidiol has a very high therapeutic index. Interest in cannabinoid therapeutics has increased significantly over the past several years as preclinical and clinical data has emerged highlighting the potential efficacy and safety benefits of cannabinoid therapeutics. Epidiolex®, a sesame oil liquid formulation of highly concentrated cannabidiol was approved by the FDA for the treatment of seizures associated with specific epilepsies, Lennox-Gastaut Syndrome, or LGS, and, Dravet Syndrome, or DS in 2018 and Tuberous Sclerosis Complex, or TSC in 2020. The cannabinoid therapeutics market is expected to grow significantly due to the potential benefits these products may provide over existing therapies.

Product Candidates

Zygel – Cannabidiol Transdermal Gel

Zygel is the first and only pharmaceutically-produced cannabidiol formulated as a permeation-enhanced gel for transdermal delivery (see Figure 1), and is patent protected through 2030.

Figure 1 — Chemical structure and transdermal gel delivery of cannabidiol.



Zygel is being developed as a clear gel that is designed to provide consistent, controlled drug delivery with convenient once- or twice-daily dosing. Because cannabidiol is virtually insoluble in water, we use a patent protected formulation containing ethanol and propylene glycol as solubilizing agents and Transcutol® HP as a permeation enhancer. All excipients in the gel have been classified as Generally Recognized as Safe, or GRAS, and have been used in transdermal products previously approved by the FDA.

The permeation enhancer in Zygel increases the delivery of cannabidiol through the layers of the skin and into the circulatory system.

Transdermal delivery allows the cannabidiol in Zygel to avoid stomach acid degradation and the first-pass liver metabolism that occurs with oral or oral mucosal delivery methods. Drugs applied transdermally are absorbed across the skin into the systemic circulation, enabling the potential to have a consistent absorption with increased bioavailability.

Development of Zygel for the Treatment of Behavioral Symptoms of Fragile X Syndrome

FXS Overview

FXS is a rare genetic condition that causes intellectual disability, anxiety disorders, behavioral and learning challenges and various physical characteristics. The impairment can range from learning disabilities to more severe cognitive or intellectual disabilities. FXS is the leading known cause of both inherited intellectual disability and autism spectrum disorder. Patients with FXS may exhibit autism like symptoms including anxiety, social impairment and social avoidance (seeks isolation from others, does not want to be with other children and avoids all types of new social engagements) and restricted/repetitive behaviors. Currently, there are no known cures or approved therapies indicated for the treatment of FXS or its symptoms. Special education and symptomatic treatments for anxiety and irritability are employed to lessen the burden of illness. Based on the 2012 U.S. Census and the National Fragile X Foundation, or NFXF, FXS prevalence is estimated at approximately 71,000 patients in the United States. According to the NFXF, FXS affects 1 in 3,600 to 4,000 males and 1 in 4,000 to 6,000 females of all races and ethnic groups. We believe that approximately 60% of all patients with FXS have a highly methylated *FMR1* gene.

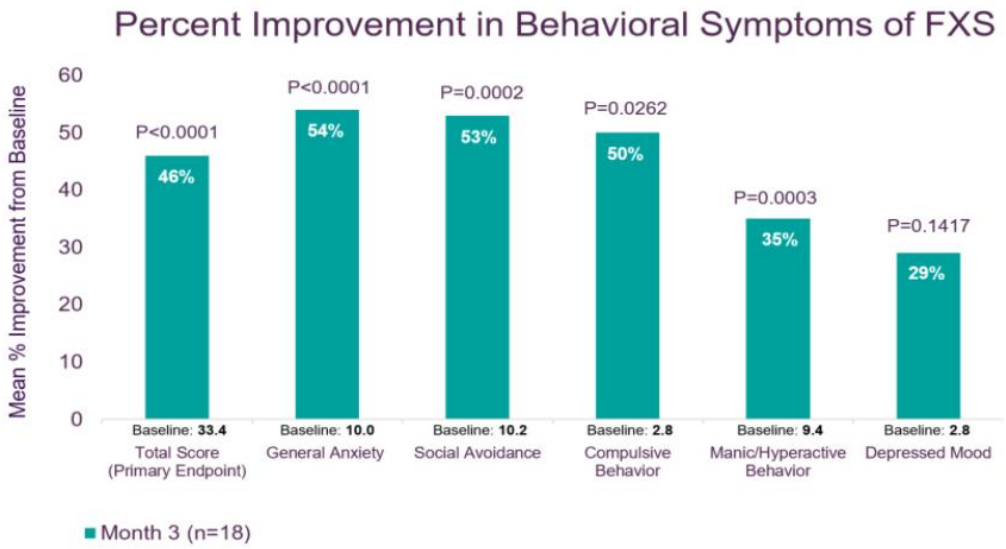
We believe Zygel may provide an effective treatment for patients with FXS that have a highly methylated *FMR1* gene based on its capacity to interact with the endocannabinoid system, which is compromised in patients with FXS. Specifically, cannabidiol modulates the endocannabinoid system by inhibiting the metabolism (breakdown) of 2-AG and anandamide. This inhibition is thought to result in increased anandamide and 2-AG availability, greater CB_1 and CB_2 activation, and increased synaptic plasticity. This modulation is the scientific basis for the use of cannabidiol in the treatment of FXS. We anticipate Zygel may be used as first line therapy to treat patients suffering from behavioral symptoms of FXS.

FAB-C

In September 2017, we reported the results for our open-label exploratory Phase 2 clinical trial designed to evaluate the safety and efficacy of Zygel in children with FXS, which we refer to as the FAB-C (Treatment of **F**ragile X Syndrome **A**nxiety and **B**ehavioral Challenges with **C**BD) trial. The primary endpoint for the trial was the change in the total score of the Anxiety, Depression, and Mood Scale, or ADAMS, from baseline to week 12. The ADAMS is a 28-item scale designed to assess general anxiety, social avoidance, compulsive behavior, manic/hyperactive behavior and depressed mood. It has been validated in patients with FXS. Twenty patients (3:1 males) ages six through 17 years (mean = 10.7) with FXS, as confirmed by molecular documentation of full mutation of the *FMR1* gene, were enrolled in the open-label FAB-C study. Zygel was added on to other medications being administered. The first six weeks of the study were designed to titrate dosing in patients. Dosing was initiated at 50 mg daily and could be increased to 250 mg daily. Weeks seven through 12 of the study were a maintenance period where patients were treated at the dose established at week six. At the completion of the study, patients could enter an open-label extension study for up to 12 months.

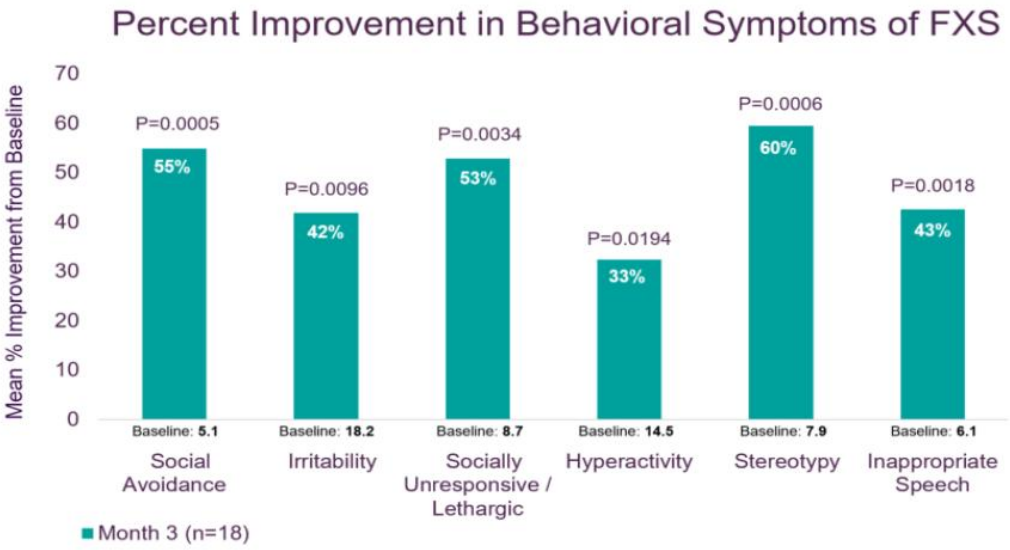
The FAB-C trial successfully met its primary endpoint, achieving a 46% improvement ($p<0.0001$) in the total score of ADAMS at week 12 compared to baseline.

Results for the ADAMS at week 12 are summarized as follows:



Zygel also achieved clinically meaningful improvements in all measures of the ABC-C_{FXS}, which addresses the key behavioral symptoms of FXS including social avoidance, repetitive movements and socially unresponsive behaviors. The study achieved statistical significance across all ABC-C_{FXS} subscales compared to baseline.

Results from the ABC-C_{FXS} at week 12 are summarized as follows:

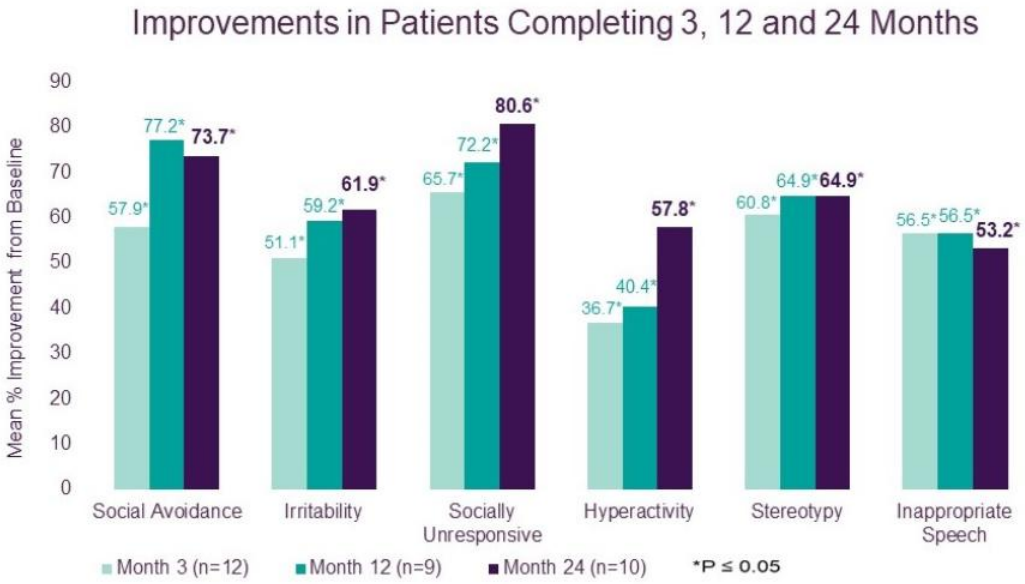


We evaluated multiple other secondary endpoints including a Clinical Global Impression of Improvement, or CGI-I, the Pediatric Anxiety Rating Scale, or PARS-R, Visual Analog Scales for Anxiety, Hyperactivity and Tantrum/Mood Lability, the Vineland Adaptive Behavior III, a Quality of Sleep measurement and the Pediatric Quality of Life, or PedsQL™. The results of the ABC-C_{FXS} and other secondary endpoints reinforce the results demonstrated in the ADAMS.

Zygel was shown to be very well tolerated, and the safety profile was consistent with data from earlier clinical trials and our other Phase 2 clinical trials for Zygel. All adverse events were considered mild to moderate and no serious adverse events were reported. No patient experienced drug-related GI events during the 12-week treatment period, and no THC was detected in the plasma. Of the 18 patients who completed the study, 13 enrolled in the open-label extension and 10 patients are still being treated with Zygel as of February 28, 2021. These patients have now been on Zygel between 45 and 48 months.

We also collected 24-month open label clinical data from the FAB-C trial regarding the long-term impact of Zygel on emotional and behavioral symptoms of FXS. The statistically significant improvements in the core emotional and behavioral symptoms of FXS versus baseline as measured by the ABC-C_{FXS} were sustained through 24 months of treatment. In the Social Avoidance subscale of the ABC-C_{FXS}, patients completing 24 months of treatment with Zygel experienced a 74% improvement in social avoidance behaviors versus baseline, compared to a 58% improvement at three months of treatment. Both results are statistically significant compared to baseline. Zygel was well tolerated in this study, no serious adverse events were reported and no clinically meaningful trends in vital signs, ECG or clinical safety laboratories, including liver function tests, were observed.

Results from the ABC-C_{FXS} at 24 months are summarized as follows:



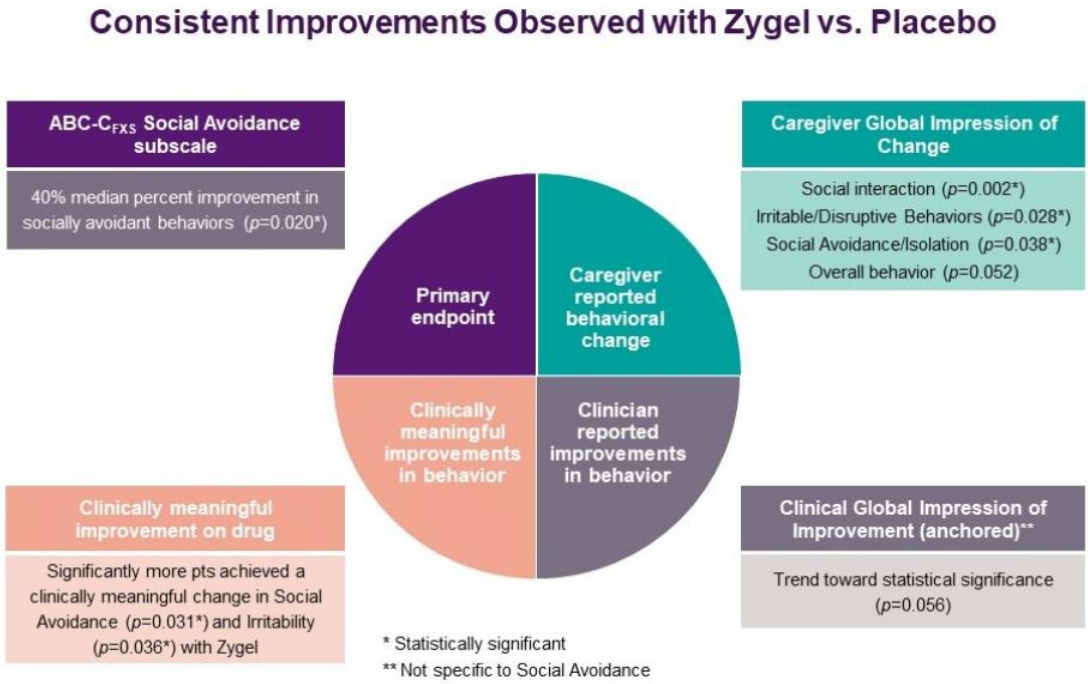
CONNECT-FX

In July 2018, we initiated the pivotal CONNECT-FX (**C**linical study **o**f Ca**nn**abidiol (CBD) in Childr**e**n and Adoles**c**en**t**s with **F**ragile **X**) clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study designed to assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the *FMR1* gene. In June 2020, we announced that Zygel did not achieve statistical significance versus placebo in the primary endpoint of improvement in the Social Avoidance subscale of the ABC-C_{FXS}. Zygel also did not demonstrate

statistical significance versus placebo in the three key secondary endpoints, which were the change from baseline to the end of the treatment period in the Irritability subscale score of the ABC-C_{FXS}, the Socially Unresponsive/Lethargic subscale score of the ABC-C_{FXS} and Improvement in Clinical Global Impression, or CGI-I.

A pre-planned ad hoc analysis of the most severely impacted patients in the trial as defined by patients having at least 90% methylation ("highly methylated") of the impacted *FMR1* gene, demonstrated those patients receiving Zygel achieved statistical significance in the primary endpoint of improvement compared to placebo (p=0.020) in the Social Avoidance subscale of the ABC-C_{FXS} at 12 weeks of treatment. This group comprised 80% of the patients enrolled in the CONNECT-FX study. We also collected caregiver-reported data from the CONNECT-FX trial. The results of the Caregiver Global Impression – Change survey showed a broad shift toward global improvement from baseline to week 12 for highly methylated patients with three of the four behavioral domains (social avoidance and isolation, irritable and disruptive behaviors, and social interactions) showing a statistically significant change in favor of patients on Zygel and the fourth domain (overall behavior) trending toward significance. These data support the statistically significant improvement observed in the CONNECT-FX primary endpoint of social avoidance in patients having a highly methylated *FMR1* gene who received Zygel compared to placebo. We also conducted psychometric analyses of the CONNECT-FX trial data that defined clinically meaningful treatment response over 12 weeks of treatment as an improvement of ≥3 points for the Social Avoidance subscale of the ABC-C_{FXS} and ≥9 points for the Irritability subscale. Through this analysis, we determined that 58.2% of patients with a highly methylated *FMR1* gene receiving Zygel achieved a clinically meaningful change in their socially avoidant behavior compared to 40.6% of placebo patients (p=0.031), and 40.3% of patients with a highly methylated *FMR1* gene receiving Zygel achieved a clinically meaningful change in Irritability compared to 23.8% of placebo patients (p=0.036).

The data collected from the CONNECT-FX trial in patients with a highly methylated *FMR1* gene can be summarized in the following chart:



In December 2020, we announced that following discussions with the FDA regarding the CONNECT-FX trial and the regulatory path forward for Zygel, we plan to conduct a double-blind, placebo-controlled pivotal trial in pediatric and adolescent patients with FXS who have a highly methylated *FMR1* gene to confirm the positive results observed in this population of responders in the CONNECT-FX trial. We plan to review the trial design and protocol for the new trial

through a Type C meeting with the FDA in the first half of 2021and expect to initiate the pivotal trial before the end of 2021.

Development of Zygel for Treatment of ASD

ASD Overview

ASD is a developmental disability affecting approximately one million pediatric and adolescent patients between the ages of five and 17 in the U.S. It is a Diagnostic and Statistical Manual of Mental Disorders, or DSM-5, diagnosis, which includes Autistic disorder, Asperger's syndrome, and Rett syndrome. It is characterized by anxiety, repetitive patterns of behavior, impairments in social communication including verbal and non-verbal communication, and deficits in developing, understanding and maintaining relationships.

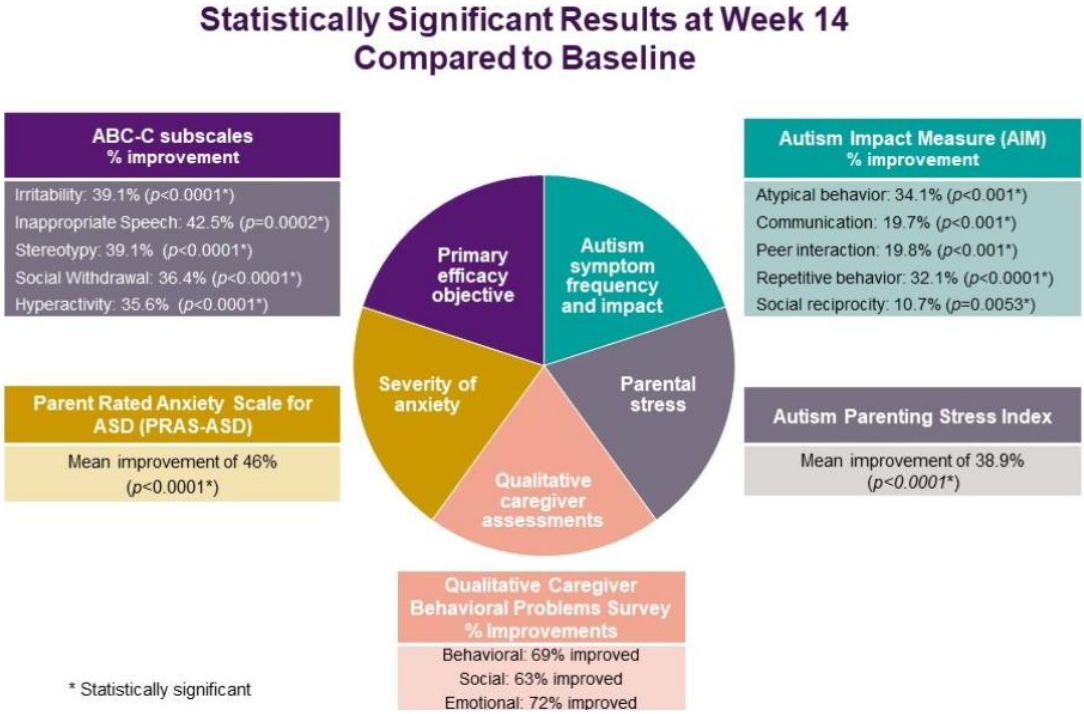
Despite high awareness and advocacy efforts, the medical need in ASD is significant and unmet. There is an accelerating rate of diagnosis, yet only two agents, risperidone and aripiprazole, have been approved by the FDA for the treatment of ASD symptoms. Both of these are atypical antipsychotics and carry a significant side effect profile, and neither is approved to address the key symptoms of social impairment and anxiety. The societal burden for ASD in the United States is expected to grow to $461 billion by 2025.

Recent studies suggest that ASD may be associated with a disruption in the endocannabinoid system, which modulates many cellular functions and molecular pathways that are altered in ASD, including GABAergic imbalance, glutamatergic transmission, oxidative stress, immune dysregulation and altered energy metabolism. Altered anandamide (an endocannabinoid) signaling may contribute to ASD-related social and communication impairments. Clinical and anecdotal data show improvement in social avoidance and anxiety in children receiving treatment with cannabidiol. Exogenous cannabidiol may modulate the endocannabinoid system and improve certain autism-related behaviors.

Phase 2 Clinical Trial

In May 2020, we reported positive top-line results of the Phase 2 BRIGHT (An Open-Label Tolerability and Efficacy Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Autism Spectrum Disorder) clinical trial, a 14- week open label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for the treatment of pediatric and adolescent patients with ASD. The trial evaluated multiple efficacy assessments, including the Aberrant Behavior Checklist – Community, or ABC-C, Autism Parenting Stress Index, Patient Reported Anxiety Scale – Autism Spectrum Disorder, or PRAS-ASD, Autism Impact Measure, or AIM, Clinical Global Impression – Severity, or CGI-S, and the Clinical Global Impression – Improvement, or CGI-I. Patients treated with Zygel demonstrated statistically significant improvement at week 14 compared to baseline for each ABC-C subscale (Irritability, Inappropriate Speech, Stereotypy, Social Withdrawal, and Hyperactivity). Patients receiving Zygel achieved statistically significant caregiver-reported improvements compared to baseline across all subscales of the AIM: Atypical behavior ($p<0.001$), Communication ($p<0.001$), Peer Interaction ($p<0.001$), Repetitive Behavior ($p<0.001$), and Social Reciprocity ($p=0.0053$). In addition, statistically significant improvements compared to baseline were observed at week 14 of treatment with Zygel in the Autism Parenting Stress Index ($p<0.0001$). We expect to discuss a path forward with the FDA in the first half of 2021. The results of the other efficacy assessments are consistent with the results demonstrated in the ABC-C.

The data derived from the BRIGHT trial can be summarized as follows:



Development of Zygel for Treatment of 22q11.2 Deletion Syndrome (22q)

22q Overview

22q is the most common contiguous gene deletion syndrome; the microdeletion occurs on the long arm of chromosome 22 at a location designated q11.2. It is a rare disorder, affecting approximately 81,000 patients in the U.S. There are no drugs with an approved indication for the treatment of 22q.

22q is considered a mid-line condition, which is a defect or condition that occurs on the anterior portion of a body, usually in the middle or center of the body, with physical symptoms including characteristic palate abnormalities, heart defects, immune dysfunction, and esophageal / GI issues. There are two primary stages of 22q patient management. During infancy, doctors address the acute physical concerns, such as anomalies of heart and palate, with surgery. Once the physical concerns are stabilized, the focus shifts to managing the neuropsychiatric symptoms. Neuropsychiatric illnesses (e.g., anxiety disorders, ASD) and learning disabilities are common in this patient population. The syndrome is associated with increased anxiety, withdrawn behavior and social interaction problems. Early onset of these core neuropsychiatric symptoms may disrupt development and quality of life in these patients and may heighten the risk of later psychotic disorders. Psychoses like schizophrenia are common in this population; there is a 25-fold increased risk of developing schizophrenia among people with 22q compared to the lifetime risk in the general population. Early control of anxiety may delay the development of such psychoses.

Cannabidiol may treat the neuropsychiatric symptoms of 22q due to its activity as an agonist at $5HT_{1A}$ receptors, an antagonist at GPR55 receptors, and a modulator of the endocannabinoid system.

Phase 2 Clinical Trial

In May 2019, we initiated the open-label Phase 2 INSPIRE (Assessing the Impact of Zygel [Transdermal Cannabidiol Gel] on Pediatric Behavioral and Emotional Symptoms of 22q11.2 Deletion Syndrome) clinical trial, a 14-week open label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for treatment of behavioral symptoms of 22q. We expect to enroll approximately 20 male and female patients (ages six through 17 years). Recruitment into the INSPIRE trial has been delayed due to the impact of COVID-19 and resulting significant travel restrictions in Australia. Once these restrictions are lifted and enrollment is complete, we will provide a timeframe for disclosing top line results of this trial. In September 2020, we were granted orphan drug designation from the FDA for the use of cannabidiol for the treatment of 22q.

Development of Zygel for Treatment of Developmental and Epileptic Encephalopathies (DEE)

DEE Overview

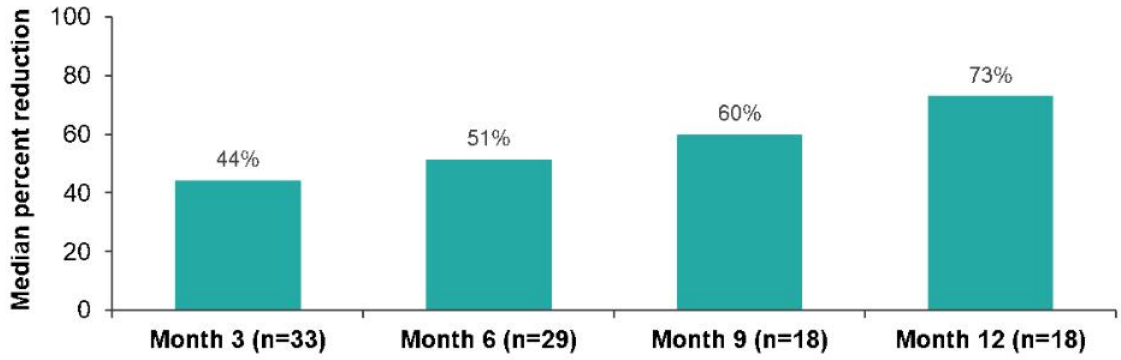
DEE is a category of rare and ultra-rare severe brain disorders that manifest with seizures or EEG abnormalities that are associated with delay or regression in cognition and/or behavior. This category includes a number of epilepsy syndromes, including DS, LGS, Doose, and Ohtahara (early infantile epileptic encephalopathy), and early-onset epilepsy syndromes caused by variants of genes including synaptic Ras GTPase activating protein 1 gene, or SYNGAP1, and sodium voltage-gated channel alpha subunit 1 gene, or SCN1A, among others. We believe, based on analysis and a recent publication (Aaberg et. al, *Epilepsia*, 2017; 58: 1880-1891) which incorporates new classification systems from ILAE that there are approximately 45,000 DEE patients in the United States.

We believe that Zygel may provide an effective treatment for epilepsy based on the anticonvulsant effects of cannabidiol due to its ability to reduce neuronal hyperexcitability shown in multiple *in vivo* models of epilepsy and clinical trials conducted. Epilepsy specialists and patient organizations have shown considerable interest in the potential therapeutic role of cannabidiol in epilepsy and especially, in children with DEE. GW Pharmaceuticals, PLC, or GW, has received approval from the FDA to market Epidiolex, a sesame oil liquid formulation of highly concentrated plant-extracted cannabidiol, in the United States for the treatment of seizures associated with DS, LGS and TSC.

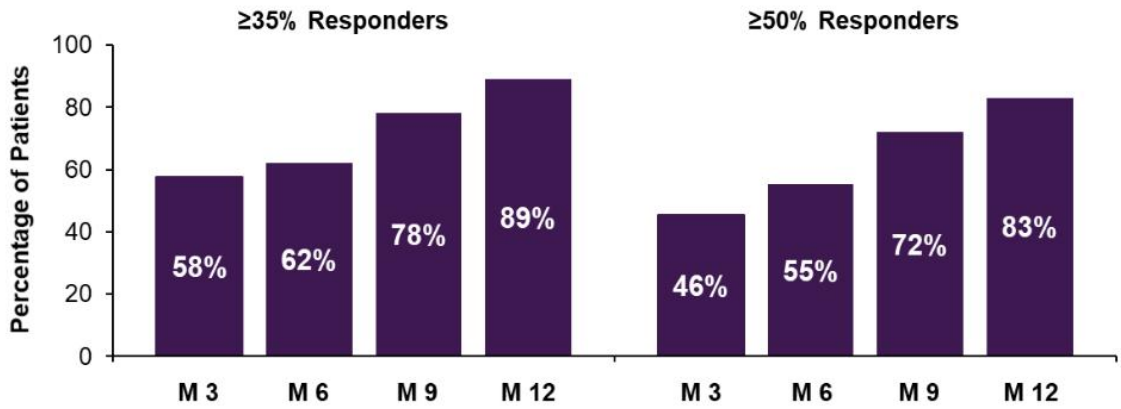
Phase 2 Clinical Trial in Children and Adolescents with DEE

In September 2019, we reported positive top-line results from the BELIEVE 1 (Open La**b**el Study to Assess the Safety and **E**fficacy of Zygel Administered as a Transderma**l** Gel to Ch**i**ldren and Adol**e**scents with De**v**elopmental and **E**pileptic Encephalopathy) clinical trial, a six-month, open-label, multi-dose clinical trial designed to evaluate the efficacy and safety of Zygel in children and adolescents (ages three through 17 years) with DEE. Enrolled patients received weight-based initial doses of 250 mg daily or 500 mg daily and during the maintenance phase patients could receive up to 1000 mg daily, of Zygel.

All 48 patients enrolled in the trial were included in the safety data for the trial. Forty-six patients were included in the modified intention-to-treat, or mITT, population. Of the 46 patients in the mITT population, 33 (72%) had focal impaired-awareness seizures, or FIAS, (previously known as complex partial seizures) and/or tonic-clonic seizures, or TCS, (focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures) at baseline. These patients experienced a median baseline seizure count of 8.2 FIAS and/or convulsive seizures. Compared to baseline seizure frequency, these patients experienced a ≥44% median reduction in these seizures from month two onwards using monthly seizure frequency. At month twelve, patients remaining in the trial experienced a 73% reduction in seizures compared to baseline.



A substantial percentage of patients achieved ≥35% and ≥50% reduction in FIAS and TCS by month three (58% and 46%, respectively), and these reductions in seizures continued through month 12 (89% and 83%, respectively).



Reduction in seizure frequency was also assessed in the 14 of 48 patients who had comorbid ASD (29%). Eleven of the 14 patients (79%) had FIAS and/or TCS (focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures) at baseline. The reduction in seizure frequency and percent of patients who achieved ≥35% and ≥50% reductions in FIAS and TCS were similar to the overall population. Compared to baseline seizure frequency, these patients experienced a ≥45% median reduction in these seizures from month two onwards. At month twelve, patients remaining in the trial experienced a 74% reduction in seizures compared to baseline. A substantial percentage of these patients achieved ≥35% and ≥50% reductions in FIAS and TCS by month three (60% and 40%, respectively), and these reductions in seizures continued through month 12 (75% and 75%, respectively).

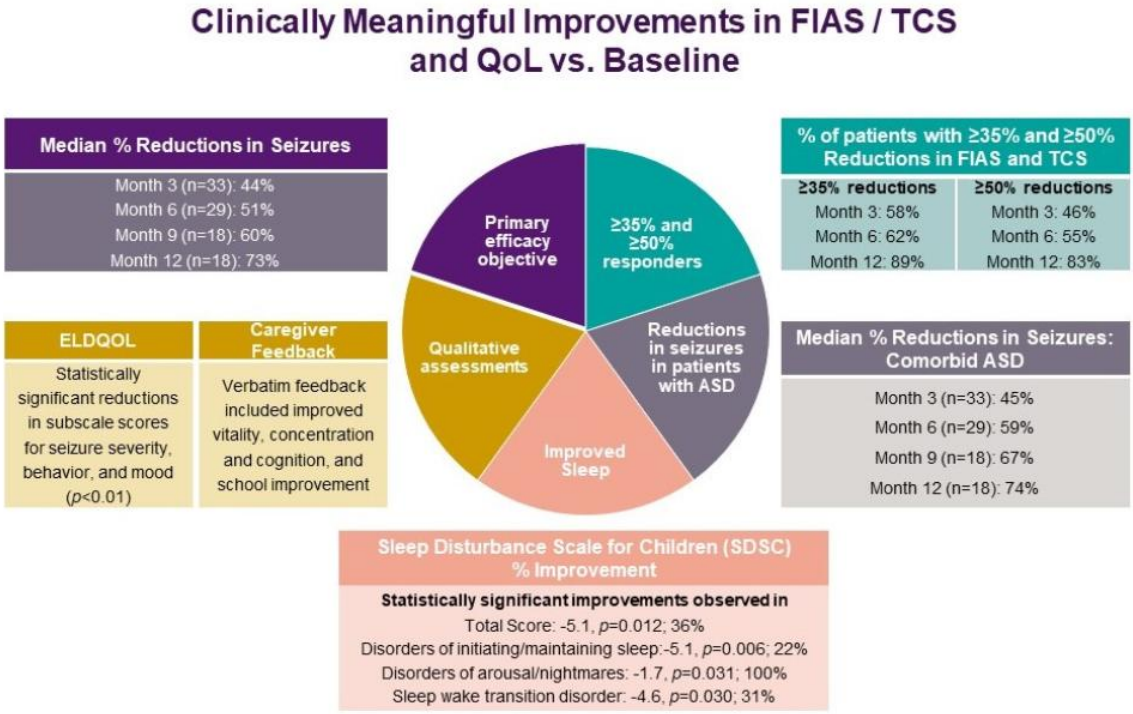
The impact of Zygel on sleep was also assessed in the trial using the Sleep Disturbance Scale for Children, or SDSC. Significant improvements were seen in the mean *t*-score from baseline for SDSC total score, disorders in initiating or

maintaining sleep, disorders of arousal/nightmares, and in sleep wake transition disorder. These changes were associated with reductions in the percentage of patients above the threshold for clinically significant sleep problems for each parameter. The mean change from baseline and percent reduction in patients above the threshold for clinically significant sleep problems were: SDSC total score (-5.1, p=0.012; 36%), disorders in initiating or maintaining sleep (-5.1, p=0.006; 22%), disorders of arousal/nightmares (-1.7, p=0.031; 100%), and in sleep wake transition disorder (-4.6, p=0.030; 31%).

In the trial, Zygel was well tolerated, and the safety profile was consistent with previously released data from Zygel clinical trials. One patient discontinued the study as a result of an application site reaction, and seven discontinued as a result of withdrawal of consent or perceived lack of efficacy. Children with DEE are medically fragile, and as such adverse events, whether unrelated or related to study drug, that occur during the trial period are common, expected and consistent with rates observed in other trials conducted in DEE. Through six months of therapy, 60% of patients experienced a treatment related adverse event. Most treatment related adverse events were mild to moderate. The most common treatment related adverse events (in >5% of patients) are application site dryness (8.3%), application site pain (8.3%), and somnolence (8.3%). Ten patients experienced a serious adverse event, or SAE, eight of which were deemed to be unrelated to study drug. Two SAEs were deemed possibly related to study drug, including one case of lower respiratory tract infection and one case of status epilepticus, both of which are common events in this patient population. There were no patient deaths during the study.

As part of the BELIEVE 1 study, caregivers were asked to provide a qualitative assessment regarding their child’s overall experiences during treatment with Zygel. Caregiver feedback to a series of open-ended questions was collected and coded by two independent reviewers. These qualitative assessments indicated improvements in alertness, awareness, or energy (58% of caregivers); seizures (51% of caregivers); cognition/concentration (47% of caregivers); socially-avoidant behaviors (44% of caregivers); and school attendance (28% of caregivers). Caregivers also assessed the impact of Zygel on their child’s quality of life using the Epilepsy and Learning Disabilities Quality of Life, or ELDQOL, scale. Statistically significant reductions in the ELDQOL subscales scores, indicating improvement, were shown for seizure severity, behavior, and mood (p<0.01).

The data collected from the BELIEVE trial can be summarized as follows:



In September 2020, we concluded iterative discussions with the FDA using their “Written Response Only” meeting format regarding the clinical pathway for Zygel in DEE. While FDA supports a development program which would evaluate the treatment of focal-impaired awareness and convulsive seizures, based on FDA feedback suggesting that we pursue an individual syndrome, we are evaluating potential target indications and expect to finalize target syndrome selection in 2021 in one or more DEE syndromes.

Early Clinical Trials

In June 2016, we completed two Phase 1 clinical trials for ZYN002 in healthy volunteers and patients with epilepsy. The first Phase 1 single rising dose clinical trial for ZYN002 in healthy human subjects and in patients with epilepsy evaluated the tolerability and pharmacokinetics, or PK, profile of ZYN002. Results from this clinical trial demonstrated that ZYN002 was safe and well-tolerated at all tested dose levels and the incidence of adverse events associated with ZYN002 was similar to placebo for both healthy subjects and epilepsy patients. The second Phase 1 clinical trial was a randomized, double-blind, placebo controlled multiple rising dose clinical trial for ZYN002 in 24 healthy volunteers and 12 patients with epilepsy to evaluate the PK profile, pharmacodynamics, or PD, and tolerability of multiple doses (200, 250, and 500 mg) of ZYN002. Each volunteer and patient received seven days of either ZYN002 or placebo. Results from this clinical trial demonstrated that ZYN002 was safe and well-tolerated at all dose levels. The twice daily dosing provided a more favorable PK profile with comparable results between healthy volunteers and epilepsy patients.

Transdermal application of ZYN002 was very well tolerated with minimal skin erythema. Skin dryness at the application site was common for both Zygel and placebo gel. Overall, the incidence of adverse events associated with ZYN002 was similar to placebo in both healthy volunteers and adult epilepsy patients. There were no reports of somnolence or fatigue and a very low incidence of gastrointestinal events was observed. There were no serious adverse events or discontinuations for healthy volunteers and epilepsy patients receiving ZYN002. One healthy volunteer receiving placebo gel developed a serious adverse event suspected to be a catheter infection and was discontinued from the study.

In addition, healthy volunteers and epilepsy patients had no drug related changes in performance on the Trail Making Test, a test of visual attention, psychomotor ability, and task switching; a divided attention task; and the Paced Auditory Serial Addition Task, or PASAT, a test that measures working memory and focused attention. These results indicate that ZYN002 did not produce impairment in critical areas of cognitive functioning often impacted by central nervous system drugs. No changes in mood symptoms as assessed by the Inventory of Depression and Anxiety Symptoms, or IDAS, and the Positive and Negative Affect Schedule, or PANAS were observed for ZYN002 suggesting that ZYN002 is not associated with declines in psychological health.

In July 2016, we completed a third Phase 1 clinical trial for ZYN002, which was a randomized, double-blind, placebo-controlled trial in 42 healthy volunteers. The volunteers received a range of cannabidiol doses from 395 mg to 504 mg daily in 2.5% and 4.2% ZYN002 formulations for fourteen days. Results from this clinical trial demonstrated that ZYN002 was very well tolerated with minimal skin erythema. Cannabidiol plasma concentrations were dose dependent and did not fluctuate at steady state. The 4.2% formulation demonstrated a comparable PK and tolerability profile to the 2.5% concentration and was easier to use due to the lower volume. There were no serious adverse events or discontinuations from this clinical trial.

Overall, in the Phase 1 program, ZYN002 was demonstrated to be safe and well tolerated, provided a favorable cannabidiol PK profile, and no THC was detected in plasma or urine.

Intellectual Property

The success of our product candidates will depend in large part on our ability to:

- obtain and maintain patent and other legal protections for the proprietary compounds, technology, inventions and improvements we consider important to our business;
- prosecute our patent applications and defend our issued patents;
- preserve the confidentiality of our trade secrets; and
- operate without infringing the patents and proprietary rights of third parties.

We internally developed our intellectual property related to our product candidates. We have sought and intend to continue to seek appropriate patent protection for our product candidates, as well as other proprietary technologies and their uses, by filing patent applications in the United States and selected other countries.

As of March 5, 2021, we owned a total of sixteen issued U.S. patents. These U.S. patents will expire between 2026 through 2038. We have already obtained additional patent term for some of the issued patents to compensate us for delays at the United States Patent and Trademark Office, or USPTO, under the patent term adjustment laws.

In addition to our U.S. intellectual property, we own 154 corresponding foreign issued patents and eight corresponding foreign patent applications.

Zygel

Our Zygel patent portfolio currently consists of eight issued patents in the United States, and six pending United States patent applications. There are seven issued patents in Canada, France, Germany, Ireland, Switzerland, and the United Kingdom, and three pending Patent Cooperation Treaty, or PCT, applications. The issued patents claim the permeation enhanced formulation of Zygel and methods of use relating to Zygel, including methods of treating FXS and ASD. The issued patents will expire between 2026 and 2038. We anticipate that any patents issued from our pending US applications or pending PCT applications will expire between 2038 and 2039.

Other

The rest of our patent portfolio relates to patents and applications owned by us and directed to other potential product candidates.

Trade Secrets and Proprietary Information

We seek to protect our proprietary information, including our trade secrets and proprietary know-how, by requiring our employees, consultants and other advisors to execute confidentiality agreements upon the commencement of their employment or engagement. These agreements generally provide that all confidential information developed or made known during the course of the relationship with us be kept confidential and not be disclosed to third parties except in specific circumstances. In the case of our employees, the agreements also typically provide that all inventions resulting from work performed for us, utilizing our property or relating to our business and conceived or completed during employment shall be our exclusive property to the extent permitted by law. Where appropriate, agreements we obtain with our consultants also typically contain similar assignment of invention obligations. Further, we require confidentiality agreements from entities that receive our confidential data or materials.

Manufacturing

The active pharmaceutical ingredients, or APIs, used in our product candidates are synthesized by contract manufacturers. Zygel is manufactured and filled into unit of use sachets by contract manufacturers.

We selected our contract manufacturers for their specific competencies in manufacturing, product design, and materials. FDA regulations require that products be produced under current Good Manufacturing Practices, or cGMPs. Our key suppliers currently meet cGMPs and we believe have sufficient capacities to meet our projected product requirements through early commercialization.

Commercial Operations

Our Vice President of Commercial and Business Development is responsible for pre-commercialization activities, including global market analysis, strategic optimization and value development associated with our product candidates, as well as business development activities as we evaluate partnering options. However, we do not currently have a fully integrated organization for the sales, marketing and distribution of pharmaceutical products. We may rely on licensing and co-promotion agreements with strategic collaborators for the commercialization of our products in the United States and other territories. If we choose to build a commercial infrastructure to support marketing in the United States, such commercial infrastructure could be expected to include a sales force supported by sales management, internal sales support, an internal marketing group and distribution support. To develop the appropriate commercial infrastructure internally, we would have to invest financial and management resources, some of which would have to be deployed prior to any confirmation that Zygel will be approved.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on proprietary products. We believe our scientific knowledge, technology, and development capabilities provide us with substantial competitive advantages, but we face potential competition from multiple sources, including major pharmaceutical, specialty pharmaceutical, and biotechnology companies; academic institutions; governmental agencies; and public and private research institutions. Successfully developed and commercialized product candidates must compete not only with existing therapies, but also with agents that may become available in the future.

We are currently studying Zygel in patients with FXS, ASD, 22q and DEE.

FXS

There are no drugs approved for the treatment of FXS or its most common symptoms, although various classes of medications are used off-label for the treatment of behavioral and mental health conditions associated with FXS. Some patients with FXS benefit from medications that treat attention deficit disorders, while others experiencing general anxiety, social anxiety and other chronic conditions may benefit from different types of anti-anxiety medications. Multiple companies are developing compounds for the treatment of FXS, including Confluence Pharmaceuticals, Allos Pharma and Tetra Therapeutics.

ASD

Two atypical antipsychotic drugs, risperidone and aripiprazole, are approved for autism-associated agitation and irritability, though neither is approved to address the key ASD symptoms of social impairment and anxiety. Various classes of medications are used off-label for the treatment of behavioral conditions associated with ASD. Early intervention can improve learning, communication and social skills, as well as underlying brain development. Applied behavior analysis, or ABA, and therapies based on its principles are the most researched and commonly used behavioral interventions for autism. Many children affected by autism also benefit from other interventions such as speech and occupational therapy. We understand that GW is studying cannabidivarin, or CBDV, for use in patients with ASD.

22q

There are no drugs approved for the treatment of 22q or its most common symptoms, although various classes of medications are used off-label for the treatment of the behavioral symptoms. There are two primary stages of 22q patient management. During infancy, doctors address the acute physical concerns, such as anomalies of heart and palate, with surgery. Once the physical concerns are stabilized, the focus shifts to managing the neuropsychiatric symptoms, with anxiety being a key symptom. Anxiety is predominately managed with selective serotonin reuptake inhibitors, or SSRIs. Cognitive behavioral therapy is also an important component of treatment. We are not aware of any studies of cannabidiol, THC or any other cannabinoid in this patient population.

In addition, various companies are working on non-cannabinoid treatments for indications similar to those that we are evaluating for Zygel, including: Confluence Pharmaceuticals with acamprosate for FXS; Tetra Therapeutics with BPN14770, a selective small molecule inhibitor of the phosphodiesterase type-4D (PDE4D) subtype, for FXS; Ovid Therapeutics with OV101, a delta selective GABA receptor agonist for FXS; Marinus Pharmaceuticals with ganaxolone for pediatric refractory epilepsies; Zogenix with fenfluramine hydrochloride (ZX-008) for LGS; Roche with RO5285119 for ASD; and Janssen with JNJ-42165279 for ASD, among others.

DEE

Within epilepsy, we intend to treat patients with DEE. Second and third generation anti-seizure medications, or ASMs (also known as antiepileptic drugs, or AEDs), continue to improve upon first generation therapies, but experts contend that a better understanding of the disorder accompanied by fundamentally innovative treatments will be required to effectively improve treatment outcomes for the high percentage of patients who remain unresponsive to ASMs. The majority of ASMs have frequent safety concerns including serious CNS adverse events and drug-drug interactions.

GW received approval in 2018 from the FDA to market Epidiolex, a sesame oil liquid formulation of highly concentrated plant extracted cannabidiol, in the United States, which is now approved for the treatment of seizures associated with DS, LGS and TSC. GW has also received marketing authorization from the European Commission, or EC, to market Epidiolex (under the trade name *Epidyolex®)* for use as adjunctive therapy of seizures associated with DS and LGS, in conjunction with clobazam. The Therapeutic Goods Administration, or TGA, in Australia has also approved Epidyolex for the treatment of LGS and DS. GW is also studying additional cannabinoids and formulations for patients

with ASD, schizophrenia, neonatal hypoxic-ischemic encephalopathy as well as other neuropsychiatric conditions. In February 2021, GW announced that they agreed to be acquired by Jazz Pharmaceuticals, plc.

In January 2021, Radius Health, Inc. acquired cannabidiol assets from Benuvia Therapeutics, which has previously acquired cannabidiol and THC formulations from Insys Therapeutics, Inc., or Insys. Insys was developing a synthetic cannabidiol oral solution compound for the potential treatment of infantile spasms, childhood absence epilepsy, Prader-Willi syndrome and other rare epilepsy syndromes. Zogenix, Inc. has also received FDA and EC approval for its product, Fintepla® (fenfluramine) oral solution, for the treatment of DS. Zogenix is also studying this product in other treatment-resistant epilepsies, including LGS.

Government Regulation and Product Approval

As a development stage pharmaceutical company that operates in the United States, we are subject to extensive regulation by the FDA, and other federal, state, and local regulatory agencies. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and its implementing regulations set forth, among other things, requirements for the research, testing, development, manufacture, quality control, safety, effectiveness, approval, labeling, storage, record keeping, reporting, distribution, import, export, advertising and promotion of our products. Although the discussion below focuses on regulation in the United States, we anticipate seeking approval for, and marketing of, our products in other countries. Generally, our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the United States, although there can be important differences. Additionally, some significant aspects of regulation in the European Union, or EU, are addressed in a centralized way through the European Medicines Agency, or EMA, and the EC but country-specific regulation remains essential in many respects. The process of obtaining regulatory marketing approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and may not be successful.

U.S. Government Regulation

The FDA is the primary body that regulates pharmaceuticals in the United States, and its regulatory authority is based in the FDC Act. Pharmaceutical products are also subject to other federal, state and local statutes and regulations. In particular, controlled substances, like cannabidiol and THC, are regulated by the U.S. Drug Enforcement Administration, or DEA. A failure to comply with any requirements during the product development, approval, or post-approval periods, may lead to administrative or judicial sanctions, which could include the imposition of a hold on clinical trials, refusal to approve pending marketing applications or supplements, withdrawal of approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution.

The steps required to obtain approval for commercialization of a new drug in the United States are lengthy, complex and expensive, and the outcome is far from certain. These steps generally include:

- completion of preclinical studies, animal studies and formulation studies in compliance with the FDA's good laboratory practices, or GLP, regulations;
- submission to the FDA of an IND to support human clinical testing in the United States;
- approval by an Institutional Review Board, or IRB, before each trial may be initiated;
- performance of adequate and well-controlled clinical trials in accordance with federal regulations and with current Good Clinical Practices, or GCPs, to establish the safety and efficacy of the investigational product candidate for each target indication;
- submission of an NDA to the FDA;
- satisfactory completion of an FDA Advisory Committee review, if applicable;

- satisfactory completion of an FDA inspection of the manufacturing facilities at which the investigational product candidate is produced to assess compliance with cGMP, and to assure that the facilities, methods and controls are adequate; and

- FDA review and approval of the NDA.

In certain cases, a drug may require scheduling by the DEA prior to commercialization. This step is required if the drug has a potential for abuse and is not currently controlled (scheduled) by the DEA or is controlled in Schedule I.

Pre-clinical Testing

Before testing any compound in humans in the United States, a company must develop pre-clinical data, generally including laboratory evaluation of product chemistry and formulation, as well as toxicological and pharmacological studies in animal species to assess safety and quality. Certain types of animal studies must be conducted in compliance with the FDA's GLP regulations and the Animal Welfare Act, which is enforced by the Department of Agriculture.

Clinical Trials

FDA regulations require that the person or entity sponsoring or conducting a clinical study in the United States for the purpose of investigating a drug candidate's safety and effectiveness submit to the FDA an IND application, which contains pre-clinical testing results and provides a basis for the FDA to conclude that there is an adequate basis for testing the drug in humans. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. Long-term pre-clinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. If the FDA does not place the proposed clinical trial in the IND application on clinical hold within this 30-day period, the clinical trial may begin. Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients under the supervision of qualified investigators. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND. Clinical trials must be reviewed, approved and conducted under the auspices of an IRB. The sponsor, investigators, and IRB must, as applicable, obtain the informed written consent of each participating subject, comply with the protocol and investigational plan, adequately monitor the clinical trial, and timely report adverse events. We filed an IND with the FDA for Zygel in FXS in 2018 and have passed the 30-day waiting period.

In addition to filing an IND with the FDA, we must receive approval from the DEA prior to commencement of any clinical trials in the United States that involve the use of Schedule I controlled substances.

We plan to submit NDAs for our product candidates to the FDA upon completion of all requisite clinical trials. The clinical investigation of an investigational product candidate is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The three phases of an investigation are as follows:

- *Phase 1.* Phase 1 involves the initial introduction of a product candidate into humans. Phase 1 clinical trials may be conducted in patients with the target disease or condition or healthy volunteers. These studies are designed to evaluate the safety, metabolism, PK and pharmacologic actions of the product candidate in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During Phase 1 clinical trials, sufficient information about the product candidate's safety, PK and pharmacological effects may be obtained to permit the design of Phase 2 clinical trials. The total number of participants included in Phase 1 clinical trials varies, but is generally in the range of 20 to 80.

- *Phase 2.* Phase 2 clinical trials are conducted to develop initial data regarding the effectiveness of the product candidate in the target disease or condition, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and additional safety risks associated with the product candidate. Phase 2 clinical trials are typically controlled and conducted in a limited patient population, usually involving no more than several hundred participants.

- *Phase 3.* Phase 3 clinical trials are controlled clinical trials conducted in an expanded subject population at geographically dispersed clinical trial sites. They are performed after preliminary evidence suggesting effectiveness of the investigational product candidate has been obtained, and are intended to further evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk profile of the product candidate, and to provide an adequate basis for labeling. Phase 3 clinical trials usually involve several hundred to several thousand participants. In most (though not all) cases, the FDA requires two adequate and well controlled Phase 3 clinical trials to support approval of a drug.

The decision to terminate development of an investigational product candidate may be made by either a health authority body, such as the FDA, or IRB/ethics committees, or by a company for various reasons. The FDA may issue a "clinical hold," ordering the temporary or permanent discontinuation of a clinical trial, or impose other sanctions, if it believes that the clinical trial is not being conducted in accordance with FDA requirements presents an unacceptable risk to the clinical trial patients, or for other reasons. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions. In some cases, clinical trials are overseen by an independent group of qualified experts organized by the trial sponsor called a data safety monitoring board, or DSMB, or data monitoring committee, or DMC. A DSMB or DMC may provide recommendations on whether or not a trial may move forward at designated check points, based on access to data from the ongoing trial. The suspension or termination of development can occur during any phase of clinical trials if it is determined that the participants or patients are being exposed to an unacceptable health risk. In addition, there are requirements for the registration of ongoing clinical trials of product candidates on public registries and the disclosure of certain information pertaining to the trials as well as clinical trial results after completion.

A sponsor may request a special protocol assessment, or SPA, the purpose of which is to reach agreement with the FDA on the design and size of certain clinical trials (including Phase 3 clinical trials), clinical studies, or animal studies to address applicable scientific and regulatory requirements. An SPA request must be made before the proposed trial begins, and if areas of agreement are reached, they will be documented in a letter. The agreement generally may not be changed by the sponsor or the FDA after the trial begins, except with the written agreement of the sponsor and the FDA or if the FDA determines that a substantial scientific issue essential to determining the safety or efficacy of the product candidate was identified after the testing began. An SPA is not binding if new circumstances arise, and there is no guarantee that a study will ultimately be adequate to support an approval even if the study is subject to an SPA.

We have conducted and plan to continue to conduct clinical trials for Zygel in the United States, Australia and New Zealand and are subject to FDA regulatory requirements as well as the regulatory requirements related to the conduct of clinical trials of the Therapeutic Goods Administration, or TGA in Australia and the New Zealand Medicines and Medical Device Safety Authority in New Zealand. We may also decide to conduct clinical trials in additional foreign countries, including the United Kingdom, Ireland and Canada and, would be subject to laws and regulations governing the conduct of such trials in those countries and any other foreign countries where we decide to study Zygel in the future.

New Drug Applications (NDA)

In order to obtain approval to market a drug in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the product candidate for the proposed indication. The application includes all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, pharmacology, manufacturing, controls and proposed packaging and labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must

be sufficient in quality and quantity to establish the safety and effectiveness of the product candidate to the satisfaction of the FDA. Data from clinical trials conducted outside the United States may be accepted by the FDA subject to certain conditions. For example, the clinical trial must be conducted in accordance with GCP requirements and the FDA must be able to validate the data from the clinical trial through an onsite inspection if it deems such inspection necessary. Where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the United States, the FDA will not approve the application on the basis of foreign data alone unless those data are considered applicable to the U.S. patient population and U.S. medical practice, the clinical trials were performed by clinical investigators of recognized competence, and the data is considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. If the drug has a potential for abuse, the NDA must include a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the federal Controlled Substances Act, or CSA. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

In most cases, the NDA must be accompanied by a substantial user fee, currently $2,875,000 for fiscal year 2021. The applicant under an approved new drug application is also subject to an annual program fee, currently $336,000 per product for fiscal year 2021. These fees are typically increased annually. There may be some instances in which the user fee is waived, including in the case of an orphan drug designation, such as with Zygel for FXS and 22q. The FDA will initially review the NDA for completeness before it accepts the NDA for filing. The FDA has up to 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. If the application is not sufficiently complete, the FDA may refuse to accept the NDA for filing and request additional information. A refusal to file, which requires resubmission of the NDA with the requested additional information, delays review of the application. If the NDA submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Most NDAs for standard review product candidates are reviewed within 12 months of submission. The FDA can extend this review to consider certain late-submitted information or information intended to clarify information already provided in the submission. Most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. The FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP. The FDA may refer applications for novel product candidates that present challenging 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 an NDA, the FDA may 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 cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or, if the FDA concludes that an NDA does not meet the regulatory standards for approval, a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. Data from clinical trials are not always conclusive, and the FDA's interpretation of data may differ from that of the sponsor's. Obtaining approval can take years, requires substantial resources and depends on a number of factors, including the severity of the targeted disease or condition, the availability of alternative treatments, and the risks and benefits demonstrated in clinical trials.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require risk evaluation and mitigation strategies, or REMS,

to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including certain changes in indications, labeling, or manufacturing processes or facilities, may require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA generally applies the same procedures and standards in reviewing NDA supplements as it does in reviewing NDAs.

From time to time, legislation is drafted, introduced and passed in the U.S. Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition to new legislation, the FDA regulations and policies are often revised or reinterpreted by the agency in ways that may significantly affect our business and our product candidates. It is impossible to predict whether further legislative or FDA regulation or policy changes will be enacted or implemented and what the impact of such changes, if any, may be.

Disclosure of Clinical Trial Information

Some countries require sponsors of clinical trials of certain regulated products, including prescription drugs to register and disclose certain clinical trial information on a public website. For example, in the United States, sponsors are required to register this information on a website maintained by the U.S. National Institutes of Health, or NIH, at www.clinicaltrials.gov. In Australia and New Zealand, sponsors register clinical trial information on a website maintained by the Australian New Zealand Clinical Trials Registry at www.anzctr.org.au. When a clinical trial is registered on these websites, certain information regarding the product, patient population, phase of investigation, study sites and investigator, and other aspects of the clinical trial must be posted. Sponsors are also obligated to disclose the results of many of these trials after completion, although under certain circumstances disclosure of the results of these trials can be delayed until the product or new indication being studied has been approved. Competitors may use this publicly-available information to gain knowledge regarding the design and progress of our development programs.

Advertising and Promotion

The FDA and other federal agencies closely regulate the marketing and promotion of drugs through, among other things, standards and regulations for direct-to-consumer advertising, promotion to healthcare practitioners, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet. A product cannot be commercially promoted before it is approved. After approval, product promotion can include only those claims relating to safety and effectiveness that are consistent with the labeling approved by the FDA. Healthcare providers are permitted to prescribe drugs for "off-label" uses — that is, uses not approved by the FDA and therefore not described in the drug's labeling — because the FDA does not regulate the practice of medicine. However, FDA historically has restricted manufacturers' communications regarding off-label uses. Broadly speaking, a manufacturer may not promote a drug for off-label use, but may engage in non-promotional, balanced communication regarding off-label use under specified conditions. Failure to comply with applicable FDA requirements and restrictions in this area may subject a company to adverse publicity and enforcement action by the FDA, the U.S. Department of Justice, or the DOJ, or the Office of the Inspector General, or OIG, of the U.S. Department of Health and Human Services, or HHS, as well as state authorities. This enforcement activity could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. In addition to FDA restrictions on marketing of pharmaceutical products, state and federal fraud and abuse and consumer protection laws have been applied to restrict certain marketing practices in the pharmaceutical industry in recent years. Some of the pertinent laws have not

been definitively interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. In addition, these laws and their interpretations are subject to change.

Other Post-Approval Regulations

After a drug receives regulatory approval, its sponsor is required to comply with a number of post-approval requirements. For example, as a condition of approval of an NDA, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization or the FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, as a holder of an approved NDA, a company is required to report adverse reactions and production problems to the FDA, to provide updated safety and efficacy information, and to comply with requirements concerning advertising and promotional labeling for any of its products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval, and the FDA periodically inspects manufacturing facilities to assess compliance with cGMP. cGMP includes requirements regarding organization and training of personnel, building and facilities, equipment, control of components and drug product containers, closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls and records and reports. In addition, changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before it can be implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon a sponsor and any third-party manufacturers that a sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance. Failure to comply with applicable cGMP requirements or the conditions of the product's approval may lead the FDA to take enforcement action, which could result in fines, civil penalties, injunctions, suspension of manufacturing operations, operating restrictions, withdrawal of FDA approval, seizure or recall of products, and criminal prosecution. Although we periodically monitor the compliance of our third-party manufacturers, we cannot be certain that our present or future third-party manufacturers will consistently comply with cGMP or other applicable FDA regulatory requirements.

Compliance

During all phases of development (pre- and post-marketing), failure to comply with applicable regulatory requirements may result in administrative or judicial sanctions. These sanctions could include the FDA's imposition of a clinical hold on trials, refusal to approve pending applications, refusal to accept clinical data from outside the United States, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, product detention or refusal to permit the import or export of products, injunctions, fines, civil penalties or criminal prosecution. Third country authorities can impose equivalent penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Controlled Substances

The CSA and its implementing regulations establish a "closed system" of distribution for controlled substances. The CSA imposes registration, security, recordkeeping and reporting, storage, manufacturing, distribution, labeling, importation, exportation, disposal and other requirements under the oversight of the DEA. The DEA is the federal agency responsible for regulating controlled substances, and requires those individuals or entities that manufacture, import, export, distribute, research, or dispense controlled substances to comply with the regulatory requirements to prevent the diversion of controlled substances to illicit channels of commerce.

Facilities that research, manufacture, distribute, import or export any controlled substance must register annually with the DEA. The DEA registration is specific to the particular location, activity(ies) and controlled substances utilized. For example, separate registrations are required for importation and manufacturing activities, and each registration authorizes which schedules of controlled substances the registrant may handle. However, certain coincident activities are permitted without obtaining a separate DEA registration, such as distribution of controlled substances by the manufacturer that produces them.

The DEA categorizes controlled substances into one of five schedules — Schedule I, II, III, IV, or V — with varying qualifications for listing in each schedule. Schedule I substances by definition have a high potential for abuse, have no currently "accepted medical use" in treatment in the United States and lack accepted safety for use under medical supervision. They may be used only in federally-approved research programs and may not be marketed or sold for dispensing to patients in the United States. Pharmaceutical products having a currently accepted medical use may be listed as Schedule II, III, IV or V substances, with Schedule II substances presenting the highest potential for abuse and physical or psychological dependence, and Schedule V substances presenting the lowest relative potential for abuse and dependence. The regulatory requirements are more restrictive for Schedule II substances than Schedule III-V substances. For example, all Schedule II drug prescriptions must be signed by a physician, physically presented to a pharmacist in most situations, and cannot be refilled. Marijuana and THC are Schedule I controlled substances under the CSA. Products approved for medical use in the United States that contain marijuana, THC or marijuana/THC extracts, must be placed in Schedules II-V, since approval by the FDA satisfies the "acceptable medical use" requirement. While marijuana and THC are controlled substances, the Agricultural Improvement Act of 2018 amended the CSA to exclude Cannabis meeting the statutory definition of hemp from the definition of marijuana. As a result, Cannabis that contains 0.3 percent or less of delta-9 THC on a dry weight basis is no longer considered a controlled substance. By extension, Cannabis-derived cannabidiol that satisfies the same limitation concerning delta-9 THC is also excluded from CSA regulatory controls. Because the definition of hemp does not expressly include synthetic equivalents of Cannabis or its derivatives, however, there is a lack of clarity about the CSA control status of pharmaceutically manufactured cannabidiol. Absent guidance to the contrary from the DEA, Cannabis and those products which contain Cannabis, that do not meet the definition of hemp remain in Schedule I of the CSA for purposes of development and research activities.

The DEA inspects all manufacturing facilities to review security, record keeping, reporting and compliance with other DEA regulatory requirements prior to issuing a controlled substance registration. The specific security requirements vary by the type of business activity and the schedule and quantity of controlled substances handled. The most stringent requirements apply to manufacturers of Schedule I and Schedule II substances. Required security measures commonly include background checks on employees and physical control of controlled substances through storage in approved vaults, safes and cages, and through use of alarm systems and surveillance cameras. An application for a manufacturing registration as a bulk manufacturer (not a dosage form manufacturer or a repacker/relabeler) for a Schedule I or II substance must be published in the Federal Register, and is open for 30 days to permit interested persons to submit comments, objections, or requests for a hearing. A copy of the notice of the Federal Register publication is forwarded by the DEA to all those registered, or applicants for registration, as bulk manufacturers of that substance. Once registered, manufacturing facilities must maintain records documenting the manufacture, receipt and distribution of all controlled substances. Manufacturers must submit periodic reports to the DEA of the distribution of Schedule I and II controlled substances, Schedule III narcotic substances, and other designated substances. Registrants must also report any controlled substance thefts or significant losses and must adhere to certain requirements to dispose of controlled substances. As with applications for registration as a bulk manufacturer, an application for an importer registration for a Schedule I or II substance must also be published in the Federal Register, which remains open for 30 days for comments. Imports of Schedule I and II controlled substances for commercial purposes are generally restricted to substances not already available from a domestic supplier or where there is not adequate competition among domestic suppliers. In addition to an importer or exporter registration, importers and exporters must obtain a permit for every import or export of a Schedule I and II substance, Schedule III, IV and V narcotic, specially designated Schedule III non-narcotics, or Schedule IV or V narcotic controlled in Schedule I or II by the Convention on Psychotropic Substances and submit import or export declarations for Schedule III, IV and V non-narcotics.

For drugs manufactured in the United States, the DEA establishes annually an aggregate quota for the amount of substances within Schedules I and II that may be manufactured or produced in the United States based on the DEA's estimate of the quantity needed to meet legitimate medical, scientific, research and industrial needs. This limited aggregate amount of *Cannabis* that the DEA allows to be produced in the United States each year is allocated among individual companies, which, in turn, must annually apply to the DEA for individual manufacturing and procurement quotas. The quotas apply equally to the manufacturing of the active pharmaceutical ingredient and production of dosage forms. The DEA may adjust aggregate production quotas a few times per year, and individual manufacturing or

procurement quotas from time to time during the year, although the DEA has substantial discretion in whether or not to make such adjustments for individual companies.

The states also maintain separate controlled substance laws and regulations, including licensing, recordkeeping, security, distribution, and dispensing requirements. State Authorities, including Boards of Pharmacy, regulate use of controlled substances in each state. Failure to maintain compliance with applicable requirements, particularly as manifested in the loss or diversion of controlled substances, can result in enforcement action that could have a material adverse effect on our business, operations and financial condition. The DEA may seek civil penalties, refuse to renew necessary registrations, or initiate proceedings to revoke those registrations. In certain circumstances, violations could lead to criminal prosecution.

We currently use contract manufacturers in the United States and Canada to manufacture the API for Zygel and contract manufacturers in the United Kingdom and Australia to manufacture the drug product. We have conducted and plan to continue to conduct clinical trials for Zygel in the United States, Australia and New Zealand. We may decide to develop, manufacture or commercialize our product candidates in additional countries. As a result, we will also be subject to controlled substance laws and regulations from the TGA in Australia, Health Canada's Office of Controlled Substances in Canada, the New Zealand Medicines and Medical Device Safety Authority in New Zealand, the Drugs & Firearms Unit (Home Office) of the National Drug Control System in the United Kingdom, and from other regulatory agencies in other countries where we develop, manufacture or commercialize Zygel in the future.

The Hatch-Waxman Act

Generic Competition

Any drug candidates approved for commercial marketing under an NDA would be subject to the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman Act. Among other things, the Hatch-Waxman Act establishes two abbreviated approval pathways for drug products that are in some way follow-on versions of already approved NDA products. The first provides that generic versions of an approved product may be approved under an Abbreviated New Drug Application, or ANDA, by a showing that the generic product is the "same as" the approved product in key respects. An ANDA provides for marketing of a drug product that has the same active ingredient(s), same strength, route of administration and dosage form as a previously approved NDA product (the "reference listed drug" or RLD) and has been shown through PK testing to be bioequivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are generally not required to conduct, or submit results of, preclinical studies or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as "therapeutic equivalents" to the RLD and can often be substituted by pharmacists under prescriptions written for the RLD. 505(b)(2) applications are the second approval pathway for follow-on drug products. 505(b)(2) applications are NDAs and must therefore contain full reports of safety and effectiveness data; however, in a 505(b)(2) application at least some of the required data is derived from studies not conducted by or for the applicant. In this regard, a 505(b)(2) application may rely on scientific literature or on the FDA's previous findings of safety and effectiveness of an approved RLD. Unlike an ANDA, a 505(b)(2) may be submitted for a product that differs in active ingredient, strength, route of administration, dosage form, or other conditions of use.

The approval of drug products submitted under these abbreviated approval pathways may be prevented by certain periods of regulatory exclusivity and/or extended patent protection provided by the Hatch-Waxman Act.

Impact of Listed Patents

An ANDA or 505(b)(2) applicant is required to certify to the FDA concerning any patents listed with the approved RLD in the FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Specifically, the applicant must certify: (i) that the required patent information has not been filed; (ii) that the listed patent has expired; (iii) the date that the listed patent will expire; or (iv) that the listed patent is invalid or will not be infringed by the new product. The ANDA or 505(b)(2) applicant may also elect to submit a statement certifying that its proposed ANDA label does not contain (or carves out) any language regarding a patented method of use rather

than certify to such listed method of use patent. If the applicant does not challenge the listed patents by filing a certification that the listed patent is invalid or will not be infringed by the new product, the ANDA or 505(b)(2) application will not be approved until all the listed patents claiming the referenced product have expired.

A certification that the new product will not infringe the RLD's listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA holder and patent owner once the ANDA or 505(b)(2) application has been accepted for filing by the FDA. The NDA holder and/or patent owner may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. If the patent was listed in the Orange Book before submission of the ANDA or 505(b)(2) NDA, the filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) application until the earliest of 30 months, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA or 505(b)(2) applicant. This regulatory stay is commonly referred to as a "30-month stay."

Marketing Exclusivity

An ANDA or 505(b)(2) application cannot be approved until the expiration of any applicable non-patent exclusivity listed in the Orange Book for the RLD.

The Hatch-Waxman Act provides certain periods of regulatory exclusivity. These include (1) five years of regulatory exclusivity for a drug product that contains a new chemical entity, or NCE, which generally means an active ingredient that contains a novel active moiety; and (2) three years of exclusivity for the approval of an NDA or supplemental NDA that contains data from new clinical investigations that were necessary for approval. Three-year exclusivity prevents the FDA from approving a follow-on product with the same conditions of approval for three years. By contrast, NCE exclusivity prevents the FDA from accepting for review an application for a follow-on product that contains the protected active moiety during the five-year period dating from the product's approval. However, if the ANDA or 505(b)(2) application contains a Paragraph IV certification, that application may be submitted four years after approval of the listed drug protected by NCE exclusivity. In that case, if timely patent litigation is filed, the regulatory stay will expire seven and a half years after the approval of the RLD, unless it terminates early based on expiration of the patent, a settlement of the patent litigation, or a decision in the litigation favorable to the ANDA or 505(b)(2) applicant.

If there is no patent listed in the Orange Book with the RLD, there can be no Paragraph IV certification; in these circumstances, no ANDA or 505(b)(2) may be filed before the expiration of the NCE exclusivity period.

Additionally, six months of marketing exclusivity in the United States is available under Section 505A of the FDC Act if, in response to a written request from the FDA, a sponsor timely submits and the agency accepts reports of requested studies relating to the use of the approved drug in the pediatric population. This six-month pediatric exclusivity period is not a standalone exclusivity period, but rather is added to any existing patent or regulatory exclusivity period for which the drug product is eligible. Pediatric exclusivity does not extend the term of the patent; instead, it extends by six months the preclusive effect of the patent on FDA's authority to approve an ANDA or 505(b)(2) application. Whether pediatric exclusivity will extend a listed patent depends on the type of patent certification provided by the follow-on applicant and the outcome of any associated litigation arising from that certification.

Patent Term Extension

The term of a patent that covers an FDA approved drug that contains an active ingredient not previously approved may be eligible for patent term extension, which provides patent term restoration as compensation for the patent term lost during the development and FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in the European Union and other foreign jurisdictions to extend the term of a patent that covers

an approved drug. In the future, if our product candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those products.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring such companies to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

In Europe, and throughout the world, other countries have enacted anti-bribery laws and/or regulations similar to the FCPA. Violations of any of these antibribery laws, or allegations of such violations, could have a negative impact on our business, results of operations and reputation.

European and Other International Government Regulation

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 trials and any commercial sales and distribution of our products. The approval process varies from country to country, and the time may be longer or shorter that that required for FDA approval. Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Some countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a CTA must be submitted to the national health authority of each EU Member State in which the clinical trial is to be conducted and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed.

To obtain regulatory approval to commercialize a new drug under European Union regulatory systems, we must submit a marketing authorization application, or MAA. In the European Union, marketing authorization for a medicinal product can be obtained through a centralized, mutual recognition, decentralized procedure, or the national procedure of an individual EU Member State. In accordance with the centralized procedure, the applicant can submit a single application for marketing authorization to the EMA to be assessed by the Committee of Medicinal Products for Human Use, or CHMP. The agency will provide a positive opinion regarding the application if it meets certain quality, safety, and efficacy requirements. Following the opinion of the EMA, the European Commission makes a final decision to grant a centralized marketing authorization that permits the marketing of a product in all 27 EU Member States and three of the four European Free Trade Association, or EFTA, States, Iceland, Liechtenstein and Norway. The centralized procedure is mandatory for certain medicinal products, including orphan medicinal products, medicinal products derived from certain biotechnological processes, advanced therapy medicinal products and certain other medicinal products containing a new active substance for the treatment of certain diseases. This route is optional for certain other products, including medicinal products that are a significant therapeutic, scientific or technical innovation, or whose authorization would be in the interest of public or animal health.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application process is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials

due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

The mutual recognition procedure is similarly based on the acceptance by the competent authorities of the EU Member States of the marketing authorization of a medicinal product by the competent authorities of other EU Member States. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America, Asia, Australia or New Zealand, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. Internationally, clinical trials are generally required to be conducted in accordance with GCP, applicable regulatory requirements of each jurisdiction and the medical ethics principles that have their origin in the Declaration of Helsinki.

Data Exclusivity

In the European Union if a marketing authorization is granted for a medicinal product containing a new active substance, that product benefits from eight years of data exclusivity, during which generic marketing authorization applications referring to the data of that product may not be accepted by the regulatory authorities, and a further two years of market exclusivity, during which such generic products may not be placed on the market. The two-year period may be extended to three years if during the first eight years a new therapeutic indication with significant clinical benefit over existing therapies is approved.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States. If the disease or condition affects more than 200,000 individuals in the United States, orphan drug designation may nevertheless be available if there is no reasonable expectation that the cost of developing and making the drug would be recovered from sales in the United States. After the FDA grants Orphan designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. In the United States, a drug that has received orphan drug designation is eligible for financial incentives, such as opportunities for grant funding towards clinical trial costs, tax credits for certain research and user fee waivers under certain circumstances. The Orphan Drug Act provides that, if a designated drug is approved for the rare disease or condition for which it was designated, the approved product will be granted seven years of orphan drug exclusivity, which means the FDA generally may not approve any other application for a product containing the same active moiety 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 drug exclusivity by means of greater effectiveness, greater safety, or providing a major contribution to patient care. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition.

In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. The EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union. Additionally, orphan drug designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug. The application for orphan designation must be submitted to the EMA and approved before an application is made for marketing authorization for the product. Once authorized, orphan medicinal products are entitled to ten years of

market exclusivity. During this ten-year period, with a limited number of exceptions, neither the competent authorities of the EU Member States, the EMA, or the European Commission are permitted to accept applications or grant marketing authorization for other similar medicinal products with the same therapeutic indication. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this latter product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity

Orphan drug designation must be requested before submission of an application for marketing approval. Products that qualify for orphan designation may also qualify for other FDA programs that are intended to expedite the development and approval process and, as a practical matter, clinical trials for orphan products may be smaller, simply because of the smaller patient population. Nonetheless, the same approval standards apply to orphan-designated products as for other drugs. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

In August 2017, President Trump signed into law the Food & Drug Administration Reauthorization Act. This legislation imposes significant new requirements for clinical trial sponsors which will affect, among other things, obtaining orphan drug designation, and the development of drugs and biological products for pediatric use.

Priority Review, Fast Track, Breakthrough Therapy and Accelerated Approval (United States)

The FDA has programs to expedite submission and consideration of certain drug products that address serious or life-threatening diseases or conditions. An application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. Priority review means that the FDA will seek to complete its first-cycle review and take action on the application within six months rather than the customary 10-month standard review period. An applicant may request priority review at the time it submits its application. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Additionally, the fast track program is intended to expedite or facilitate the process for reviewing new drugs that demonstrate the potential to address unmet medical needs involving serious or life-threatening diseases or conditions. If a drug receives fast track designation, the FDA may consider reviewing sections of the NDA on a rolling basis, rather than requiring the entire application to be submitted to begin the review. Products with fast track designation also may be eligible for more frequent meetings and correspondence with the FDA about the product's development. In May 2019, we received Fast Track designation from the FDA for treatment of behavioral symptoms associated with FXS. Other FDA programs intended to expedite development and review include accelerated approval (*i.e.*, approval on the basis of a surrogate endpoint that is reasonably likely to predict clinical benefit) and breakthrough therapy designation, which is available for drugs under development for serious or life-threatening conditions and where preliminary clinical evidence shows that the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. If a drug receives breakthrough therapy designation, it will be eligible for all of the benefits of fast track designation, as well as for more intensive guidance from the FDA on an efficient drug development program and a commitment from the agency to involve senior FDA managers in such guidance. Even if a product qualifies for fast track designation or breakthrough therapy designation, the FDA may later decide that the product no longer meets the conditions for these designations, and/or may determine that the product does not meet the standards for approval.

Accelerated Review (European Union)

Under the Centralized Procedure in the European Union, the maximum timeframe for the evaluation of a MAA is 210 days (excluding "clock stops," when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human Use, or CHMP). Accelerated

evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest. Three cumulative criteria must be fulfilled in such circumstances: the seriousness of the disease (e.g., heavy disabling or life-threatening diseases) to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days.

Healthcare Reform

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the Affordable Care Act, was intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Among the provisions of the Affordable Care Act that have been implemented since enactment and are of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee imposed on any entity that manufactures or imports specified branded prescription drugs or biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the U.S. civil False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer’s outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers’ Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- requirements to report certain financial arrangements with physicians and teaching hospitals;
- a requirement to annually report certain information regarding drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation’s automatic reductions to several government programs. These reductions included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. Subsequent litigation extended the 2% reduction, on average, to 2025.

There have been significant ongoing efforts to modify or eliminate the Affordable Care Act. For example, the Tax Cuts and Jobs Act enacted on December 22, 2017 repealed the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code, commonly referred to as the individual mandate, beginning in 2019. The Joint Committee on Taxation estimates that the repeal will result in over 13 million fewer Americans maintaining their health insurance coverage over the next ten years and is likely to lead to increases in insurance premiums. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act was unconstitutional in its entirety because the "individual mandate" was repealed by Congress. On November 10, 2020, the U.S. Supreme Court heard arguments on the case. A ruling is expected in 2021.

In 2018, Congress has proposed further legislation to repeal or revise the Affordable Care Act, which if enacted, may have a significant impact on the health care system. We expect that further changes to the Affordable Care Act, as well as other healthcare reform measures that have been and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product, and could seriously harm our future revenue. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may compromise our ability to generate revenue, attain profitability or commercialize our product candidates. President Biden's administration is likely to implement numerous policies that could result in repeal or other significant changes to the executive orders issued by the former Trump administration and other legislation enacted during the past four years. The impact of any such potential changes is difficult to predict, although we expect a continued focus on health care and drug pricing legislation.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payors. Third-party payors include government health administrative authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA approved drugs for a particular indication. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. Our product candidates, if approved, may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the Medicare Modernization Act, enacted by the U.S. Congress in 2003, changed the way Medicare covers and pays for pharmaceutical products, including creating the Medicare Part D prescription drug benefit, which became effective at the beginning of 2006. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, to obtain payments under this program, we would be required to sell products to Medicare recipients through prescription drug plans operating pursuant to this legislation. These plans will likely negotiate discounted prices for our products. In addition, we will be subject to the rules and regulations issued by CMS from time to time for Medicare Part D, such as the requirement, to include drug price increases and lower cost therapeutic alternatives on its Part D Explanation of Benefits that Medicare Part D sends members to inform Medicare beneficiaries about possible ways to lower their out of pocket costs by considering a lower cost medication.

Existing federal law requires pharmaceutical manufacturers to pay rebates to state governments, based on a statutory formula, on covered outpatient drugs reimbursed by the Medicaid program as a condition of having their drugs paid for

by Medicaid. Rebate amounts for a product are determined by a statutory formula that is based on prices defined in the statute: AMP, which must be calculated for all products that are covered outpatient drugs under the Medicaid program, and best price, which must be calculated only for those covered outpatient drugs that are a single source drug or innovator multiple source drug, such as biologic products. Manufacturers are required to report AMP and best price for each of their covered outpatient drugs to the government on a regular basis. Additionally, some state Medicaid programs have imposed a requirement for supplemental rebates over and above the formula set forth in federal law, as a condition for coverage. In addition to the Medicaid rebate program, federal law also requires that if a pharmaceutical manufacturer wishes to have its outpatient drugs covered under Medicaid as well as under Medicare Part B, it must sign a "Master Agreement" obligating it to provide a formulaic discount of approximately 24% known as the federal ceiling price for drugs sold to the U.S. Departments of Defense (including the TRICARE retail pharmacy program), Veterans Affairs, the Public Health Service and the Coast Guard, and also provide discounts through a drug pricing agreement meeting the requirements of Section 340B of the Public Health Service Act, for outpatient drugs sold to certain specified eligible healthcare organizations. The formula for determining the discounted purchase price under the 340B drug pricing program is defined by statute and is based on the AMP and rebate amount for a particular product as calculated under the Medicaid drug rebate program, discussed above.

Different pricing and reimbursement schemes exist in other countries. In the European Union, each EU Member States can restrict the range of medicinal products for which its national health insurance system provides reimbursement and can control the prices of medicinal products for human use marketed on its territory. As a result, following receipt of marketing authorization in an EU Member State, through any application route, the applicant is required to engage in pricing discussions and negotiations with the competent pricing authority in the individual EU Member State. The governments of the EU Member States influence the price of pharmaceutical 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. Some EU Member States operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. 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 EU Member States allow companies to fix their own prices for medicines but monitor and control company profits. Others adopt a system of reference pricing, basing the price or reimbursement level in their territories either on the pricing and reimbursement levels in other countries or on the pricing and reimbursement levels of medicinal products intended for the same therapeutic indication. Further, some EU Member States approve a specific price for the medicinal product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, we may face competition for our product candidates from lower-priced products in foreign countries that have placed price controls on pharmaceutical products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

Health Technology Assessment, or HTA, of medicinal products, however, is becoming an increasingly common part of the pricing and reimbursement procedures in some EU Member States. These EU Member States include France, Germany, Ireland, Italy and Sweden. HTA is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally focuses on the clinical efficacy and effectiveness, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the healthcare system. Those elements of medicinal products are compared with other treatment options available on the market.

The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU Member States. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product varies between EU Member States.

In addition, pursuant to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, a voluntary network of national authorities or bodies responsible for HTA in the individual EU Member States was

established. The purpose of the network is to facilitate and support the exchange of scientific information concerning HTAs. This may lead to harmonization of the criteria taken into account in the conduct of HTAs between EU Member States and in pricing and reimbursement decisions and may negatively affect price in at least some EU Member States.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on pharmaceutical pricing. With few exceptions (e.g., limitations on Medicare Part D sponsors concerning certain formulary changes), coverage policies and third-party reimbursement rates may change at any time.

Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

In the United States, our activities are potentially subject to additional regulation, particularly once third-party reimbursement becomes available for one or more of our products, by various federal, state and local authorities in addition to the FDA, including CMS, other divisions of HHS (for example, the OIG), the DOJ and individual U.S. Attorney offices within the DOJ, and state and local governments.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some business arrangements from prosecution, the exemptions and safe harbors are drawn narrowly and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from federal Anti-Kickback Statute liability. The reach of the Anti-Kickback Statute was broadened by the Affordable Care Act, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds or knowingly making, using or causing to be made or used, a false record or statement material to an obligation to pay money to the government, or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Pharmaceutical and other healthcare companies have been investigated and reached substantial financial settlements under these laws for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes that extend to non-government health benefit programs.

The Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or

representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services.

The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, requires certain pharmaceutical and biological manufacturers to engage in extensive tracking of payments or transfers of value to physicians and teaching hospitals and public reporting of the payment data. Pharmaceutical and biological manufacturers with products for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program are required to track such payments, and must submit a report on or before the 90th day of each calendar year disclosing reportable payments made in the previous calendar year.

Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. Some state laws also require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to certain health care providers in those states. Some of these states also prohibit certain marketing-related activities including the provision of gifts, meals, or other items to certain health care providers. In addition, California, Connecticut, Nevada and Massachusetts require pharmaceutical companies to implement compliance programs or marketing codes of conduct.

In addition, we are subject to data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the U.S., numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the FTC Act), govern the collection, use, disclosure and protection of health-related and other personal information. Failure to comply with data protection laws and regulations could result in government enforcement actions and create liability for us (which could include civil and/or criminal penalties), private litigation and/or adverse publicity that could negatively affect our operating results and business. HIPAA, as amended by HITECH, and its implementing regulations, among other things, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. HIPAA also prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services. Although we are not directly subject to HIPAA other than with respect to providing certain employee benefits, we potentially could be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information maintained by a HIPAA-covered entity (e.g., a healthcare provider or a health plan) in a manner that is not authorized or permitted by HIPAA. In addition, the California Consumer Privacy Act, or CCPA, became effective on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal data. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. Similar laws have been proposed at the federal level and in other states.

To the extent that we continue to conduct clinical trials or seek to commercialize our products outside of the United States, we will also be subject to a variety of foreign data protection laws and regulations. For example, in the European Union, the General Data Protection Regulation, or GDPR, imposes strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. For our clinical trials in Australia, to the extent that the sites for our trials include certain university, company or government agencies, we may be subject to restrictions and data protection obligations under the Privacy Act 1988 (Cth). We may, otherwise, be subject to additional data protection laws in Australia in the states and territories in which we conduct our trials, which have similar restrictions on our ability to collect, analyze and transfer medical records and other patient data. All of these laws may impact our business. Our failure to comply with these privacy laws or significant changes in the laws restricting our ability to obtain required patient information could significantly impact our business and our future business plans.

Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government programs, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of pre-marketing product approvals, private "qui tam" actions brought by individual whistleblowers in the name of the government or refusal to allow us to enter into supply contracts, including government contracts, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

In addition, at the federal level, the Drug Supply Chain Security Act, or DSCA, regulates the distribution and tracing of prescription drugs. The DSCA imposes requirements to ensure accountability in prescription drug distribution, for example, it requires manufacturers to affix a product identifier to each package and case of a prescription drug product intended for sale. A product identifier is an electronically-readable graphic that contains information including the product's unique numerical identifier, lot number, and expiration date. The DSCA also requires relevant parties and to identify and remove illegitimate products from the market, including products that are counterfeit, stolen, intentionally contaminated, or otherwise harmful. The Prescription Drug Marketing Act, its implementing regulations and state laws also regulate the distribution of prescription drug product samples.

In order to distribute products commercially, we must also comply with state law requirements for registration of manufacturers and wholesale distributors of pharmaceutical products, including, in some states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Several states, and more recently some large cities, have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, register their sales representatives, and/or limit other specified sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

Scientific Advisors

We have established a clinical advisory board and we regularly seek advice and input from these experienced clinical leaders on matters related to our research and development programs. The members of our clinical advisory board consist of experts across a range of key disciplines relevant to our programs. We intend to continue to leverage the broad expertise of our advisors by seeking their counsel on important topics relating to our product development and clinical development programs. Our scientific advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us. In addition, our clinical advisors may have arrangements with other companies to assist those companies in developing products or technologies that may compete with ours. All of our clinical advisors are affiliated with other entities and devote only a small portion of their time to us.

Our current clinical advisors are set forth in the table below:

Name	Title
Elizabeth Berry-Kravis, MD, PhD†	Professor of Pediatrics, Neurological Sciences, Biochemistry Rush University Medical Center
Craig Erickson, MD†	Associate Professor of Psychiatry, Director, Fragile X Research and Treatment Center, Medical Director, P3SW Developmental Disabilities Inpatient Unit, Director of Research, The Kelly O'Leary Center for Autism Spectrum Disorders, Cincinnati Children's Hospital Medical Center
Randi J. Hagerman, MD†	Medical Director, UC Davis MIND Institute; Distinguished Professor, Endowed Chair in Fragile X Research, Department of Pediatrics, UC Davis School of Medicine
Steven J. Siegel, MD, PhD†	Chair, Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California
Nicole Tartaglia, MD†	Associate Professor, Pediatrics-Developmental Pediatrics, University of Colorado Denver School of Medicine/Children’s Hospital of Colorado
Dennis Dlugos, MD, MSCE*	Professor of Neurology and Pediatrics at Children’s Hospital of Philadelphia (CHOP) and the University of Pennsylvania School of Medicine
Jacqueline French, MD*	Professor of Neurology, NYU Langone Medical Center
Daniel Friedman, MD*	Clinical Assistant Professor, Department of Psychiatry, NYU Langone Medical Center
John Messenheimer, MD*	Consultant, Neurologist/Epileptologist, John Messenheimer PLLC
Michael Rogawski, MD, PhD*	Professor of Neurology, UC Davis Center for Neuroscience
Rodney Radtke, MD*	Professor of Neurology, Duke University Medical Center

* Epilepsy † FXS

Corporate Information

We were incorporated in Delaware in January 2007.

Our primary executive offices are located at 80 W. Lancaster Avenue, Suite 300, Devon, PA 19333 and our telephone number is (484) 581-7505. Our website address is www.zynerba.com. The information contained in, or that can be accessed through, our website is not part of this Report.

Zynerba is a registered U.S. trademark. All other trademarks, trade names or service marks referred to in this Report are the property of their respective owners.

Human Capital

The pharmaceutical industry is highly competitive. Attracting, developing and retaining talented people experienced in medical, clinical development, regulatory, manufacturing, finance and other positions is crucial to executing our strategy and our ability to compete effectively. Currently, one third of our employees hold advanced degrees in areas of expertise that are critical to our mission and our success, including medicine, pharmacy, biology, business and law. Our ability to recruit and retain such talent depends on a number of factors, including compensation and benefits, career opportunities and work environment. To that end, we offer compensation and incentives that include market-competitive pay, equity grants and performance bonuses, healthcare benefits, a retirement savings plan, paid time off and flexible work schedules. We embrace our Company culture and strive to foster a collaborative, inclusive and productive work environment. We value the contributions of our employees, particularly in the face of the challenges posed by the COVID-19 pandemic and have provided flexible working schedules and the ability to work from home to help maintain their health and safety as well as business continuity.

As of March 5, 2021, we had 26 full-time employees. All of our employees are located in the U.S., with the exception of one employee located in Australia. In addition to our employees, we rely on third parties in the United States and in various parts of the world to conduct our preclinical studies and clinical trials, to provide services, including data management, statistical analysis and electronic compilation related to our development of Zygel, and to supply API and drug product for our clinical trials. We have no collective bargaining agreements with our employees and none are represented by labor unions.

Available information

Our internet website address is http://www.zynerba.com. Our Annual Report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, any amendments to those reports, proxy and registration statements filed or furnished with the Securities and Exchange Commission, or SEC, are available free of charge through our website. We make these materials available through our website as soon as reasonably practicable after we electronically file such materials with, or furnish such materials to, the SEC. The reports filed with the SEC by our executive officers and directors pursuant to Section 16 under the Exchange Act are also made available, free of charge on our website, as soon as reasonably practicable after copies of those filings are provided to us by those persons. These materials can be accessed through the “Investor Relations” section of our website. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Report. In addition, our SEC filings are available at the SEC’s website at http://www.sec.gov.

Item 1A.

Risk Factors

The risk factors summarized and detailed below could materially harm our business, operating results and/or financial condition, impair our future prospects and/or cause the price of our common stock to decline. These are not all of the risks we face, and other factors not presently known to us or that we currently believe are immaterial may also affect our business if they occur. A summary of the material risks that may affect our business, operating results and financial condition include, but are not necessarily limited to, those relating to:

Risks Related to Our Financial Position and Capital Needs

- We have incurred significant losses since our inception and anticipate that we will continue to incur losses in the future.
- We currently have no commercial revenue and may never become profitable.
- We will require additional capital to fund our operations and if we fail to obtain necessary financing, we will not be able to complete the development and commercialization of our product candidates.
- With regard to our Australian government research and development income tax incentive refunds, if our research and development expenditures are not deemed to be eligible for the refund, proposed modifications to the tax incentive program are enacted, or the tax incentive program is discontinued by the Australian government, it could have a negative effect on our future cash flows and the funding of future research and development projects.

Risks Related to our Business

- We are largely dependent on the success of our product candidates, which are still in clinical development, and will require significant capital resources and years of clinical development effort.
- Because the results of preclinical studies and earlier clinical trials are not necessarily predictive of future results, our product candidates may not have favorable results in our planned clinical trials.
- Failures or delays in our clinical trials of Zygel could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.
- We intend to expend our limited resources to pursue Zygel for certain indications and may fail to capitalize on other product candidates or other indications for Zygel that may be more profitable or for which there is a greater likelihood of success.
- Business interruptions, including any interruptions resulting from COVID-19, could cause a disruption of our operations and may materially and adversely affect our business and financial conditions.
- Product shipment delays could have a material adverse effect on our business, results of operations and financial condition.
- Even if we are able to commercialize Zygel, the product may not receive coverage and adequate reimbursement from third-party payors, which could harm our business.
- If we are unable to develop sales, marketing and distribution capabilities or enter into agreements with third parties to perform these functions on acceptable terms, we may be unable to generate revenue.
- Negative public perception of cannabidiol and cannabis-related products and misconceptions about the nature of our business may generate public controversy.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.
- We are subject to securities class action litigation, which is expensive, can divert management attention, and, if resolved unfavorably, could expose us to significant liabilities.
- Failure to protect our information technology infrastructure against cyber-based attacks, network security breaches, service interruptions, or data corruption could significantly disrupt our operations and adversely affect our business and operating results.

Risks Related to Government Regulation

- The regulatory approval processes of the FDA, the EMA and other comparable foreign regulatory 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.
- We have conducted and are conducting clinical trials for Zygel outside the United States and anticipate conducting additional clinical trials for Zygel outside the United States, and the FDA may not accept data from such trials.
- The 2018 Farm Bill and other legislation regarding cannabis may impact our business.
- Zygel will be subject to controlled substance laws and regulations; failure to receive necessary approvals may delay the launch of our products and failure to comply with these laws and regulations may adversely affect the results of our business operations.
- Increased scrutiny on drug pricing or changes in pricing regulations could restrict the amount that we are able to charge for our product candidates, which could adversely affect our revenue and results of operations.
- We have been granted orphan drug status by the FDA for the use of cannabidiol for the treatment of FXS and 22q, but we may be unable to maintain the benefits associated orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.
- Serious adverse events or other safety risks could require us to abandon development and preclude, delay or limit approval of our product candidates, or limit the scope of any approved label or market acceptance.
- Even though our product candidate has received Fast Track designation, the FDA may not approve it at all or any sooner than other product candidate that does not have Fast Track designation.

Risks Related to Our Dependence on Third Parties

- We rely on third parties to conduct our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates.
- We rely on third-party manufacturers and suppliers to produce preclinical and clinical supplies and intend to rely on third-party manufacturers for commercial supplies of APIs and final dosage forms for Zygel, if approved.

Risks Related to Our Intellectual Property

- If we are unable to protect our intellectual property rights or if our intellectual property rights are inadequate for our technology and product candidates, our competitive position could be harmed.
- 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.
- We may become subject to claims by third parties either asserting that we or our employees have misappropriated their intellectual property or claiming ownership of what we regard as our own intellectual property.
- We may become involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful and have a material adverse effect on the success of our business.

Risks Related to Ownership of Our Common Stock

- The market price and trading volume of our stock may be volatile.
- Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.
- Our certificate of incorporation also provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

General Risks Related to Ownership of Securities

- If we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.
- Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

You should consider carefully the following risks and uncertainties when reading this Annual Report. If any of the following risks actually occurs, our business, financial condition and results of operations could be materially and adversely affected. In that event, the trading price of our common stock could decline. Although we believe that we have identified and discussed below the key risk factors affecting our business, there may be additional risks and uncertainties that are not presently known or that are not currently believed to be significant that may adversely affect our performance or financial condition.

Risks Related to Our Financial Position and Capital Needs

We have incurred significant losses since our inception and anticipate that we will continue to incur losses in the future.

We are a clinical stage pharmaceutical company dedicated to the development and commercialization of innovative transdermal pharmaceutically-produced cannabinoid treatments for rare and near-rare neuropsychiatric disorders in patients with high unmet medical needs. Since our inception in January 2007, we have devoted substantially all of our resources to the development of our product candidates. We have generated significant operating losses since our inception. Our net losses for the years ended December 31, 2020, 2019 and 2018 were approximately $51.3 million, $32.9 million and $39.9 million, respectively. As of December 31, 2020, we had an accumulated deficit of $202.2 million. Substantially all of our losses have resulted from expenses incurred in connection with our research and development programs and from general and administrative costs associated with our operations.

We expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate these losses will increase as we continue the research and development of, and clinical trials for, our product candidates. In addition to budgeted expenses, we may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. If our product candidates fail in clinical trials or do not gain regulatory approval, or even if approved, fail to achieve market acceptance, we may never become profitable. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods.

Due to our limited operating history and history of losses, any predictions about our future success, performance or viability may not be accurate.

We currently have no commercial revenue and may never become profitable.

To date, the only revenue we have generated has been from the receipt of research grants and payments for research services. Our ability to generate revenue and become profitable depends upon our ability to obtain regulatory approval for, and successfully commercialize, our product candidates that we may develop, in-license or acquire in the future.

Even if we are able to successfully achieve regulatory approval for these product candidates, we do not know what the reimbursement status of our product candidates will be or when any of these products will generate revenue for us, if at all. We have not generated, and do not expect to generate for the foreseeable future, any product revenue, and we expect to continue to incur significant operating losses for the foreseeable future due to the cost of research and development, preclinical studies and clinical trials and the regulatory approval process for our product candidates. The amount of future losses is uncertain and will depend, in part, on the rate of growth of our expenses.

Our ability to generate revenue from our product candidates also depends on a number of additional factors, including our ability to:

- successfully complete development activities, including the remaining preclinical studies and ongoing and planned clinical trials for our product candidates;
- complete and submit NDAs to the FDA and MAAs to the EMA, and obtain regulatory approval for indications for which there is a commercial market;

- complete and submit applications to, and obtain regulatory approval from, other foreign regulatory authorities;
- manufacture any approved products in commercial quantities and on commercially reasonable terms;
- develop a commercial organization, or find suitable partners, to market, sell and distribute approved products in the markets in which we have retained commercialization rights;
- achieve acceptance among patients, clinicians and advocacy groups for any products we develop;
- obtain coverage and adequate reimbursement from third parties, including government payors; and
- set a commercially viable price for any products for which we may receive approval.

We are unable to predict the timing or amount of increased expenses, or when or if we will be able to achieve or maintain profitability. Even if we are able to complete the processes described above, we anticipate incurring significant costs associated with commercializing our product candidates.

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

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial and increasing amounts to conduct further research and development, preclinical testing and clinical trials of our product candidates, to seek regulatory approvals and reimbursement for our product candidates and to launch and commercialize any product candidates for which we receive regulatory approval. As of December 31, 2020, we had approximately $59.2 million in cash and cash equivalents. We believe that cash and cash equivalents as of December 31, 2020, and the net proceeds of $42.2 million in cash generated between January 1, 2021 and February 9, 2021 from sales under the Controlled Equity Offering[SM] Sales Agreement with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., or the 2019 Sales Agreement, are sufficient to fund operations and capital requirements well into the first half of 2024. The progress of Zygel for each target indication is uncertain because it is difficult to predict our spending for our product candidates prior to obtaining FDA approval due to numerous factors, including, without limitation, the rate of progress of clinical trials, the results of preclinical studies and clinical trials for such indication, the costs and timing of seeking and obtaining FDA and other regulatory approvals for clinical trials and FDA guidance regarding clinical trials for such indication. Moreover, changing circumstances may cause us to expend cash significantly faster than we currently anticipate, and we may need to spend more cash than currently expected because of circumstances beyond our control. For these reasons, 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 preclinical studies and clinical trials for our product candidates;
- any change in the clinical development plans or target indications for these product candidates;
- the number and characteristics of product candidates that we develop or may in-license;
- the terms of any collaboration agreements we may choose to execute;
- the outcome, timing and cost of meeting regulatory requirements established by the DEA, the FDA, the EMA or other comparable foreign regulatory authorities;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;

- the timing, outcome and impact of current and future legal proceedings;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us;
- the effect of competing product and market developments;
- the extent to which health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic, could disrupt our operations or materially and adversely affect our business and financial conditions;
- the costs and timing of the implementation of commercial scale manufacturing activities; and
- the cost of establishing, or outsourcing, sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own.

We cannot be certain that additional funding will be available on acceptable terms, or at all. 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 one or more of our product candidates or one or more of our other research and development initiatives.

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

We may seek additional capital through a combination of private and public equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, existing ownership interests will be diluted, and the terms of such financings may include liquidation or other preferences that adversely affect the rights of existing stockholders. Debt financings may be coupled with an equity component, such as warrants to purchase shares, which could also result in dilution of our existing stockholders' ownership. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business and may result in liens being placed on our assets and intellectual property. If we were to default on such indebtedness, we could lose such assets and intellectual property. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, or grant licenses on terms that are not favorable to us.

We receive Australian government research and development income tax incentive refunds. If our research and development expenditures are not deemed to be eligible for the refund, proposed modifications to the tax incentive program are enacted, or the tax incentive program is discontinued by the Australian government, it could have a negative effect on our future cash flows and the funding of future research and development projects.

Our subsidiary, Zynerba Pharmaceuticals Pty Ltd., is incorporated in Australia where we are currently engaged in research and development activities for Zygel. Our subsidiary is eligible to participate in the Australian Federal Government's Research and Development Tax Incentive program, under which the government provides a cash refund for a portion of eligible research and development expenditures (45% for fiscal years beginning prior to July 1, 2016 and 43.5% for fiscal years beginning on or after July 1, 2016) by small Australian entities, which are defined as Australian entities with less than A$20 million in revenue, having a tax loss.

The Research and Development Tax Incentive refund is offered by the Australian federal government for eligible research and development purposes based on the filing of an annual application. As part of this program, our subsidiary

applied for and received cash refunds from the Australian Taxation Office for a percentage of the research and development costs expended by our subsidiary in Australia. Since the fiscal year ended December 31, 2015, we have been receiving Research and Development Tax Incentive refunds related to research and development expenditures we make, and we expect to continue to receive refunds under this program for eligible research and development expenditures in Australia.

Certain research and development expenses incurred outside of Australia may also be eligible for the Australian research and development tax incentive program. To receive a cash refund with respect to such expenses incurred outside of Australia, the expenses must have been for eligible research and development activities, as determined by AusIndustry, and the expenditures must have a scientific link to the Australian activities, be unable to be conducted in Australia and be less than the expenditures for activities conducted in Australia, as determined by the ATO.

In December 2018, our subsidiary submitted an Advance Overseas Finding, or AOF, application to AusIndustry for a determination that its activities are eligible research and development activities, which was approved by AusIndustry in July 2019. As a result of this finding, we believe our subsidiary is eligible to receive a cash refund from the ATO for qualifying expenditures related to its research and development activities outside of Australia in 2018, 2019 and 2020. During the year ended December 31, 2019, we recorded $8.3 million as an incentive and tax receivable and recorded a corresponding credit to research and development expense for amounts expected to be received through the AOF for the period January 1, 2018 through December 31, 2019. In June 2020, the ATO informed us that we may not qualify for the AOF program based on their interpretation of certain eligibility requirements. Although we continue to believe that we comply with the relevant conditions of the AOF program that were in place when we received our original approval from AusIndustry, we determined in 2020 that it is no longer probable that the AOF claim will be received. As a result, during the three months ended June 30, 2020, we recorded a full reserve against the AOF receivable. While we will continue to pursue the full refund of our reimbursed expenditures from the ATO, there can be no assurance that all expenditures will be approved for refund.

To the extent that some or all of our research and development expenditures are deemed to be “ineligible,” then our refunds may decrease or be eliminated. In addition, the Australian government may in the future modify the requirements of, reduce the amounts of the refunds available under, or discontinue the Research and Development Tax Incentive program. Any such change in the Research and Development Tax Incentive program would have a negative effect on our future cash flows.

Changes in tax laws and unanticipated tax liabilities could adversely affect our effective income tax rate and ability to achieve profitability.

We are subject to income taxes in the United States and Australia. Our effective income tax rate in the future could be adversely affected by a number of factors including changes in the mix of earnings in countries with differing statutory tax rates, changes in the valuation of deferred tax assets and liabilities and changes in tax laws. We regularly assess all of these matters to determine the adequacy of our tax provision which is subject to discretion. If our assessments are incorrect, it could have an adverse effect on our business and financial condition. There can be no assurance that income tax laws and administrative policies with respect to the income tax consequences generally applicable to us or to our subsidiaries will not be changed in a manner which adversely affects our shareholders.

Our ability to use our net operating loss carryforwards and other tax attributes may be limited.

As of December 31, 2020, we had U.S. net operating loss, or NOL, carryforwards of approximately $129.7 million for U.S. federal income tax and state tax purposes available to offset future taxable income, prior to consideration of annual limitations that may be imposed under Section 382 of the Internal Revenue Code of 1986, as amended, or Section 382. Our NOL carryforwards begin to expire in 2028 if not utilized.

Our NOL carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under Section 382, and corresponding provisions of U.S. state law, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation’s ability

to use its pre-change U.S. NOLs and other pre-change tax attributes, such as research and development tax credits, to offset its post-change income may be limited. We have not performed any analyses under Section 382 and cannot forecast or otherwise determine our ability to derive benefit from our various federal or state tax attribute carryforwards. As a result, if we earn net taxable income, our ability to use our pre-change NOL carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

In addition, we may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, including in any future offerings, some of which may be outside of our control. If we determine that an ownership change has occurred and our ability to use our NOL carryforwards is materially limited, it would harm our future operating results by effectively increasing our future tax obligations.

Our federal and state government grants could subject us to audits and could require us to repay funds previously awarded to us.

Prior to our initial public offering, or IPO, most of our revenue was from the receipt of state and federal research grants. As of December 31, 2020, we have been granted approximately $7.9 million in federal and state research grants (all of which was granted prior to 2016). During 2018, we discontinued research and development studies associated with a previous grant and returned $0.7 million to the grantor in early 2019. Although we are not currently conducting research under any grants, we may be subject to audits by government agencies for previous grants. As part of an audit, these agencies may review our performance, cost structures and compliance with applicable laws, regulations, policies and standards and the terms and conditions of the grant. If any of our expenditures are found to be unallowable or allocated improperly or if we have otherwise violated terms of the grant, we may be required to repay funds previously disbursed. Accordingly, an audit could result in a material adjustment to our results of operations and financial condition.

Risks Related to our Business and Industry

We are largely dependent on the success of our product candidates, which are still in clinical development, and will require significant capital resources and years of clinical development effort.

We currently do not have any marketed products. Our business depends almost entirely on the successful clinical development, regulatory approval and commercialization of our product candidates, and substantial additional clinical development and regulatory approval efforts will be required before we are permitted to commence commercialization, if ever. The clinical trials and manufacturing and marketing of our product candidates will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, Australia, the European Union, Canada, and other jurisdictions where we intend to test and, if approved, market our product candidates. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through preclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication, and potentially in specific patient populations. This process can take many years and may include post-marketing studies and surveillance, which would require the expenditure of substantial resources beyond our existing funds. Of the large number of drugs in development for approval in the United States and the European Union, only a small percentage successfully complete the FDA regulatory approval process or are granted a marketing authorization by the European Commission or the other competent authorities in the EU Member States, as applicable, and are commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our research, development and clinical programs, we cannot assure you that any of our product candidates will be successfully developed or commercialized.

Because the results of preclinical studies and earlier clinical trials are not necessarily predictive of future results, Zygel may not have favorable results in our planned clinical trials.

Any positive results from our preclinical testing and Phase 1 and Phase 2 clinical trials of Zygel may not necessarily be predictive of the results from our ongoing clinical trials for Zygel in patients with FXS, DEE, ASD and 22q, and any

planned or proposed additional clinical trials. For example, the results with respect to the ad hoc analysis of the most severely impacted patients in the CONNECT FX trial may not be indicative of positive results in our planned pivotal clinical trial in patients with highly methylated *FMR1* gene for 2021 or any other future trials. In addition, our interpretation of clinical data or our conclusions based on our preclinical in vitro and in vivo models may prove inaccurate. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical trials after achieving positive results in preclinical and early clinical development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical findings while clinical trials were underway or safety or efficacy observations in clinical trials, including adverse events. Moreover, preclinical and clinical data can be susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA approval or a marketing authorization granted by the European Commission. If we fail to produce positive results in our ongoing or planned clinical trials of Zygel for the treatment symptoms of FXS, DEE, ASD or 22q, the development timeline and regulatory approval and commercialization prospects for Zygel, and, correspondingly, our business and financial prospects, would be materially adversely affected. Given all of these uncertainties, you should not place undue reliance on early data.

We may experience difficulties in managing our growth and expanding our operations.

We have limited resources to carry out objectives for our current and future pre-clinical studies and clinical trials. Since October 2015, we have conducted numerous clinical trials and plan to conduct clinical trials in the future, which is a time-consuming, expensive and uncertain process. In addition, while we have experienced management and expect to contract out many of the activities related to conducting these programs, we are a small company with only 26 employees and therefore have limited internal resources both to conduct pre-clinical studies and clinical trials and to monitor third-party providers. As our product candidates advance through clinical trials and potential regulatory approval and commercialization, we will need to expand our development, regulatory, commercial and manufacturing operations, either by expanding our internal capabilities or contracting with other organizations to provide these capabilities for us. In the future, we expect to have to manage additional relationships with collaborators or partners, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures.

Failures or delays in our clinical trials of Zygel could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.

Successful completion of clinical trials is a prerequisite to submitting an NDA to the FDA or an MAA to the EMA. Clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. A product candidate can unexpectedly fail at any stage of clinical development. The historic failure rate for product candidates is high due to scientific feasibility, findings related to safety and efficacy, changing regulatory standards and standards of medical care and other variables. In addition, inconclusive results or results that are not deemed statistically significant may cause delays in clinical development or lead us to reevaluate and redesign our clinical development programs. We do not know whether our clinical trials will begin or be completed on schedule, if at all, as the commencement and completion of clinical trials can be delayed or prevented for a number of reasons, including, among others:

- delays in reaching or failing to reach agreement on acceptable terms with prospective clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different clinical trial sites;
- clinical sites or investigators deviating from trial protocol, failing to conduct the trial in accordance with applicable regulatory requirements, or dropping out of a trial or failure of third-party clinical trial managers to meet their contractual obligations or deadlines;
- delays or inability in manufacturing or obtaining sufficient quantity or quality of a product candidate or other materials necessary to conduct clinical trials due to regulatory and manufacturing constraints;

- delay or failure in reaching agreement with the FDA or a foreign regulatory authority on the design of a given trial, or in obtaining authorization to commence a trial;
- difficulties obtaining IRB, DEA or comparable foreign regulatory authority, or ethics committee approval to conduct a clinical trial;
- challenges in recruiting and enrolling patients to participate in clinical trials, including the size and nature of the patient population, the proximity of patients to clinical trial sites, eligibility criteria for the clinical trial, the nature of the clinical trial protocol, the availability of approved effective treatments for the relevant indication and competition from other clinical trial programs for similar indications;
- severe or unexpected toxicities or drug-related side effects experienced by patients in our clinical trials or by individuals using drugs similar to our product candidates;
- DEA or comparable foreign regulatory authority-related recordkeeping, reporting or security violations at a clinical trial site, leading the DEA, state authorities or comparable foreign regulatory authorities to suspend or revoke the site's controlled substance registration and causing a delay or termination of planned or ongoing clinical trials;
- delays related to health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic;
- regulatory concerns with cannabinoid products generally and the potential for abuse of those products;
- difficulties retaining patients who have enrolled in a clinical trial who may withdraw due to lack of efficacy, side effects, personal issues or loss of interest and difficulties having subjects return for post-treatment follow-up;
- ambiguous or negative interim results; or
- lack of adequate funding to continue the clinical trial.

In addition, a clinical trial may be suspended or terminated by us, the FDA, an IRB, an ethics committee, a data safety monitoring board or other foreign regulatory authorities overseeing the clinical trial at issue due to a number of factors, including, among others:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical trial protocols;
- inspection of the clinical trial operations or clinical trial sites by the FDA, the DEA, the EMA or other foreign regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;
- unforeseen safety issues, including any safety issues that may be identified in our ongoing and planned studies and trials;
- adverse side effects or lack of effectiveness; and
- changes in government regulations or administrative actions.

If our clinical trials fail or are delayed for any of the above reasons, our development costs may increase, our approval process could be delayed and our ability to commercialize our product candidates could be materially harmed, which could have a material adverse effect on our business, financial condition or results of operations.

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

Because we have limited financial and managerial resources, we are focusing on research programs relating to Zygel for certain indications, which concentrates the risk of product failure in the event Zygel proves to be unsafe or ineffective or inadequate for clinical development or commercialization. In particular, we are studying Zygel in patients with FXS, DEE, ASD and 22q. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications for Zygel that could later prove to have greater commercial potential. We may also deem it advisable to refocus our clinical development programs based on clinical trial results. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on proprietary research and development programs relating to Zygel may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for Zygel, we may relinquish valuable rights to Zygel 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 Zygel.

Business interruptions, including any interruptions resulting from COVID-19, could cause a disruption of our operations and may materially and adversely affect our business and financial conditions.

All of our employees are located in the U.S., with the exception of one employee located in Australia. In addition to our employees, we rely on third parties in the United States and in various parts of the world to conduct our preclinical studies and clinical trials, to provide services, including data management, statistical analysis and electronic compilation related to our development of Zygel, and to supply API for Zygel and drug product for our clinical trials. If we, or any of these third-party partners encounter any disruptions to our or their respective operations or facilities, or if we or any of these third-party partners were to shut down for any reason, including by fire, natural disaster, such as a hurricane, tornado or severe storm, power outage, systems failure, labor dispute, pandemic or other unforeseen disruption, then we or they may be prevented or delayed from effectively operating our or their business, respectively. In December 2019, a novel strain of the Coronavirus (COVID-19) emerged in China and has spread to almost every country, including the United States, and could materially and adversely impact our operations or those of our third-party partners. We continue to closely monitor the COVID-19 pandemic, including any potential to impact our clinical development plans and timelines going forward. In response to COVID-19, for our clinical development programs that were ongoing and/or completed during 2020, we implemented multiple measures consistent with the FDA's guidance on the conduct of clinical trials of medical products during the COVID-19 pandemic, including remote site monitoring and patient visits using telemedicine where needed, direct to patient drug shipment from investigator sites, and local community study related clinical laboratory collection. If necessary, we expect to employ similar measures in any ongoing or planned clinical trials that could affected by the pandemic in the future. Although we did not experience delays in the delivery of

our topline results for our CONNECT-FX and BRIGHT clinical trials, we did experience a delay in patient recruitment into our INSIPRE trial due to significant travel restrictions in Australia in response to the COVID-19 pandemic.

Additionally, continued spread of the coronavirus globally could negatively impact our manufacturing and supply chain for Zygel, our clinical trial timelines, our financial condition and our results of operation. The extent to which the coronavirus and global efforts to contain its spread will impact our operations will depend on future developments, which are highly uncertain and cannot be predicted at this time, and include the duration, severity and scope of the outbreak and the actions taken to contain or treat the coronavirus outbreak.

Even if we are able to commercialize Zygel, the product may not receive coverage and adequate reimbursement from third-party payors, which could harm our business.

The availability of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of our product candidates, if approved, will depend substantially on the extent to which the costs of these product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize Zygel. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

In the United States, the Medicare Modernization Act established the Medicare Part D program and provided authority for limiting the number of drugs that will be covered in any therapeutic class thereunder. The Medicare Modernization Act, including its cost reduction initiatives, could decrease the coverage available for any of our approved products. Furthermore, private payors often follow Medicare in setting their own coverage policies. Therefore, any reduction in coverage that results from the Medicare Modernization Act may result in a similar reduction from private payors.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by CMS, an agency within HHS, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree.

The intended use of a drug product by a physician can also affect pricing. For example, CMS could initiate a National Coverage Determination administrative procedure, by which the agency determines which uses of a therapeutic product would and would not be reimbursable under Medicare. This determination process can be lengthy, thereby creating a long period during which the future reimbursement for a particular product may be uncertain.

Outside the United States, particularly in EU Member States, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations or the successful completion of HTA procedures with governmental authorities can take considerable time after receipt of marketing authorization for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Certain countries allow companies to fix their own prices for medicines but monitor and control company profits. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU Member States and parallel distribution, or arbitrage between low-priced and high-priced EU member states, could further reduce prices. In some countries, we or our collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of any product candidate approved for marketing is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, financial condition, results of operations or prospects could be adversely affected.

If we are unable to develop sales, marketing and distribution capabilities or enter into agreements with third parties to perform these functions on acceptable terms, we may be unable to generate revenue.

We do not currently have any sales, marketing or distribution capabilities. If Zygel is approved, we will need to develop internal sales, marketing and distribution capabilities to commercialize such products, which would be expensive and time-consuming, or enter into collaborations with third parties to perform these services. If we decide to market our products directly, we will need to commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and supporting distribution, administration and compliance capabilities. If we rely on third parties with such capabilities to market our products or decide to co-promote products with collaborators, we will need to establish and maintain marketing and distribution arrangements with third parties, and there can be no assurance that we will be able to enter into such arrangements on acceptable terms or at all. In entering into third-party marketing or distribution arrangements, any revenue we receive will depend upon the efforts of the third parties and there can be no assurance that such third parties will establish adequate sales and distribution capabilities or be successful in gaining market acceptance of any approved product. If we are not successful in commercializing any product approved in the future, either on our own or through third parties, our business, financial condition and results of operations could be materially adversely affected.

Our product candidates, if approved, may be unable to achieve broad market acceptance and, consequently, limit our ability to generate revenue from new products.

Even if our product candidates are approved by regulatory approval authorities, our ability to generate significant revenue depends on the acceptance of our product candidates by physicians, patients and payers. The market acceptance of any product depends on a number of factors, including but not limited to awareness of a product's availability and benefits, the indication statement and warnings approved by regulatory authorities in the product label, continued demonstration of efficacy and safety in commercial use, perceptions by members of the health care community, including physicians, about the safety and effectiveness of our drugs, physicians' willingness to prescribe the product, reimbursement from third-party payors such as government healthcare systems and insurance companies, the price of the product, pharmacological benefit and cost-effectiveness of our products relative to competing products; the nature of any post-approval risk management plans mandated by regulatory authorities, competition, and the effectiveness of marketing and distribution efforts. Any factors preventing or limiting the market acceptance of our product candidates could have a material adverse effect on our business, results of operations and financial condition.

If we receive regulatory approvals, we intend to market Zygel in multiple jurisdictions where we have limited or no operating experience and may be subject to increased business and economic risks that could affect our financial results.

If we receive regulatory approvals, we may plan to market Zygel in jurisdictions where we have limited or no experience in marketing, developing and distributing our products. Certain markets have substantial legal and regulatory complexities that we may not have experience navigating. We are subject to a variety of risks inherent in doing business internationally, including risks related to the legal and regulatory environment in non-U.S. jurisdictions, including with respect to privacy and data security, trade control laws and unexpected changes in laws, regulatory requirements and enforcement, as well as risks related to fluctuations in currency exchange rates and political, social and economic instability in foreign countries. If we are unable to manage our international operations successfully, our financial results could be adversely affected.

In addition, controlled substance legislation may differ in other jurisdictions and could restrict our ability to market our products internationally. Most countries are parties to the Single Convention on Narcotic Drugs 1961, which governs international trade and domestic control of narcotic substances, including *Cannabis* extracts. Countries may interpret and implement their treaty obligations in a way that creates a legal obstacle to us obtaining marketing approval for Zygel in those countries. These countries may not be willing or able to amend or otherwise modify their laws and regulations to permit Zygel to be marketed, or such amendments may take a prolonged period of time. We would be unable to market Zygel in countries with such obstacles in the near future or perhaps at all without modification to laws and regulations.

Negative public perception of cannabidiol and cannabis-related products and misconceptions about the nature of our business may generate public controversy.

Political and social pressures and adverse publicity could lead to delays in approval of, and increased expenses for, our product candidates. These pressures could also limit or restrict the introduction and marketing of our product candidates. Adverse publicity from *Cannabis*, or misuse or adverse side effects from *Cannabis* or other cannabinoid products, or confusion of our products with *Cannabis*, may adversely affect the commercial success or market penetration achievable by our product candidates. The nature of our business attracts a high level of public and media interest, and in the event of any resultant adverse publicity, our reputation may be harmed.

Any inability to attract and retain qualified key management and technical personnel would impair our ability to implement our business plan.

Our success largely depends on the continued service of key management and other specialized personnel. The loss of one or more members of our senior management team or other key employees could delay our research and development programs and materially harm our business, financial condition, results of operations and prospects. The relationships that our team has cultivated within the life sciences industry makes us particularly dependent upon their continued employment with us. Because our management team is not obligated to provide us with continued service, they could terminate their employment or services with us at any time without penalty, subject to providing any required advance notice. We do not maintain key person life insurance policies for any members of our management team. Our future success and growth will depend in large part on our continued ability to attract and retain other highly qualified scientific, technical and management personnel, as well as personnel with expertise in clinical testing, manufacturing, governmental regulation and commercialization. We face competition for personnel from other companies, universities, public and private research institutions, government entities and other organizations.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of drugs is highly competitive. We compete with a variety of multinational pharmaceutical companies and specialized biotechnology companies, as well as products and processes being developed at universities and other research institutions. Our competitors have developed, are developing or will develop product candidates and processes competitive with our product candidates. Competitive therapeutic treatments include those that have already been approved and accepted by the medical community and any new treatments that may enter the market. We believe that a significant number of products are currently available or are under development and may become commercially available in the future, for the treatment of indications for which we may try to develop product candidates. If Zygel is approved for the indications we are currently pursuing, it will compete with a range of therapeutic treatments that are either in development or currently marketed. See the section titled “Business — Competition.”.

More established companies may have a competitive advantage over us due to their greater size, cash flows and institutional experience. Compared to us, many of our competitors may have significantly greater financial, technical and human resources. As a result of these factors, our competitors may have an advantage in marketing their approved products and may obtain regulatory approval of their product candidates before we are able to, which may limit our ability to develop or commercialize our product candidates. Our competitors may also develop drugs that are safer, more effective, more widely used and less expensive than ours, and may also be more successful than us in manufacturing and marketing their products. These advantages could materially impact our ability to develop and, if approved, commercialize Zygel successfully.

Our product candidates may compete with other FDA approved cannabinoid drugs, including therapies such as GW’s Sativex or Epidiolex. Our product candidates may also compete with medicinal and recreational marijuana, in markets where the recreational and/or medical use of marijuana is legal. There is support in the United States for further legalization of marijuana at both the state and federal levels. In markets where recreational and/or medicinal marijuana is not legal, our product candidates may compete with marijuana purchased in the illegal drug market. We cannot assess

the extent to which patients may utilize marijuana obtained illegally for the treatment of the indications for which we are developing Zygel.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These companies compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and subject registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Product liability lawsuits against us could cause us to incur substantial liabilities.

Our use of Zygel in clinical trials and the sale of Zygel, if approved, exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers or others selling or otherwise coming into contact with Zygel. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, including as a result of interactions with alcohol or other drugs, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things:

- withdrawal of patients from our clinical trials;
- substantial monetary awards to patients or other claimants;
- decreased demand for Zygel following marketing approval, if obtained;
- damage to our reputation and exposure to adverse publicity;
- increased FDA warnings on product labels or increased warnings imposed by the European Commission;
- litigation costs;
- distraction of management’s attention from our primary business;
- loss of revenue; and
- the inability to successfully commercialize Zygel, if approved.

Our current product liability insurance coverage 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 our product candidates, we intend to expand our 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. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our share price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our financial condition, results of operations, business and prospects could be materially adversely affected.

We are subject to securities class action litigation, which is expensive, can divert management attention, and, if resolved unfavorably, could expose us to significant liabilities.

We are subject to securities litigation, which is described further in Part II of this Annual Report in "Notes to Consolidated Financial Statements, Note 12. Commitments and Contingencies and incorporated by reference in Part I, Item 3—*Legal Proceedings*. We have recently reached a negotiated agreement in principle to settle one of these actions, the putative shareholder class action, which is subject to the preliminary and final approval of the court. If the settlement is not approved, this action and any additional litigation could result in substantial costs and a diversion of management's resources and attention. In addition, any adverse determination could expose us to significant liabilities, which could have a material adverse effect on our business, financial condition, and results of operations.

Failure to protect our information technology infrastructure against cyber-based attacks, network security breaches, service interruptions, or data corruption could significantly disrupt our operations and adversely affect our business and operating results.

We rely on information technology, telephone networks and systems, including the internet, to process and transmit sensitive electronic information and to manage or support a variety of business processes and activities. We use enterprise information technology systems to record, process, and summarize financial information and results of operations for internal reporting purposes and to comply with regulatory, financial reporting, legal, and tax requirements. Despite the implementation of security measures, our information technology systems, and those of our third-party contractors and consultants, are vulnerable to a cyber-attack, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption. Any such successful attacks could result in the theft of intellectual property or other misappropriation of assets, or otherwise compromise our confidential or proprietary information and disrupt our operations. Cyber-attacks are becoming more sophisticated and frequent, and our systems could be the target of malware and other cyber-attacks. We have invested in our systems and the protection of our data to reduce the risk of an intrusion or interruption, and we monitor our systems on an ongoing basis for any current or potential threats. Nonetheless, our computer systems are subject to penetration and our data protection measures may not prevent unauthorized access. We can give no assurances that these measures and efforts will prevent interruptions or breakdowns. If we are unable to detect or prevent a security breach or cyber-attack or other disruption from occurring, then we could incur losses or damage to our data, or inappropriate disclosure of our confidential information or that of others; and we could sustain damage to our reputation, suffer disruptions to our research and development and incur increased operating costs including increased cybersecurity and other insurance premiums, costs to mitigate any damage caused and protect against future damage, and be exposed to additional regulatory scrutiny or penalties and to civil litigation and possible financial liability. For instance, the loss of preclinical or clinical data could result in delays in our development and regulatory filing efforts and significantly increase our costs.

We face risks related to our collection and use of data, which could result in investigations, inquiries, litigation, fines, legislative and regulatory action and negative press about our privacy and data protection practices.

We are subject to U.S. data protection laws and regulations (i.e., laws and regulations that address privacy and data security) at both the federal and state levels. The legislative and regulatory landscape for data protection continues to evolve, and in recent years there has been an increasing focus on privacy and data security issues. Numerous federal and state laws, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws, govern the collection, use, and disclosure of health-related and other personal information. In addition, our business processes some personal data, including some data related to health. When conducting clinical trials, we face risks associated with collecting trial participants' data, especially health data, in a manner consistent with applicable laws and regulations. We also face risks inherent in handling large volumes of data and in protecting the security of such data. We could be subject to attacks on our systems by outside parties or fraudulent or inappropriate behavior by our service providers or employees. Third parties may also gain access to users' accounts using stolen or inferred credentials, computer malware, viruses, spamming, phishing attacks or other means, and may use such access to obtain users' personal data or prevent use of their accounts. Data breaches could result in a violation of applicable U.S. and international privacy, data protection and other laws, and subject us to individual or consumer class action litigation and governmental investigations and proceedings by federal, state and local regulatory entities in the United States and

by international regulatory entities, resulting in exposure to material civil and/or criminal liability. Further, our general liability insurance and corporate risk program may not cover all potential claims to which we are exposed and may not be adequate to indemnify us for all liability that may be imposed.

As our operations and business grow, we may become subject to or affected by new or additional data protection laws and regulations and face increased scrutiny or attention from regulatory authorities. In the United States, HIPAA imposes, among other things, certain standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information. Certain states have also adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. Such laws and regulations will be subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. In addition, California enacted the California Consumer Privacy Act, or CCPA. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal data. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability, and many similar laws have been proposed at the federal level and in other states. In the event that we are subject to or affected by HIPAA, the CCPA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition. In addition, Australia and other countries have also adopted data protection laws and regulations, which impose significant compliance obligation.

This risk is enhanced in certain jurisdictions and, as we expand our operations domestically and internationally, we may become subject to additional laws in other jurisdictions, such as the EU's General Data Protection Regulation, or GDPR, which became effective in May 2018. The GDPR applies extraterritorially and imposes several stringent requirements for controllers and processors of personal data, including, for example, higher standards for obtaining consent from individuals to process their personal data, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention of information, increased requirements pertaining to special categories of personal data and pseudonymised (i.e., key-coded) data and additional obligations when we contract third-party processors in connection with the processing of the personal data. Any failure, or perceived failure, by us to comply with privacy and data protection laws, rules and regulations could result in proceedings or actions against us by governmental entities or others. These proceedings or actions may subject us to significant penalties and negative publicity, require us to change our business practices, increase our costs and severely disrupt our business.

In addition, under certain circumstances, we may be considered liable for non-compliance by our third-party service providers under the HIPAA, GDPR, the CCPA or other privacy laws and regulations. We could be liable for, or face reputational harm as a result of, their actions if, for example, they fail to comply with applicable statutory and regulatory requirements. These or similar instances of noncompliance by our third-party partners with privacy laws and regulations could have an adverse impact on our reputation and business.

Risks Related to Government Regulation

The regulatory approval processes of the FDA, the EMA and other comparable foreign regulatory 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.

We are not permitted to market our product candidates in the United States or the European Union until we receive approval of an NDA from the FDA or an MAA from the European Commission, respectively, or in any foreign countries until we receive the requisite approval from such countries. Prior to submitting an NDA to the FDA or an MAA to the EMA for approval of our product candidates, we will need to complete our preclinical studies and clinical trials. Successfully completing our clinical program and obtaining approval of an NDA or MAA is a complex, lengthy,

expensive and uncertain process, and the FDA or EMA may delay, limit or deny approval of our product candidates for many reasons, including, among others, because:

- we may not be able to demonstrate that our product candidates are safe and effective in treating patients to the satisfaction of the FDA or EMA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or EMA for marketing approval;
- the FDA or EMA may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the FDA or EMA may require that we conduct additional clinical trials;
- the FDA or EMA or other applicable foreign regulatory authorities may not approve the formulation, labeling or specifications of our product candidates;
- the CROs and other contractors that we may retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA or EMA may find the data from preclinical studies and clinical trials insufficient to demonstrate that Zygel is safe and effective for their proposed indications;
- the FDA or EMA may disagree with our interpretation of data from our preclinical studies and clinical trials;
- the FDA or EMA may not accept data generated at our clinical trial sites or may disagree with us over whether to accept efficacy results from clinical trial sites outside the United States or outside the European Union, as applicable, where the standard of care is potentially different from that in the United States or in the European Union, as applicable;
- if our NDAs or MAAs are submitted to the FDA or EMA, as applicable, the regulatory authorities may have difficulties scheduling the necessary review meetings in a timely manner, may recommend against approval of our application or may recommend or require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA may require development of a REMS, which would use risk minimization strategies to ensure that the benefits of certain prescription drugs outweigh their risks, as a condition of approval or post-approval, and the European Commission may grant only conditional marketing authorization or impose specific obligations as a condition for marketing authorization, or may require us to conduct post-authorization safety studies;
- the FDA, DEA, European Commission or other applicable foreign regulatory agencies may not approve the manufacturing processes or facilities of third-party manufacturers with which we contract or DEA or other applicable foreign regulatory agency quotas may limit the quantities of controlled substances available to our manufacturers; or
- the FDA, European Commission or other applicable foreign regulatory agencies may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could increase development costs, jeopardize our ability to obtain regulatory approval for and successfully market our product candidates and generate product revenue. Moreover,

because our business is almost entirely dependent upon Zygel, any such setback with regard to Zygel in our pursuit of regulatory approval, in any of our planned indications, could have a material adverse effect on our business and prospects.

We have conducted and are conducting clinical trials for Zygel outside the United States and anticipate conducting additional clinical trials for Zygel outside the United States, and the FDA may not accept data from such trials.

For Zygel, we have reported results from clinical trials which were conducted in Australia and New Zealand. We also have ongoing clinical trials in Australia and New Zealand. We anticipate that we will conduct additional clinical trials for Zygel in countries outside the United States, subject to applicable regulatory approval. We plan to submit NDAs for Zygel to the FDA upon completion of all requisite clinical trials. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of such study data by the FDA is subject to certain conditions. For example, the clinical trial must be conducted in accordance with GCP requirements and the FDA must be able to validate the data from the clinical trial through an onsite inspection if it deems such inspection necessary. Where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the United States, the FDA will not approve the application on the basis of foreign data alone unless those data are considered applicable to the U.S. patient population and U.S. medical practice, the clinical trials were performed by clinical investigators of recognized competence, and the data is considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. In addition, such clinical trials would be subject to the applicable local laws of the foreign jurisdictions where the clinical trials are conducted. If the drug has a potential for abuse, the NDA must include a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the federal Controlled Substances Act, or CSA. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known. There can be no assurance the FDA will accept data from clinical trials conducted outside of the United States. If the FDA does not accept any such data, it would likely result in the need for additional clinical trials, which would be costly and time-consuming and delay aspects of our development plan.

In addition, the conduct of clinical trials outside the United States could have a significant impact on us. Risks inherent in conducting international clinical trials include:

- foreign regulatory requirements that could burden or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple foreign regulatory schema;
- foreign currency fluctuations which could negatively impact our financial condition since certain payments are paid in local currencies;
- manufacturing, customs, shipment and storage requirements;
- cultural differences in medical practice and clinical research; and
- diminished protection of intellectual property in some countries.

Even if Zygel receives regulatory approval, it may still face future development and regulatory difficulties.

If we obtain regulatory approval for Zygel, such approval would be subject to extensive ongoing requirements by the DEA, FDA, EMA and other foreign regulatory authorities, including requirements related to the manufacture, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting of safety and other post-market information. The safety profile of any product will continue to be closely monitored by the FDA, EMA and other comparable foreign regulatory authorities. If the FDA, EMA, DEA or any other comparable foreign regulatory authority becomes aware of new safety information after approval of any of our product candidates, these regulatory authorities may require labeling changes or establishment of

a REMS, impose significant restrictions on a product's indicated uses or marketing, initiate a change in the drug's controlled substance schedule, impose ongoing requirements for potentially costly post-approval studies or post-market surveillance, impose a recall or seek to withdraw marketing approval altogether.

In addition, manufacturers of therapeutic products and their facilities are subject to continual review and periodic inspections by the FDA, the EMA and other comparable foreign regulatory authorities for compliance with cGMP. Further, manufacturers of controlled substances must obtain and maintain necessary DEA and state registrations and registrations with applicable foreign regulatory authorities, and must establish and maintain processes to ensure compliance with DEA and state requirements and requirements of applicable foreign regulatory authorities governing, among other things, the storage, handling, security, recordkeeping and reporting for controlled substances. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

- issue untitled letters, letters of administration or warning letters;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require us to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval or suspend or revoke the facility's controlled substance registration;
- suspend any ongoing clinical trials;
- require us to enter into a Memorandum of Agreement settling administrative or civil claims which can require the implementation of costly compliance programs;
- refuse to approve pending applications or supplements to applications filed by us; or
- seize or detain products or require us to initiate a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and may otherwise have a material adverse effect on our business, financial condition and results of operations. Non-compliance with requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

The 2018 Farm Bill and other legislation regarding cannabis may impact our business.

The 2018 Farm Bill excludes hemp from the definition of marijuana for purposes of the CSA and legalizes the cultivation and commercial sale of hemp in the United States, subject to state regulation and continuing oversight by federal regulatory agencies. Under the 2018 Farm Bill, the term ''hemp'' means the plant Cannabis sativa L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis. This definition of hemp includes only plant derived hemp products. The 2018 Farm Bill declassified

this type of hemp as a Schedule I substance and shifted regulatory authority from the DEA to the U.S. Department of Agriculture, or USDA. The 2018 Farm Bill outlines a regulatory plan for hemp production and gives primary regulatory authority to the states. According to the National Conference of State Legislatures, at least 47 states have enacted legislation to establish industrial hemp cultivation and productions programs to regulate the production of hemp.

The U.S. Department of Agriculture, or USDA, issued an Interim Final Rule, or IFR, on October 31, 2019, establishing the Domestic Hemp Production Program. This program provides the parameters for federal licensing of hemp production, as well as for approval of licensing plans established by states and Native American tribes. Under the IFR, and confirmed by the Final Rule issued by the USDA on January 15, 2021, hemp containing THC levels greater than 0.3 percent remains a Schedule I controlled substance.

Notwithstanding the removal of plant-derived hemp from the CSA, the 2018 Farm Bill did not alter the FDA's authority to regulate products containing cannabis or cannabis-derived compounds under the FDC Act. Hemp products that qualify as drugs, food, dietary supplements, veterinary products, and cosmetics will continue to be regulated by FDA under the applicable regulatory frameworks. Following passage of the 2018 Farm Bill, the FDA reaffirmed its enforcement authority and reiterated the requirement that a cannabis product (hemp-derived or otherwise) that is marketed with a claim of therapeutic benefit, or with any other disease claim, be approved by the FDA for its intended use before it may be introduced into interstate commerce. Currently, the FDA treats cannabidiol as a pharmaceutical product, and any product containing cannabidiol must go through the drug approval process and demonstrate the safety and efficacy of the formulation at issue to receive FDA approval. To date, the FDA has approved one such product, Epidiolex, which contains a purified form of cannabidiol, for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome and Tuberous sclerosis complex for patients one year of age and older. The FDA has also approved three other compounds that contain synthetic forms of THC or THC-like substances.

The 2018 Farm Bill does not directly impact us because the pharmaceutical-grade, synthetically-produced cannabidiol used in the manufacture of Zygel remains a Schedule I controlled substance under the CSA and the development of Zygel remains subject to FDA regulations**.** Given the continuing uncertainty surrounding future state and federal regulations and the continuing barriers that still exist for cannabis and cannabis-derived compounds, such as cannabidiol, in certain product categories due to FDA regulation, it is unknown what impact the removal of hemp from the CSA, and any resulting commercialization of hemp products, may have on our business.

Zygel will be subject to controlled substance laws and regulations; failure to receive necessary approvals may delay the launch of our products and failure to comply with these laws and regulations may adversely affect the results of our business operations.

Zygel contains controlled substances as defined in the CSA. Controlled substances that are pharmaceutical products are subject to a high degree of regulation under the CSA, which establishes, among other things, certain registration, manufacturing quotas, security, recordkeeping, reporting, import, export and other requirements administered by the DEA. The DEA classifies controlled substances into five schedules: Schedule I, II, III, IV or V substances. Schedule I substances by definition have a high potential for abuse, have no currently "accepted medical use" in the United States, lack accepted safety for use under medical supervision, and may not be prescribed, marketed or sold in the United States. Pharmaceutical products approved for use in the United States may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse among such substances. Schedule I and II drugs are subject to the strictest controls under the CSA, including manufacturing and procurement quotas, security requirements and criteria for importation. In addition, dispensing of Schedule II drugs is further restricted. For example, they may not be refilled without a new prescription.

While *Cannabis* and certain of its derivatives are Schedule I controlled substances, products approved for medical use in the United States that contain *Cannabis* or *Cannabis* extracts must be placed in Schedules II - V, since approval by the FDA satisfies the "accepted medical use" requirement. In 2018 the FDA approved Epidiolex, a sesame oil oral solution of cannabidiol and the DEA scheduled Epidiolex to Schedule V. In 2020, the DEA descheduled Epidiolex. If Zygel receives FDA approval, the DEA will make a scheduling determination and place it in a schedule other than Schedule I

in order for it to be prescribed to patients in the United States. Based on the scheduling decision the DEA made with respect to Epidiolex, if approved by the FDA, we believe, but cannot be certain, that the finished dosage forms of Zygel will be listed by the DEA as a Schedule V controlled substance. However, the DEA must issue an order scheduling the drug within 90 days after FDA approves the drug and DEA receives a scientific and medical evaluation and scheduling recommendation from the HHS. Furthermore, if the FDA, DEA or any foreign regulatory authority determines that Zygel may have potential for abuse, it may require us to generate more clinical data than that which is currently anticipated, which could increase the cost and/or delay the launch of Zygel.

Because Zygel contains active ingredients of *Cannabis*, which are Schedule I substances, to conduct preclinical studies and clinical trials with Zygel in the United States prior to approval, each of our research sites must submit a research protocol to the DEA and obtain and maintain a DEA researcher registration that will allow those sites to handle and dispense Zygel and to obtain the product from our manufacturer. If the DEA delays or denies the grant of a research registration to one or more research sites, the preclinical studies or clinical trials could be significantly delayed, and we could lose and be required to replace clinical trial sites, resulting in additional costs.

If for some reason Zygel becomes scheduled as Schedule II or III controlled substance we will also need to identify wholesale distributors with the appropriate DEA registrations and authority to distribute the products to pharmacies and other healthcare providers, and these distributors would need to obtain Schedule II or III distribution registrations. The failure to obtain, or delay in obtaining, or the loss of any of those registrations could result in increased costs to us. If Zygel is a Schedule II drug, pharmacies would have to maintain enhanced security with alarms and monitoring systems, and they must adhere to additional recordkeeping and inventory requirements. This may discourage some pharmacies from carrying the product. Furthermore, state and federal enforcement actions, regulatory requirements, and legislation intended to reduce prescription drug abuse, such as the requirement that physicians consult a state prescription drug monitoring program, may make physicians less willing to prescribe, and pharmacies to dispense, Schedule II products. Further, if Zygel is a Schedule II drug, DEA must establish an annual aggregate quota for the amount that may be manufactured or produced in the United States based on the DEA's estimate of the quantity needed to meet legitimate medical, scientific, research and industrial needs. This limited aggregate amount that the DEA allows to be produced in the United States each year is allocated among individual companies, which, in turn, must annually apply to the DEA for individual manufacturing and procurement quotas. The quotas apply equally to the manufacturing of the active pharmaceutical ingredient and production of dosage forms. The DEA may adjust aggregate production quotas a few times per year, and individual manufacturing or procurement quotas from time to time during the year, although the DEA has substantial discretion in whether or not to make such adjustments for individual companies. A failure by us to obtain adequate quota could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We may manufacture the commercial supply of Zygel outside of the United States. If Zygel is approved by the FDA and classified as a Schedule II or III substance, an importer can import for commercial purposes if it obtains from the DEA an importer registration and files an application with the DEA for an import permit for each import. The failure to identify an importer or obtain the necessary import authority, including specific quantities, could affect the availability of Zygel and have a material adverse effect on our business, results of operations and financial condition. In addition, an application for a Schedule II importer registration must be published in the Federal Register, and there is a waiting period for third-party comments to be submitted.

Individual states have also established controlled substance laws and regulations. Though state-controlled substance laws often mirror federal law, because the states are separate jurisdictions, they may separately schedule our product candidates as well. While some states automatically schedule a drug based on federal action, other states schedule drugs through rulemaking or a legislative action. State scheduling may delay commercial sale of any product for which we obtain federal regulatory approval and adverse scheduling could have a material adverse effect on the commercial attractiveness of such product. We or our partners must also obtain separate state registrations, permits or licenses in order to be able to obtain, handle, and distribute controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions by the states in addition to those from the DEA or otherwise arising under federal law.

We currently use contract manufacturers in the United States and Canada to produce the API for Zygel and contract manufacturers in the United Kingdom and Australia to manufacture the drug product for our clinical trials. For Zygel, we have conducted and plan to continue to conduct clinical trials in Australia, New Zealand and the United States. In addition, we may decide to develop, manufacture or commercialize our product candidates in additional countries. As a result, we will also be subject to controlled substance laws and regulations from the TGA in Australia, Health Canada's Office of Controlled Substances in Canada, the New Zealand Medicines and Medical Device Safety Authority in New Zealand, the Drugs & Firearms Unit (Home Office) of the National Drug Control System in the United Kingdom, and from other regulatory agencies in other countries where we develop, manufacture or commercialize Zygel in the future. We plan to submit NDAs for Zygel to the FDA upon completion of all requisite clinical trials and may require additional DEA approvals at such time as well.

Product shipment delays could have a material adverse effect on our business, results of operations and financial condition.

The shipment, import and export of Zygel and the API used to manufacture Zygel will require import and export licenses. In the United States, the FDA, U.S. Customs and Border Protection, and the DEA; in Canada, the Canada Border Services Agency, Health Canada; in Europe, the EMA and the European Commission; in Australia and New Zealand, the Australian Customs and Board Protection Service, the TGA, the New Zealand Medicines and Medical Device Safety Authority and the New Zealand Customs Service; and in other countries, similar regulatory authorities, regulate the import and export of pharmaceutical products that contain controlled substances. Specifically, the import and export process requires the issuance of import and export licenses by the relevant controlled substance authority in both the importing and exporting country. We may not be granted, or if granted, maintain, such licenses from the authorities in certain countries. Even if we obtain the relevant licenses, shipments of API and our product candidates may be held up or lost in transit, which could cause significant delays and may lead to product batches being stored outside required temperature ranges. Inappropriate storage may damage the product shipment resulting in delays in clinical trials or, upon commercialization, a partial or total loss of revenue from one or more shipments of API or Zygel. A delay in a clinical trial or, upon commercialization, a partial or total loss of revenue from one or more shipments of API or Zygel could have a material adverse effect on our business, results of operations and financial condition.

Failure to obtain regulatory approval in jurisdictions outside the United States and the European Union would prevent our product candidates from being marketed in those jurisdictions.

In order to market and sell our products in jurisdictions other than the United States and the European Union, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The regulatory approval process outside the United States and the European Union generally includes all of the risks associated with obtaining FDA approval or the approval from the European Commission but can involve additional testing. We may need to partner with third parties in order to obtain approvals outside the United States and the European Union. In addition, in many jurisdictions worldwide, it is required that the product be approved for reimbursement before the product can be approved for sale in such jurisdiction. We may not obtain approvals from regulatory authorities outside the United States and the European Union on a timely basis, if at all. Even if we were to receive approval in the United States or the European Union, approval by the FDA or the European Commission does not ensure approval by regulatory authorities in other countries or jurisdictions. Similarly, approval by one regulatory authority outside the United States and the European Union would not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA or the European Commission. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market. If we are unable to obtain approval of our product candidates by regulatory authorities in other foreign jurisdictions, the commercial prospects of those product candidates may be significantly diminished and our business prospects could decline.

The Affordable Care Act and any changes in healthcare law may increase the difficulty and cost for us to successfully commercialize our products and affect the prices we may obtain.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that may affect our ability to profitably sell our product and product candidates, if approved. The

United States government, state legislatures and foreign governments also have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

The Affordable Care Act was intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the Affordable Care Act that have been implemented since enactment and are of importance to the commercialization of our product and product candidates, if approved, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs or biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the U.S. civil False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- 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;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- requirements to report certain financial arrangements with physicians and teaching hospitals;
- a requirement to annually report certain information regarding drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

There have been significant ongoing judicial, administrative, executive and legislative efforts to modify or eliminate the Affordable Care Act. For example, the Tax Act enacted on December 22, 2017, repealed the shared responsibility payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code, commonly referred to as the individual mandate. The Trump administration issued executive orders which sought to reduce burdens associated with the Affordable Care Act and modified how it was implemented. Other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater

than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. Subsequent litigation extended the 2% reduction, on average, to 2030 unless additional Congressional action is taken. However, pursuant to the Coronavirus Aid, Relief and Economic Security Act, or CARES Act, the 2% Medicare sequester reductions have been suspended from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic. On January 2, 2013, the American Taxpayer Relief Act was signed into law, which, among other things, 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.

The Affordable Care Act has also been subject to challenges in the courts. On December 14, 2018, a Texas U.S. District Court Judge ruled that the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional and remanded the case to the Texas District Court to reconsider its earlier invalidation of the entire Affordable Care Act. An appeal was taken to the U.S. Supreme Court which heard oral arguments in the case on November 10, 2020. A ruling is expected in 2021.

Further changes to and under the Affordable Care Act remain possible, although the new Biden administration has signaled that it plans to build on the Affordable Care Act and expand the number of people who are eligible for subsidies under it. President Biden indicated that he intends to use executive orders to undo changes to the Affordable Care Act made by the Trump administration and would advocate for legislation to build on the Affordable Care Act. It is unknown what form any such changes or any law would take, and how or whether it may affect our business in the future. We expect that changes or additions to the Affordable Care Act, the Medicare and Medicaid programs, changes allowing the federal government to directly negotiate drug prices and changes stemming from other healthcare reform measures, especially with regard to healthcare access, financing or other legislation in individual states, could have a material adverse effect on the healthcare industry.

We expect that the Affordable Care Act, as well as other healthcare reform measures that have and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for our product and product candidates, if approved, and could seriously harm our future revenues. Any reduction in reimbursement from Medicare, Medicaid, or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain and maintain profitability of our product and product candidates, if approved.

Increased scrutiny on drug pricing or changes in pricing regulations could restrict the amount that we are able to charge for our product candidates, which could adversely affect our revenue and results of operations.

Drug pricing by pharmaceutical companies is currently under increased scrutiny and is expected to continue to be the subject of intense political and public debate in the United States. Specifically, there have been U.S. Congressional inquiries and hearings with respect to pharmaceutical drug pricing practices, including the investigation of specific price increases by several pharmaceutical companies. Additionally, several states have passed laws designed to, among other things, bring more transparency to drug pricing, and other states may pursue similar initiatives in the future. We cannot predict the extent to which our business may be affected by these or other potential future legislative or regulatory developments. However, increased scrutiny on drug pricing, negative publicity related to the pricing of pharmaceutical drugs generally, or changes in pricing regulations could restrict the amount that we are able to charge for our product candidates, which could have a material adverse effect on our revenue and results of operations.

We have been granted orphan drug status by the FDA for the use of cannabidiol for the treatment of FXS and 22q, but we may be unable to maintain the benefits associated orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.

Regulatory authorities in some jurisdictions, including the United States and European Union, may designate drugs for relatively small patient populations as orphan drugs. The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals annually in the United States, or, if the disease or condition affects more than 200,000 individuals annually in the United States, if there is no reasonable expectation that the cost of developing and making the drug would be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug.

In the United States, orphan drug designation entitles a party to financial incentives, such as opportunities for grant funding towards clinical trial costs, tax credits for certain research and user fee waivers under certain circumstances. In addition, if a product receives the first FDA approval for the drug and indication for which it has orphan drug designation, the product is entitled to seven years of market exclusivity, which means the FDA may not approve any other application for the same drug 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 drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable so that market exclusivity is no longer justified.

We may lose orphan drug status if the FDA determines that the request for designation was materially defective or if we are unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition. Moreover, orphan drug exclusivity may not effectively protect our product candidates from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA or comparable foreign regulatory authority can subsequently approve the same drug for the same condition if such regulatory authority concludes that the later drug is clinically superior if it is shown to be safer, more effective or makes a major contribution to patient care. 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.

Serious adverse events or other safety risks could require us to abandon development and preclude, delay or limit approval of our product candidates, or limit the scope of any approved label or market acceptance.

As is the case with pharmaceuticals generally, it is likely that there may be side effects and adverse events associated with our product candidates' use. 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 comparable foreign regulatory authorities. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Moreover, if our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may elect to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for the product candidate if approved. We may also be required to modify our study plans based on findings in our ongoing clinical trials. It is possible that as we test our product candidates in larger, longer and more extensive clinical trials, or as the use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by subjects. If such side effects become known later in development or upon approval, if any, such findings may harm our business, financial condition and prospects significantly.

Even though our product candidate has received Fast Track designation, the FDA may not approve it at all or any sooner than other product candidate that does not have Fast Track designation.

We have received Fast Track designation from the FDA for Zygel for the treatment of behavioral symptoms associated with FXS. Fast Track designation does not ensure that we will receive marketing approval or that approval will be granted within any particular timeframe. We may not experience a faster development, regulatory review or approval process with Fast Track designation compared to conventional FDA procedures. Additionally, the FDA may withdraw Fast Track designation, for reasons such as it comes to believe a drug candidate no longer adequately addresses an unmet medical need. Fast Track designation alone does not guarantee qualification for the FDA's priority review procedures. If we seek Fast Track designation for other product candidates, we may not receive such a designation from the FDA.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing approval. As a pharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. Restrictions under applicable federal and state healthcare laws and regulations that may affect our ability to operate include the following:

- the U.S. federal healthcare Anti-Kickback Statute impacts our marketing practices, educational programs, pricing policies and relationships with healthcare providers or other entities, by prohibiting, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;

- federal civil and criminal false claims laws and civil monetary penalty laws impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment of government funds (including through reimbursement by Medicare or Medicaid or other federal health care programs), which has been applied to impermissible promotion of pharmaceutical products for off-label uses, or making a false statement or record to avoid, decrease or conceal an obligation to pay money to the federal government;

- HIPAA, as amended by HITECH, among other things, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services;

- HIPAA, as amended by HITECH, among other things, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, and imposes notification obligations in the event of a breach of the privacy or security individually identifiable health information;

- the federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, requires applicable manufacturers of covered drugs, devices, biologics and medical supplies to report annually to HHS information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members;

- numerous federal and state laws and regulations that address privacy and data security, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the FTC Act), govern the collection, use, disclosure and protection of health-related and other personal information;

- analogous state laws and regulations, such as state anti-kickback laws, false claims laws and privacy and security of health information laws, may apply to sales or marketing arrangements, claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, or health information; and

- certain state laws require pharmaceutical companies to adopt codes of conduct consistent with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; restrict certain marketing-related activities including the provision of gifts, meals, or other items to certain health care providers; and/or require drug manufacturers to report information related to payments and other transfers of value to physicians and certain other healthcare providers or marketing expenditures.

Comparable laws and regulations exist in the countries within the European Economic Area, or EEA. Although such laws are partially based upon European Union law, they may vary from country to country. Healthcare specific, as well as general European Union and national laws, regulations and industry codes constrain, for example, our interactions with government officials and healthcare professionals, and the collection and processing of personal health data. Non-compliance with any of these laws or regulations could lead to criminal or civil liability.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, or those of our third-party service providers, are found to be in

violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any physicians or other healthcare 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.

Also, the U.S. Foreign Corrupt Practices Act and similar worldwide anti-bribery laws generally prohibit companies and their intermediaries from making improper payments to non-U.S. officials for the purpose of obtaining or retaining business. Our internal control policies and procedures may not protect us from reckless or negligent acts committed by our employees, future distributors, licensees or agents. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violations of these laws, or allegations of such violations, could result in fines, penalties or prosecution and have a negative impact on our business, results of operations and reputation.

Recent federal legislation and actions by state and local governments may permit reimportation of drugs from foreign countries into the United States, including foreign countries where the drugs are sold at lower prices than in the United States, which could materially adversely affect our business and financial condition.

We may face competition for Zygel, if approved, from cheaper cannabinoid therapies sourced from foreign countries that have placed price controls on pharmaceutical products. The Medicare Modernization Act contains provisions that may change U.S. importation laws and expand pharmacists' and wholesalers' ability to import cheaper versions of an approved drug and competing products from Canada, where there are government price controls. These changes to U.S. importation laws would not take effect unless and until the Secretary of Health and Human Services certifies that the changes will pose no additional risk to the public's health and safety and would result in a significant reduction in the cost of products to consumers. The Secretary of Health and Human Services issued a final rule in September 2020 allowing the submission of reimportation proposals to the FDA for review and approval. Proponents of drug reimportation, including certain state legislatures, may attempt to pass legislation that would directly allow reimportation under certain circumstances. Approval of importation proposals by the FDA and additional legislation, regulations or other government actions, including actions by the states, could decrease the price we receive for any products that we may develop, including Zygel, and adversely affect our future revenues and prospects for profitability.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could subject us to significant liability and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with DEA, FDA or EMA regulations or similar regulations of other foreign regulatory authorities or to provide accurate information to the DEA, FDA, EMA or other foreign regulatory authorities. In addition, misconduct by employees could include intentional failures to comply with certain manufacturing standards, to comply with U.S. federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, to report financial information or data accurately or to disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have implemented, and will enforce, a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity, such as employee training on enforcement of the Code of Business Conduct and Ethics, 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 be in compliance with such laws or regulations. 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 fines or other sanctions.

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates.

We rely on CROs, clinical data management organizations and consultants to design, conduct, supervise and monitor our preclinical studies and clinical trials. We and our CROs are required to comply with various regulations, including GCP, which are enforced by regulatory agencies, including the FDA, and guidelines of the Competent Authorities of Member States of the EEA and comparable foreign regulatory authorities to ensure that the health, safety and rights of patients are protected in clinical development and clinical trials, and that trial data integrity is assured. Regulatory authorities ensure compliance with these requirements through periodic inspections of trial sponsors, principal investigators and trial sites. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. If we or any of our CROs fail to comply with applicable requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the European Commission or other 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 such requirements. In addition, our clinical trials must be conducted with products produced under cGMP requirements, which mandate, among other things, the methods, facilities and controls used in manufacturing, processing and packaging of a drug product to ensure its safety and identity. Failure to comply with these regulations may require us to repeat preclinical studies and clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and preclinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for 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 our product candidates. As a result, our operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed or reduced. In addition, operations of our CROs could be affected by earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. If their facilities are unable to operate because of an accident or incident, even for a short period of time, some or all of our research and development programs may be harmed or delayed, and our operations and financial condition could suffer.

Because we have relied on third parties, our internal capacity to perform these functions is limited. Outsourcing these functions involves risk that third parties may not perform to our standards, may not produce results in a timely manner or may fail to perform at all. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers. To the extent we are unable to identify and successfully manage the performance of third-party service providers in the future, our business may be adversely affected. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We rely on third-party manufacturers and suppliers to produce preclinical and clinical supplies and intend to rely on third-party manufacturers for commercial supplies of APIs and final dosage forms for Zygel, if approved.

We rely on third parties to supply the materials for, and manufacture, our research and development, and preclinical and clinical trial supplies and APIs. We do not own manufacturing facilities or supply sources for such components and materials. There can be no assurance that our supply of research and development, preclinical and clinical development

drugs and other materials will not be limited, interrupted, restricted in certain geographic regions or of satisfactory quality or continue to be available at acceptable prices. In particular, any replacement of our API manufacturer could require significant effort and expertise because there may be a limited number of qualified manufacturers.

The manufacturing process for our product candidates is subject to review by the FDA, EMA, DEA and other foreign regulatory authorities. Suppliers and manufacturers must meet applicable manufacturing requirements and undergo rigorous facility and process validation tests required by regulatory authorities in order to comply with regulatory standards such as cGMP. In addition, our manufacturers must ensure consistency among batches, including preclinical, clinical and, if approved, marketing batches. Demonstrating such consistency may require typical manufacturing controls as well as clinical data. Our manufacturers must also ensure that our batches conform to complex release specifications. Further, manufacturers of controlled substances must obtain and maintain necessary DEA and state registrations and registrations with applicable foreign regulatory authorities, and must establish and maintain processes to ensure compliance with DEA and state requirements and requirements of applicable foreign regulatory authorities governing, among other things, the storage, handling, security, recordkeeping and reporting for controlled substances. In the event that any of our suppliers or manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into an agreement with another third-party, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills or technology to another third-party and a feasible alternative may not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third-party manufacture our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget.

We expect to continue to rely on third-party manufacturers if we receive regulatory approval for any product candidate. To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner consistent with contractual and regulatory requirements, including those related to quality control and assurance. If we are unable to obtain or maintain third-party manufacturing for product candidates, or to do so on commercially reasonable terms, we may not be able to develop and commercialize our product candidates successfully. Our or a third party's failure to execute on our manufacturing requirements could adversely affect our business in a number of ways, including:

- an inability to initiate or continue preclinical studies or clinical trials of product candidates under development;
- delay in submitting regulatory applications, or receiving regulatory approvals, for product candidates;
- loss of the cooperation of a collaborator;
- subjecting our product candidates to additional inspections by regulatory authorities; and
- in the event of approval to market and commercialize a product candidate, the withdrawal of such approval and/or an inability to meet commercial demands for our products.

In addition, our ability to obtain materials from these suppliers could be disrupted if the operations of these manufacturers are affected by earthquakes, power shortages, telecommunications failures, cybersecurity breaches, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions. If their facilities are unable to operate because of an accident or incident, even for a short period of time, some or all of our research and development programs may be harmed or delayed, and

our operations and financial condition could suffer. Our third-party manufacturers also may use hazardous materials, including chemicals and compounds that could be dangerous to human health and safety or the environment, and their operations may also produce hazardous waste products. In the event of contamination or injury, our third-party manufacturers could be held liable for damages or be penalized with fines in an amount exceeding their resources, which could result in our clinical trials or regulatory approvals being delayed or suspended.

If a collaborative partner terminates or fails to perform its obligations under an agreement with us, the commercialization of Zygel, if approved, could be delayed or terminated.

We are not currently party to any collaborative arrangements for the commercialization of Zygel, if approved, or similar arrangements, although we may pursue such arrangements before any commercialization of Zygel, if approved. If we enter into future collaborative arrangements for the commercialization of any product candidate or similar arrangements and any of our collaborative partners does not devote sufficient time and resources to a collaboration arrangement with us, we may not realize the potential commercial benefits of the arrangement, and our results of operations may be materially adversely affected. In addition, if any such future collaboration partner were to breach or terminate its arrangements with us, the commercialization of any product candidate could be delayed, curtailed or terminated.

Much of the potential revenue from future collaborations may consist of contingent payments, such as payments for achieving regulatory milestones or royalties payable on sales of drugs. The milestone and royalty revenue that we may receive under these collaborations will depend upon our collaborators' ability to successfully develop, introduce, market and sell new products. In addition, collaborators may decide to enter into arrangements with third parties to commercialize products developed under collaborations using our technologies, which could reduce the milestone and royalty revenue that we may receive, if any. Future collaboration partners may fail to develop or effectively commercialize products using our products or technologies, which could have a material adverse effect on our operating results and financial condition.

Risks Related to Our Intellectual Property

If we are unable to protect our intellectual property rights or if our intellectual property rights are inadequate for our technology and product candidates, our competitive position could be harmed.

Our commercial success will depend in large part on our ability to obtain and maintain patent and other intellectual property protection in the U.S. and other countries with respect to our proprietary technology and products. We rely on trade secret, patent, copyright and trademark laws, and confidentiality and other agreements with employees and third parties, all of which offer only limited protection. We seek to protect our proprietary position by filing and prosecuting patent applications in the United States and abroad related to our novel technologies and products that are important to our business.

The patent positions of biotechnology and pharmaceutical companies generally are highly uncertain, involve complex legal and factual questions and have in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patents are highly uncertain. The steps we have taken to protect our proprietary rights may not be adequate to preclude misappropriation of our proprietary information or infringement of our intellectual property rights, both inside and outside the United States. Our pending applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Further, the examination process may require us to narrow the claims for our pending patent applications, which may limit the scope of patent protection that may be obtained if these applications issue. We do not know whether any of the pending patent applications for any of our product candidates will result in the issuance of patents that protect our technology or products, or if any of our issued patents will effectively prevent others from commercializing competitive technologies and products. The rights already granted under any of our currently issued patents and those that may be granted under future issued patents may not provide us with the proprietary protection or competitive advantages we are seeking. 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 sufficient, our competitors could develop and commercialize technology and products similar or superior to ours, and our ability to successfully commercialize our technology and

products may be adversely affected. It is also possible that we will fail to identify patentable aspects of inventions made in the course of our development and commercialization activities before it is too late to obtain patent protection on them.

Because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our issued patents may be challenged in the courts or patent offices in the U.S. and abroad. Such challenges may result in the loss of patent protection, the narrowing of claims in such patents or the invalidity or unenforceability of such patents, 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 for our technology and products. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing. Therefore, we cannot be certain that we were the first to make the inventions claimed in our owned patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Protecting against the unauthorized use of our patented technology, trademarks and other intellectual property rights is expensive, difficult and may in some cases not be possible. In some cases, it may be difficult or impossible to detect third-party infringement or misappropriation of our intellectual property rights, even in relation to issued patent claims, and proving any such infringement may be even more difficult.

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 U.S. PTO and various foreign national or international patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and various foreign national or international patent agencies in several stages over the lifetime of the patent. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of patent rights include, but are not limited to, failure to timely file national and regional stage patent applications based on our international patent application, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may become subject to claims by third parties either asserting that we or our employees have misappropriated their intellectual property or claiming ownership of what we regard as our own intellectual property.

Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidates, and to use our related proprietary technologies without violating the intellectual property rights of others. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates, including interference or derivation proceedings before the U.S. PTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third-party to continue commercializing our product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Under certain circumstances, we could be forced, including by court order, to cease commercializing the applicable product candidate. In addition, in any such proceeding or litigation, we could be found liable for monetary damages. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Any claims by third parties that we have misappropriated their confidential information or trade secrets could have a similar negative impact on our business.

While our preclinical studies and clinical trials are ongoing, we believe that the use of Zygel in these preclinical studies and clinical trials falls within the scope of the exemptions provided by 35 U.S.C. Section 271(e) in the United States, which exempts from patent infringement liability activities reasonably related to the development and submission of information to the FDA, or the Clinical Development Exemption. As Zygel progresses toward commercialization, the possibility of a patent infringement claim against us increases. We attempt to ensure that our product candidates and the methods we employ to manufacture them, as well as the methods for their uses we intend to promote, do not infringe other parties' patents and other proprietary rights. There can be no assurance they do not, however, and competitors or other parties may assert that we infringe their proprietary rights in any event.

We are aware of issued U.S. patents and corresponding foreign patents owned by a third-party with claims that are generally directed to a method of treating partial seizures and complex partial seizures by administering cannabidiol to a patient where the cannabidiol is present in an amount to provide a daily dose of at least 400mg. We are also aware of issued U.S. patents owned by such third-party generally directed to methods of treating types of seizures (e.g. atonic, convulsive and focal) in LGS and DS patients by administering cannabidiol with specific purities to a patient, in specified dosing ranges and/or in combination with other drugs. If Zygel is approved by the FDA for the treatment of the indications claimed in these patents and has a label that contains dosing of Zygel with cannabidiol that meets the claimed dosing ranges, purity limitations and/or recited combinations at or above the claimed doses, these patents could be construed to cover Zygel for the claimed indications and such third-party may then seek to enforce its patents by filing patent infringement lawsuits against us. In such lawsuits, we may incur substantial expenses defending our rights to commercialize Zygel for refractory epilepsy, LGS or DS, and in connection with such lawsuits and under certain circumstances, it is possible that we could be required to cease or delay the commercialization of Zygel for refractory epilepsy, LGS or DS, as applicable, and/or be required to pay monetary damages or other amounts, including royalties on the sales of Zygel for refractory epilepsy, LGS or DS. Moreover, such lawsuits may also consume substantial time and resources of our management team and board of directors. The threat or consequences of such lawsuits may also result in royalty and other monetary obligations, which may adversely affect our results of operations and financial condition.

We may become involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful and have a material adverse effect on the success of our business.

Competitors may infringe our patents or misappropriate or otherwise violate our intellectual property rights. To counter infringement or unauthorized use, litigation may be necessary in the future to enforce or defend our intellectual property rights, to protect our trade secrets or to determine the validity and scope of our own intellectual property rights or the proprietary rights of others. Also, third parties may initiate legal proceedings against us to challenge the validity or scope of intellectual property rights we own, or we may initiate legal proceedings against third parties to challenge the validity or scope of their intellectual property rights. These proceedings can be expensive and time consuming. Many of our current and potential competitors have the ability to dedicate substantially greater resources to defend their intellectual property rights than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating our intellectual property. Litigation could result in substantial costs and diversion of management resources, which could harm our business and financial results. In addition, in an infringement proceeding, a court may decide that a patent owned by us is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our common stock.

If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of our technology and products could be significantly diminished.

We rely on trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our current and former employees, consultants, outside scientific collaborators, sponsored researchers, contract manufacturers, vendors and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, we cannot guarantee that we have executed these agreements with each party that may have or have had access to our trade secrets. Any party with whom we or they have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches.

Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they disclose such trade secrets, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third-party, our competitive position would be harmed.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive. Therefore, we have filed applications and/or obtained patents only in key markets such as the United States, Canada, Japan and Europe. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may be able to export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to pharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, an April 2020 report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. As a result, proceedings to enforce our patent rights in certain foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business and could be unsuccessful.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

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. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). However, the applicable authorities, including the FDA and the U.S. PTO, and any equivalent regulatory authorities in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in

development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

Intellectual property rights 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 compounds 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;
- we might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own;
- we might not have been the first to file patent applications covering certain of our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own may not provide us with any competitive advantages, or may be held invalid or unenforceable as a result of legal challenges;
- our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for certain research and development activities, as well as in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Risks Related to Ownership of Our Common Stock

The market price and trading volume of our stock may be volatile.

The trading price of our common stock has been, and may continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. For example, during the period from January 1, 2021 to February 28, 2021, the trading price of our common stock has ranged from $3.23 and $9.00 per share. In addition, the trading volume of our common stock may fluctuate and cause significant price variations to occur. In addition to the factors discussed in this “Risk Factors” section and elsewhere in this Report, these factors include:

- results of clinical trials of Zygel or product candidates of our competitors;
- the success of competitive products;
- regulatory actions with respect to our product candidates or our competitors’ products and product candidates;
- actual or anticipated changes in our growth rate relative to our competitors;

- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- regulatory or legal developments in the United States and other countries;
- 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 our preclinical and clinical development programs;
- the results of our efforts to in-license or acquire additional product candidates or products;
- actual or anticipated 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;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our common stock;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical sector; and
- general economic, industry and market conditions.

These broad market and industry factors may decrease the market price of our common stock, regardless of our actual operating performance.

The stock market in general has, from time to time, experienced extreme price and volume fluctuations. In addition, in the past, following periods of volatility in the overall market and decreases in the market price of a company's securities, securities class action litigation has often been instituted against these companies. We are subject to securities litigation, as described further in Part II of this Annual Report in "Notes to Consolidated Financial Statements, Note 12. Commitments and Contingencies and incorporated by reference in Part I, Item 3—*Legal Proceedings*. This litigation, and any other securities class actions that may be brought against us, could result in substantial costs and a diversion of our management's attention and resources.

Insiders have substantial influence over us and could delay or prevent a change in corporate control.

Our executive officers, directors, and holders of 5.0% or more of our capital stock collectively beneficially own approximately 9.1% of our voting stock at March 5, 2021. This concentration of ownership could harm the market price of our common stock by:

- delaying, deferring or preventing a change in control of our company;

- impeding a merger, consolidation, takeover or other business combination involving our company; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.

The interests of this group of stockholders may not always coincide with the interests of our other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including by seeking a premium value for their common stock, and might negatively affect the prevailing market price for our common stock.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be our stockholders' sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be our stockholders' sole source of gain for the foreseeable future.

Future sales and issuances of our common stock or rights to purchase common stock pursuant to our equity incentive plan could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that significant additional capital will be needed in the future to continue our planned operations. To raise capital, we may sell substantial amounts of common stock or securities convertible into or exchangeable for common stock. These future issuances of common stock or common stock-related securities, together with the exercise of outstanding options and any additional shares issued in connection with acquisitions, if any, may result in material dilution to our investors. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to those of holders of our common stock.

Pursuant to our equity incentive plan, our compensation committee is authorized to grant equity-based incentive awards to our directors, executive officers and other employees and service providers. As of March 5, 2021, there were 2,273,070 shares of our common stock available for future grant under our Amended and Restated 2014 Omnibus Incentive Compensation Plan, as amended, or 2014 Equity Plan. Future equity incentive grants and issuances of common stock under the 2014 Equity Plan may result in material dilution to our stockholders and may have an adverse effect on the market price of our common stock.

Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our sixth amended and restated certificate of incorporation and amended and restated bylaws, as well as provisions of Delaware law, could make it more difficult for a third-party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders, or remove our current management. These include provisions that:

- permit our board of directors to issue up to 10 million shares of preferred stock, with any rights, preferences and privileges as it may designate;
- provide that all vacancies on our board of directors, including as a result of newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent;

- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide advance notice in writing, and also specify requirements as to the form and content of a stockholder's notice;

- require that the amendment of certain provisions of our certificate of incorporation and bylaws relating to anti-takeover measures may only be approved by a vote of 66 2/3% of our outstanding capital stock;

- do not provide for cumulative voting rights, thereby allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election; and

- provide that special meetings of our stockholders may be called only by the board of directors or by such person or persons designated by a majority of the board of directors to call such meetings.

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, who are responsible for appointing the members of our management. Because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which may discourage, delay or prevent someone from acquiring us or merging with us whether or not it is desired by or beneficial to our stockholders. Under Delaware law, a corporation may not, in general, engage in a business combination with any holder of 15.0% or more of its capital stock unless the holder has held the stock for three years or, among other things, the board of directors has approved the transaction. Any provision of our certificate of incorporation or bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our certificate of incorporation also provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our sixth amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our sixth amended and restated certificate of incorporation or our amended and restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation 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 and financial condition.

If securities or industry analysts publish inaccurate or unfavorable research about our business, our stock price and trading volume could decline.

The trading market for our common stock depends in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who cover us downgrade our stock or publish inaccurate or unfavorable research about our business, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

General Risks Relating to the Ownership of Securities

If we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. We are required, under Section 404 of the Sarbanes-Oxley Act, to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting. This assessment includes disclosure of any material weaknesses identified by our management in our internal control over financial reporting. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting that results in more than a reasonable possibility that a material misstatement of annual or interim financial statements will not be prevented or detected on a timely basis. Section 404 of the Sarbanes-Oxley Act also requires an attestation from our independent registered public accounting firm on the effectiveness of our internal control over financial reporting.

Our compliance with Section 404 requires that we incur substantial accounting expense and expend significant management efforts. We may not be able to complete our evaluation, testing and any required remediation in a timely fashion. During the evaluation and testing process, if we identify one or more material weaknesses in our internal control over financial reporting, we will be unable to assert that our internal control over financial reporting is effective. We cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting once that firm begins its Section 404 attestation, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by the Nasdaq Stock Market, the SEC, or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

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

As a public company, we have incurred and are continuing to incur significant legal, accounting and other expenses that we did not incur as a private company, and these expenses may increase even more after we are no longer an “emerging growth company.” We are subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act, the

Dodd-Frank Wall Street Reform and Protection Act, as well as rules adopted, and to be adopted, by the SEC and Nasdaq Stock Market. Our management and other personnel devote a substantial amount of time to these compliance initiatives.

Moreover, these rules and regulations have substantially increased our legal and financial compliance costs and made some activities more time-consuming and costly. The increased costs have increased our net loss. These rules and regulations may make it more difficult and more expensive for us to maintain sufficient liability insurance coverage for our directors and officers. We cannot predict or estimate the amount or timing of additional costs we may continue to incur to respond to these requirements. The ongoing impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our company headquarters are located in Devon, Pennsylvania where we occupy 10,877 square feet of office space. In March 2021, the Company extended its lease for office space until May 31, 2024.

Item 3. Legal Proceedings

Information regarding legal proceedings is provided in Part II of this Annual Report in “Notes to Consolidated Financial Statements, Note 12. Commitments and Contingencies.”

Item 4. Mine Safety Disclosure

None.

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 traded on the Nasdaq Global Market since August 5, 2015 under the symbol “ZYNE.”

Holders of Common Stock

As of March 5, 2021, there were 49 holders of record of our common stock.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We do not anticipate declaring or paying, in the foreseeable future, any cash dividends on our capital stock. We expect to continue to incur significant expenses and operating losses for the foreseeable future. We intend to retain all available funds and any future earnings, to support our operations and finance the growth and development of our business. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our board of directors may deem relevant.

Issuer Repurchases of Equity Securities

None.

Securities Authorized for Issuance Under Equity Compensation Plans

Other information about our equity compensation plans is incorporated herein by reference to Part III, Item 12 of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

None.

Item 6. Selected Financial Data

This section should be read together with our consolidated financial statements and accompanying notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations" appearing elsewhere in this Report. We derived the selected consolidated statements of operations data for the years ended December 31, 2020, 2019 and 2018 and the selected consolidated balance sheet data as of December 31, 2020 and 2019 from our audited consolidated financial statements and accompanying notes appearing elsewhere in this Annual Report on Form 10-K. The selected consolidated statements of operations data for the years ended December 31, 2017 and 2016 and the selected consolidated balance sheet data as of December 31, 2018, 2017 and 2016 have been derived from financial statements not included in this Annual Report on Form 10-K. The selected consolidated financial data in this section are not intended to replace our consolidated financial statements and the related notes. Our historical consolidated results are not necessarily indicative of the results that may be expected in the future.

Statements of Operation Data:

	Year Ended December 31,				
	2020	2019	2018	2017	2016
Revenue	$ —	$ —	$ 86,000	$ —	$ 7,250
Operating expenses:					
Research and development	35,654,994	20,384,049	27,245,043	22,806,107	16,784,626
General and administrative	16,407,548	13,935,761	13,238,787	10,016,902	6,430,252
Total operating expenses	52,062,542	34,319,810	40,483,830	32,823,009	23,214,878
Loss from operations	(52,062,542)	(34,319,810)	(40,397,830)	(32,823,009)	(23,207,628)
Other income (expense):					
Interest income	243,992	1,522,138	961,323	519,554	80,222
Foreign exchange (loss) gain	481,719	(145,911)	(474,668)	291,151	(189,497)
Loss on disposal of equipment	—	—	—	—	(99,147)
Total other income (expense)	725,711	1,376,227	486,655	810,705	(208,422)
Loss before income taxes	(51,336,831)	(32,943,583)	(39,911,175)	(32,012,304)	(23,416,050)
Income tax (benefit)	—	—	—	—	(27,543)
Net loss	$ (51,336,831)	$ (32,943,583)	$ (39,911,175)	$ (32,012,304)	$ (23,388,507)
Per share information:					
Net loss per share basic and diluted [1]	$ (1.90)	$ (1.50)	$ (2.61)	$ (2.48)	$ (2.58)
Basic and diluted weighted average shares outstanding	27,022,931	22,000,203	15,308,886	12,914,814	9,070,232

(1) Refer to note 2(l) of our audited financial statements for a description of the method used to calculate net loss per share, basic and diluted, and the basic and diluted weighted average shares outstanding.

	As of December 31,				
	2020	2019	2018	2017	2016
BALANCE SHEET DATA:					
Cash and cash equivalents	$ 59,157,187	$ 70,063,242	$ 59,763,773	$ 62,510,277	$ 30,965,791
Total assets	74,056,776	87,764,596	67,327,443	69,054,309	36,554,274
Total liabilities	13,913,248	12,167,853	9,725,782	8,104,721	6,966,966
Total stockholders' equity	60,143,528	75,596,743	57,601,661	60,949,588	29,587,308

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

The following discussion summarizes the significant factors affecting the operating results, financial condition, liquidity and cash flows of our company as of and for the periods presented below. The following discussion and analysis should be read in conjunction with the financial statements and the related notes thereto included elsewhere in this Report. The statements in this discussion regarding industry outlook, our expectations regarding our future performance, liquidity and capital resources and all other non-historical statements in this discussion are forward-looking statements and are based on the beliefs of our management, as well as assumptions made by, and information currently available to, our management. Actual results could differ materially from those discussed in or implied by forward-looking statements as a result of various factors, including those discussed below and elsewhere in this Report, particularly in the section entitled "Risk Factors."

Overview

Company Overview

We are the leader in pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders. We are committed to improving the lives of patients and their families living with severe, chronic health conditions including Fragile X syndrome, or FXS, autism spectrum disorder, or ASD, 22q11.2 deletion syndrome, or 22q, and a heterogeneous group of rare and ultra-rare epilepsies known as developmental and epileptic encephalopathies, or DEE.

Cannabinoids are a class of compounds derived from *Cannabis* plants. The two primary cannabinoids contained in *Cannabis* are cannabidiol and Tetrahydrocannabinol, or THC. Clinical and preclinical data suggest that cannabidiol has positive effects on treating behavioral symptoms of FXS, ASD, 22q and seizures in patients with epilepsy.

We are currently developing Zygel, the first and only pharmaceutically-produced cannabidiol formulated as a permeation-enhanced gel for transdermal delivery, which is patent protected through 2030. Five additional patents expiring in 2038 are directed to methods of use relating to Zygel, including methods of treating FXS and ASD.

In preclinical animal studies, Zygel's permeation enhancer increased delivery of cannabidiol through the layers of the skin and into the circulatory system. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism of cannabidiol when delivered transdermally. In addition, an *in vitro* study published in *Cannabis and Cannabinoid Research* in April 2016 demonstrated that cannabidiol is degraded to THC (the major psychoactive cannabinoid in *Cannabis)* in an acidic environment such as the stomach. As a result, we believe such degradation may lead to increased psychoactive effects if cannabidiol is delivered orally. These effects may be avoided with the transdermal delivery of Zygel, which maintains cannabidiol in a neutral pH. Zygel is being developed as a clear gel with once- or twice-daily dosing and is targeting treatment of behavioral symptoms of FXS, ASD and 22q and the reduction of seizures in patients with DEE syndromes. We have been granted orphan drug designations from United States Food and Drug Administration, or FDA, for the use of cannabidiol for the treatment of FXS and for the treatment of 22q. In May 2019, we received Fast Track designation from the FDA for treatment of behavioral symptoms associated with FXS. The FDA's Fast Track program is designed to facilitate the development of drugs intended to treat serious conditions and fill unmet medical needs and can lead to expedited review by the FDA in order to get new important drugs to the patient earlier.

Our clinical program for Zygel includes clinical trials evaluating Zygel in the treatment of behavioral symptoms of FXS, ASD and 22q and the reduction of seizures and the treatment of associated symptoms in patients with DEE syndromes. As of March 2021, the Zygel safety database across all clinical studies conducted by us includes data from 906 volunteers and patients. Across these clinical studies, Zygel has been well tolerated and consistent with previously reported data.

CONNECT-FX Trial (FXS)

In June 2020 we announced results of our pivotal CONNECT-FX clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study designed to assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the *FMR1* gene. While Zygel did not achieve statistical significance versus placebo in the primary endpoint of improvement in the Social Avoidance subscale of the Aberrant Behavior Checklist – Community FXS (ABC-C_{FXS}), a pre-planned ad hoc analysis of the most severely impacted patients in the trial, as defined by patients having at least 90% methylation ("highly methylated") of the impacted *FMR1* gene, demonstrated that those patients receiving Zygel achieved statistical significance in the primary endpoint of improvement at 12 weeks of treatment in the Social Avoidance subscale of the ABC-C_{FXS} compared to placebo. Following discussions with the FDA regarding the CONNECT-FX trial and the regulatory path forward for Zygel, we plan to conduct a double-blind for Zygel, placebo-controlled pivotal trial in pediatric and adolescent patients with FXS who have a highly methylated *FMR1* gene to confirm the positive results observed in the CONNECT-FX trial. We plan to review the trial design and protocol for the new trial through a Type C meeting with the FDA in the first half of 2021 and expect to initiate the pivotal trial before the end of 2021.

Phase 2 BRIGHT Trial (ASD)

In May 2020, we reported positive top-line results of the Phase 2 BRIGHT clinical trial, a 14- week open label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for the treatment of pediatric and adolescent patients with ASD. Patients treated with Zygel demonstrated statistically significant improvement at week 14 compared to baseline for each ABC-C subscale (Irritability, Inappropriate Speech, Stereotypy, Social Withdrawal, and Hyperactivity). The results of the other efficacy assessments were consistent with the results demonstrated in the ABC-C. We expect to discuss a path forward with the FDA in the first half of 2021.

Phase 2 INSPIRE Trial (22q)

In May 2019, we initiated the open-label Phase 2 INSPIRE clinical trial, a 14-week open label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for treatment of behavioral symptoms of 22q. We expect to enroll approximately 20 male and female patients (ages six through 17 years). Recruitment into the INSPIRE trial has been delayed due to the impact of COVID-19 and resulting significant travel restrictions in Australia. Once these restrictions are lifted and enrollment is complete, we will provide a timeframe for disclosing top line results of this trial. In September 2020, we were granted orphan drug designation from the FDA for the use of cannabidiol for the treatment of 22q.

Phase 2 BELIEVE Trial (DEE)

In September 2019, we reported top-line results from the Phase 2 BELIEVE clinical trial, a six-month, open-label, multi-dose clinical trial designed to evaluate the efficacy and safety of Zygel in children and adolescents (ages three through 17 years) with DEE. Following discussions with the FDA regarding the clinical pathway for Zygel in DEE, we plan to pursue individual syndromes. We are evaluating potential target indications and expect to finalize target syndrome selection for one or more DEE syndromes in 2021.

Zygel Clinical Development Timelines

We are closely monitoring the progression of the COVID-19 pandemic, including its potential impact on our clinical development plans and timelines going forward. In response to COVID-19, for our current clinical development programs, we implemented multiple measures consistent with the FDA's guidance on the conduct of clinical trials of medical products during the COVID-19 pandemic, including remote site monitoring and patient visits using telemedicine where needed, direct to patient drug shipment from investigator sites, and local study-related clinical laboratory collection. Except with respect to our Phase 2 open-label INSPIRE trial, timelines for delivery of top-line results for our

clinical trials were not adversely impacted by COVID-19 and we intend to implement similar measures, as necessary, for our planned clinical trials in 2021.

We have never been profitable and have incurred net losses since inception. Our net losses were $51.3 million, $32.9 million and $39.9 million for the years ended December 31, 2020, 2019, and 2018, respectively. As of December 31, 2020, our accumulated deficit was $202.2 million. We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability.

Financial Operations Overview

The following discussion sets forth certain components of our consolidated statements of operations as well as factors that impact those items.

Research and Development Expenses — Our research and development expenses relating to our product candidates consisted of the following:

- expenses associated with preclinical development and clinical trials;
- personnel-related expenses, such as salaries, benefits, travel and other related expenses, including stock-based compensation;
- payments to third-party CROs, CMOs, contractor laboratories and independent contractors; and
- depreciation, maintenance and other facility-related expenses.

We expense all research and development costs as incurred. Clinical development expenses for our product candidates are a significant component of our current research and development expenses. Generally speaking, expenses associated with clinical trials will increase as our clinical trials progress. Product candidates in later stage clinical development generally have higher research and development expenses than those in earlier stages of development, primarily due to increased size and duration of the clinical trials. We track and record information regarding external research and development expenses for each grant, study or trial that we conduct. We use third-party CROs, CMOs, contractor laboratories and independent contractors in preclinical studies and clinical trials. We recognize the expenses associated with third parties performing these services for us in our preclinical studies and clinical trials based on the percentage of each study completed at the end of each reporting period.

Our Australian subsidiary, Zynerba Pharmaceuticals Pty Ltd, or the Subsidiary, is incorporated in Australia and is eligible to participate in an Australian research and development tax incentive program. As part of this program, the Subsidiary is eligible to receive a cash refund from the Australian Taxation Office for a percentage of the research and development costs expended by the Subsidiary in Australia. The cash refund is available to eligible companies with an annual aggregate revenue of less than $20.0 million (Australian dollars) during the reimbursable period. We estimate the amount of cash refund we expect to receive related to the Australian research and development tax incentive program and record the incentives when it is probable 1) we will comply with relevant conditions of the program and 2) the incentive will be received.

Certain research and development expenses incurred with respect to Zygel outside of Australia may also be eligible for the Australian research and development tax incentive program. To receive a cash refund with respect to such expenses incurred outside of Australia, the expenses must have been for eligible research and development activities, as determined by AusIndustry, and the expenditures must have a scientific link to the Australian activities, be unable to be conducted in Australia and be less than the expenditures for activities conducted in Australia, as determined by the ATO. In December 2018, the Subsidiary submitted an AOF application to AusIndustry for a determination that its activities are eligible research and development activities, which was approved by AusIndustry in July 2019.

As a result of this finding, we believe the Subsidiary is eligible to receive a cash refund from the ATO for qualifying expenditures related to its research and development activities outside of Australia in 2018, 2019 and 2020. During the year ended December 31, 2019, we recorded $8.3 million as an incentive and tax receivable and recorded a corresponding credit to research and development expense for amounts expected to be received through the AOF for the period January 1, 2018 through December 31, 2019. As of December 31, 2020, incentive and tax receivables included $9.0 million related to the AOF. The increase of $0.7 million was due to unrealized foreign currency gains related to the remeasurement of the Subsidiary's assets and liabilities.

We evaluate the Subsidiary's eligibility under tax incentive programs as of each balance sheet date based on the most current and relevant data available. If the Subsidiary is deemed to be ineligible or unable to receive the Australian research and development tax credit, or the Australian government significantly reduces or eliminates the tax credit, the actual cash refund we receive may materially differ from our estimates. In June 2020, the ATO informed us that we may not qualify for the AOF program based on their interpretation of certain eligibility requirements. Although we continue to believe that we comply with the relevant conditions of the AOF program that were in place when we received our original approval from AusIndustry, we have determined it is no longer probable that the AOF claim will be received. As a result, during the three months ended June 30, 2020, we recorded a full reserve against the AOF receivable.

The following table summarizes research and development expenses for the years ended December 31, 2020, 2019 and 2018.

	Year ended December 31,		
	2020	2019	2018
Research and development expenses - before R&D incentive	$ 29,437,551	$ 31,549,954	$ 30,631,258
Research and development incentive (non-AOF)	(1,890,252)	(2,895,896)	(3,386,215)
Research and development expenses (before impact of AOF)	27,547,299	28,654,058	27,245,043
AOF - cumulative change in estimate for the period 1/1/18 through 12/31/19	—	(8,270,009)	—
Amounts reserved against AOF refund	8,107,695	—	—
Total research and development expenses	$ 35,654,994	$ 20,384,049	$ 27,245,043

Excluding the 2020 change in research and development expenses related to the AOF, we expect research and development expenses to decrease in 2021 as compared to 2020 as we concluded our pivotal CONNECT-FX clinical trial during 2020. We expect to initiate another pivotal trial in FXS before the end of 2021. These expenditures are subject to numerous uncertainties regarding timing and cost to completion. Completion of our preclinical development and clinical trials may take several years or more and the length of time generally varies according to the type, complexity, novelty and intended use of a product candidate. The cost of clinical trials may vary significantly over the life of a project as a result of differences arising during clinical development, including, among others:

- the number of sites included in the clinical trials;
- the length of time required to enroll suitable patients;
- the size of patient populations participating in the clinical trials;
- the duration of patient follow-ups;
- the development stage of the product candidates; and
- the efficacy and safety profile of the product candidates.

Due to the early stages of our research and development, we are unable to determine the duration or completion costs of our development of our product candidates. As a result of the difficulties of forecasting research and development costs

of our product candidates as well as the other uncertainties discussed above, we are unable to determine when and to what extent we will generate revenue from the commercialization and sale of an approved product candidate.

General and Administrative Expenses — General and administrative expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our executive, finance, legal, human resource, investor relations and commercial functions. Our general and administrative expenses also include facility and related costs not included in research and development expenses, professional fees for legal services, including patent-related expenses, litigation settlement expenses, consulting, tax and accounting services, insurance, market research and general corporate expenses. We expect that our general and administrative expenses will increase for the next several years as we increase our headcount with the continued development and potential commercialization of our product candidates.

Interest Income — Interest income primarily consists of interest earned on balances maintained in our money market bank account.

Foreign Exchange Gain (Loss) — Foreign exchange gain (loss) relates to the effect of exchange rates on transactions incurred by the Subsidiary.

Income Taxes — As of December 31, 2020, we had $129.7 million of federal operating loss carryforwards and $3.7 million of research tax credit carryforwards available to offset future taxable income and income tax, respectively. These operating loss and research tax credit carryforwards will begin to expire in 2028 and 2027, respectively. At December 31, 2020 and 2019, we concluded that a full valuation allowance is necessary for our deferred tax assets.

The closing of our IPO in August 2015, together with our follow-on equity offerings, private placements and other transactions that have occurred since our inception, may trigger, or may have already triggered, an “ownership change” pursuant to Section 382 of the Internal Revenue Code of 1986. If an ownership change is triggered, it will limit our ability to use some of our net operating loss carryforwards. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo further ownership changes in the future, which could further limit our ability to use net operating loss carryforwards. As a result, if we generate taxable income, our ability to use some of our net operating loss carryforwards to offset U.S. federal taxable income may be subject to limitations, which could result in increased future tax liability to us. Additionally, U.S. tax laws limit the time during which these carryforwards may be applied against future taxes; therefore, we may not be able to take full advantage of these carryforwards for federal income tax purposes.

Critical Accounting Estimates

Our management’s discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the financial statements, and the reported amounts of revenues and expenses during the reported period. In accordance with GAAP, we base our estimates on historical experience, known trends and events and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying amounts of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

We define our critical accounting policies as those that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations, as well as the specific manner in which we apply those principles. While our significant accounting policies are more fully discussed in note 2 to our audited consolidated financial statements appearing elsewhere in this Report, we believe that the following accounting policy is critical to the process of making significant judgments and estimates in the preparation of our financial statements.

Research and Development Expenses

We rely on third parties to conduct our preclinical studies and clinical trials, and to provide services, including data management, statistical analysis and electronic compilation. At the end of each reporting period, we compare the payments made to each service provider to the estimated progress towards completion of the related project. Factors that we will consider in preparing these estimates include the number of patients enrolled in studies, milestones achieved and other criteria related to the efforts of our vendors. These estimates will be subject to change as additional information becomes available. Depending on the timing of payments to vendors and estimated services provided, we will record net prepaid or accrued expenses related to these costs.

Results of Operations

Comparison of the Years Ended December 31, 2020 and December 31, 2019

	Year Ended December 31,		Increase (Decrease)	
	2020	2019	$	%
Operating expenses:				
Research and development	$ 35,654,994	$ 20,384,049	$ 15,270,945	75 %
General and administrative	16,407,548	13,935,761	2,471,787	18 %
Total operating expenses	52,062,542	34,319,810	17,742,732	52 %
Loss from operations	(52,062,542)	(34,319,810)	(17,742,732)	52 %
Other income	725,711	1,376,227	(650,516)	(47)%
Net loss	$ (51,336,831)	$ (32,943,583)	$ (18,393,248)	56 %

Research and Development Expenses

	Year ended December 31,	
	2020	2019
Research and development expenses (before impact of AOF)	$ 27,547,299	$ 28,654,058
AOF - cumulative change in estimate for the period 1/1/18 through 12/31/19	—	(8,270,009)
Amounts reserved against AOF refund	8,107,695	—
Total research and development expenses	$ 35,654,994	$ 20,384,049

Excluding AOF activity for the years ended December 31, 2020 and 2019, research and development expenses decreased by $1.1 million, or 4%, to $27.5 million for the year ended December 31, 2020 from $28.7 million for the year ended December 31, 2019. The decrease was primarily related to decreased clinical trial and manufacturing costs associated with our Zygel program, partially offset by an increase in employee-related costs and a reduction in the non-AOF Australian research and development incentive.

General and Administrative Expenses

General and administrative expenses increased by $2.5 million, or 18%, to $16.4 million for the year ended December 31, 2020 from $13.9 million for the year ended December 31, 2019. The increase was primarily related to legal fees and litigation settlement expenses related to our shareholder lawsuits, increases in liability insurance for our directors and officers and higher employee-related costs, including recruiting costs; partially offset by decreases in pre-commercialization expense for our product candidates.

Other Income

During the years ended December 31, 2020 and 2019, we recognized $0.2 million and $1.5 million, respectively, in interest income. The decrease in interest income was primarily related to lower average interest rates earned on our investments. During the year ended December 31, 2020, we recognized a foreign currency gain of $0.5 million and

during the year ended December 31, 2019, we recognized a foreign currency loss of $0.1 million. Foreign currency gains and losses are due primarily to the remeasurement of the Subsidiary's assets and liabilities, which are denominated in the local currency to the Subsidiary's functional currency, which is the U.S. dollar.

Liquidity and Capital Resources

Since our inception in 2007, we have devoted most of our cash resources to research and development and general and administrative activities. We have financed our operations primarily with the proceeds from the sale of equity securities (most notably our initial public offering, our follow-on public offerings and sales under our "at-the-market" offering) and convertible promissory notes, state and federal grants and research services.

To date, we have not generated any revenue from the sale of products, and we do not anticipate generating any revenue from the sales of products for the foreseeable future. We have incurred losses and generated negative cash flows from operations since inception. As of December 31, 2020, our principal sources of liquidity were our cash and cash equivalents of $59.2 million. Our working capital was $59.5 million as of December 31, 2020.

Management believes that cash and cash equivalents as of December 31, 2020 and the net proceeds from the $42.2 million in cash generated between January 1, 2021 and February 9, 2021 from sales under the 2019 Sales Agreement (defined below), are sufficient to fund operations and capital requirements well into the first half of 2024. The economic effects of the COVID-19 pandemic remain fluid and management will continue to closely monitor the situation to ensure our cash and cash equivalents will help us manage the impact of the COVID-19 pandemic on our business and related liquidity needs. Substantial additional financings will be needed to fund our operations and to complete clinical development of and to commercially develop our product candidates. There is no assurance that such financing will be available when needed or on acceptable terms. Our ability to access the capital markets or otherwise raise such capital may be adversely impacted by potential worsening global economic conditions and the recent disruptions to, and volatility in, financial markets in the United States and worldwide resulting from the ongoing COVID-19 pandemic.

Equity Financings

In August 2019, we entered into a Controlled Equity Offering^{SM} Sales Agreement, or the 2019 Sales Agreement, with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., as sales agents pursuant to which we may sell, from time to time, up to $75.0 million of our common stock. From January 1, 2021 through February 9, 2021, we have sold and issued 10,244,326 shares of our common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $4.22 per share, resulting in gross proceeds of $43.2 million. Net proceeds after deducting commissions and offering expenses were $42.2 million. In 2020, we sold and issued 6,596,873 shares of our common stock in the open market at a weighted-average selling price of $4.81 per share, for gross proceeds of $31.7 million and net proceeds, after deducting commissions and offering expenses, of $30.7 million. In 2019, we sold and issued 13,381 shares of our common stock in the open market at a weighted-average selling price of $7.00 per share, for gross and net proceeds of $0.1 million. As of February 9, 2021, we had utilized the entire $75.0 million under the 2019 Sales Agreement.

Debt

We had no debt outstanding as of December 31, 2020 or 2019.

Future Capital Requirements

During the year ended December 31, 2020, net cash used in operating activities was $41.3 million, and our accumulated deficit as of December 31, 2020 was $202.2 million. Our expectations regarding future cash requirements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make in the future. To the extent that we enter into any of those types of transactions, we may need to raise substantial additional capital.

We expect to continue to incur substantial additional operating losses for at least the next several years as we continue to develop our product candidates and seek marketing approval and, subject to obtaining such approval, the eventual commercialization of our product candidates. If we obtain marketing approval for any of our product candidates, we will incur significant sales, marketing and manufacturing expenses. In addition, we expect to incur additional expenses to add operational, financial and information systems and personnel, including personnel to support our planned product commercialization efforts. We also expect to continue to incur significant costs to comply with corporate governance, internal controls and similar requirements associated with operating as a public reporting company.

Our future use of operating cash and capital requirements will depend on many forward-looking factors, including the following:

- the initiation, progress, timing, costs and results of preclinical studies and clinical trials for our product candidates;
- the clinical development plans we establish for these product candidates;
- the number and characteristics of product candidates that we may develop or in-license;
- the terms of any collaboration agreements we may choose to execute;
- the outcome, timing and cost of meeting regulatory requirements established by the DEA, the FDA, the EMA or 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 intellectual property disputes, including patent infringement actions brought by third parties against us;
- costs and timing of the implementation of commercial scale manufacturing activities;
- the cost of establishing, or outsourcing, sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to independently commercialize our products;
- the extent to which health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic, could disrupt our operations or materially and adversely affect our business and financial conditions; and
- the timing and outcome of the ATO’s review regarding our eligibility to receive tax credits related to the AOF.

To the extent that our capital resources are insufficient to meet our future operating and capital requirements, we will need to finance our cash needs through public or private equity offerings, debt financings, collaboration and licensing arrangements or other financing alternatives. We have no committed external sources of funds. Additional equity or debt financing or collaboration and licensing arrangements may not be available on acceptable terms, if at all.

If we raise additional funds by issuing equity securities, our stockholders will experience dilution.

Cash Flows

The following table summarizes our cash flows from operating, investing and financing activities for the years ended December 31, 2020 and December 31, 2019.

	Year Ended December 31,	
	2020	2019
Statement of Cash Flows Data:		
Total net cash (used in) provided by:		
Operating activities	$ (41,314,040)	$ (34,817,976)
Investing activities	(445,314)	(129,390)
Financing activities	30,853,299	45,246,835
Net (decrease) increase in cash and cash equivalents	$ (10,906,055)	$ 10,299,469

Operating Activities

For the year ended December 31, 2020, cash used in operating activities was $41.3 million, compared to $34.8 million for the year ended December 31, 2019. The increase from the comparable 2019 period was primarily the result of changes in prepaid expenses, accounts payable and accrued expenses.

Excluding any cash that may be received from the July 2019 AOF application, we expect cash used in operating activities to decrease in 2021 as compared to 2020, as we concluded our pivotal CONNECT-FX clinical trial during 2020. We expect to initiate another pivotal trial in FXS before the end of 2021.

Investing Activities

For the year ended December 31, 2020 and 2019, cash used in investing activities primarily represented the cost of expenditures made for manufacturing equipment.

Financing Activities

Cash provided by financing activities for the year ended December 31, 2020 consisted of $30.9 million in net proceeds from sales of our shares of common stock under the 2019 Sales Agreement. Cash provided by financing activities for the year ended December 31, 2019 consisted primarily of $45.0 million in net proceeds from sales of our shares of common stock under the 2017 Sales Agreement and $0.1 million under the 2019 Sales Agreement.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements, except for operating leases, or relationships with unconsolidated entities or financial partnerships, such as entities often referred to as structured finance or special purpose entities.

Recently Adopted Accounting Pronouncements

For descriptions of recently issued accounting pronouncements, see “Note 2 – Summary of Significant Accounting Policies – Recently Adopted Accounting Pronouncements” of our Notes to Consolidated Financial Statements included above in Item 8 of this report.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to various market risks, which may result in potential losses arising from adverse changes in market rates, such as interest rates and foreign exchange rates. We do not enter into derivatives or other financial instruments for trading or speculative purposes nor do we engage in any hedging activities. As of December 31, 2020, we had cash and

cash equivalents of $59.2 million consisting primarily of cash and money market account balances. Because of the short-term maturities of our cash and cash equivalents, we do not believe that an immediate 10% increase in interest rates would have any significant impact on the realized value of our investments. Accordingly, we do not believe we are exposed to material market risk with respect to our cash and cash equivalents.

We have engaged third parties to manufacture our product candidates in Australia, Canada and the United Kingdom and to conduct clinical trials for our product candidates in the United States, Australia and New Zealand. Manufacturing and research costs related to these operations are paid for in a combination of U.S. dollars and local currencies, limiting our foreign currency exchange rate risk, however, our financial statements are reported in U.S. dollars and changes in foreign currency exchange rates could significantly affect our financial condition, results of operations, or cash flows. If we conduct clinical trials and seek to manufacture a more significant portion of our product candidates outside of the United States in the future, we could incur significant foreign currency exchange rate risk.

Item 8. Financial Statements and Supplementary Data

The following financial statements are filed as a part of this Annual Report on Form 10-K:

Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Zynerba Pharmaceuticals, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Zynerba Pharmaceuticals, Inc. and subsidiary (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2020, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated 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 consolidated 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 consolidated 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 consolidated 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 consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Evaluation of prepaid development expenses and accrued research and development expenses

As discussed in Notes 2, 4 and 6 to the consolidated financial statements, research and development costs are expensed as incurred, which include accrued external research and development expenses incurred under arrangements with third parties, such as contract research organizations (CROs) that conduct clinical trials and contract manufacturing organizations (CMOs). At the end of each reporting period, the Company compares the payments made to each service provider to the estimated progress towards completion of the related project, considering factors such as the number of patients enrolled in studies, milestones achieved and other criteria related to the efforts of its vendors. Depending on the timing of payments to vendors and estimated services provided, the Company will record net prepaid or accrued expenses related to these costs. The prepaid development expenses and accrued research and development expenses were $0.9 million and $5.0 million, respectively, as of December 31, 2020.

We identified the evaluation of prepaid development expenses and accrued research and development expenses for CROs and CMOs as a critical audit matter. Evaluating the sufficiency of audit evidence obtained over research and development costs, including the factors described above, required especially subjective auditor judgment due to the nature of evidence available regarding the cost of research and development activities incurred as of year-end under the arrangements with CROs and CMOs.

The following are the primary procedures we performed to address this critical audit matter. For a sample of contracts with CROs and CMOs, we examined the provisions in the contracts, invoices and communications received from third parties related to the project status, and management’s analysis of costs incurred as of year-end. For these contracts, we evaluated the relevant factors used in determining the costs incurred for CROs and CMOs as of year-end. We also compared the Company’s estimate of costs incurred as of year-end to a selection of third-party invoices and communication from third parties received after year-end. We assessed the sufficiency of audit evidence obtained related to prepaid development expenses and accrued research and development costs incurred by CROs and CMOs by evaluating the cumulative results of the audit procedures.

/s/ KPMG LLP

We have served as the Company’s auditor since 2014.

Philadelphia, Pennsylvania
March 10, 2021

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 59,157,187	$ 70,063,242
Incentive and tax receivables	9,042,586	14,613,969
Prepaid expenses and other current assets	5,166,401	2,378,812
Total current assets	73,366,174	87,056,023
Property and equipment, net	585,403	362,724
Right-of-use assets	105,199	345,849
Total assets	$ 74,056,776	$ 87,764,596
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 2,522,716	$ 4,740,981
Accrued expenses	11,280,843	7,073,506
Lease liabilities	109,689	243,677
Total current liabilities	13,913,248	12,058,164
Lease liabilities, long-term	—	109,689
Total liabilities	13,913,248	12,167,853
Stockholders' equity:		
Preferred stock, $0.001 par value; 10,000,000 shares authorized; no shares issued or outstanding	—	—
Common stock, $0.001 par value; 200,000,000 shares authorized; 29,975,264 shares issued and outstanding at December 31, 2020 and 23,211,391 shares issued and outstanding at December 31, 2019	29,975	23,211
Additional paid-in capital	262,286,008	226,409,156
Accumulated deficit	(202,172,455)	(150,835,624)
Total stockholders' equity	60,143,528	75,596,743
Total liabilities and stockholders' equity	$ 74,056,776	$ 87,764,596

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS

	Year ended December 31,		
	2020	2019	2018
Revenue	$ —	$ —	$ 86,000
Operating expenses:			
Research and development	35,654,994	20,384,049	27,245,043
General and administrative	16,407,548	13,935,761	13,238,787
Total operating expenses	52,062,542	34,319,810	40,483,830
Loss from operations	(52,062,542)	(34,319,810)	(40,397,830)
Other income (expense):			
Interest income	243,992	1,522,138	961,323
Foreign exchange gain (loss)	481,719	(145,911)	(474,668)
Total other income	725,711	1,376,227	486,655
Net loss	$ (51,336,831)	$ (32,943,583)	$ (39,911,175)
Net loss per share basic and diluted	$ (1.90)	$ (1.50)	$ (2.61)
Basic and diluted weighted average shares outstanding	27,022,931	22,000,203	15,308,886

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
YEARS ENDED DECEMBER 31, 2018, 2019 and 2020

	Common stock		Additional paid-capital	Accumulated deficit	Total stockholders' equity
	Shares	Amount			
Balance at December 31, 2017	**13,553,873**	**$ 13,554**	**$ 138,916,900**	**$ (77,980,866)**	**$ 60,949,588**
Issuance of common stock, net of issuance costs	4,062,500	4,062	29,933,443	—	29,937,505
Issuance of restricted stock	10,500	11	(11)	—	—
Stock-based compensation expense	—	—	6,625,743	—	6,625,743
Net loss	—	—	—	(39,911,175)	(39,911,175)
Balance at December 31, 2018	**17,626,873**	**17,627**	**175,476,075**	**(117,892,041)**	**57,601,661**
Issuance of common stock, net of issuance costs	5,534,935	5,534	45,181,536	—	45,187,070
Issuance of restricted stock	8,600	9	(9)	—	—
Exercise of stock options	40,983	41	189,659	—	189,700
Stock-based compensation expense	—	—	5,561,895	—	5,561,895
Net loss	—	—	—	(32,943,583)	(32,943,583)
Balance at December 31, 2019	**23,211,391**	**23,211**	**226,409,156**	**(150,835,624)**	**75,596,743**
Issuance of common stock, net of issuance costs	6,596,873	6,597	30,699,492	—	30,706,089
Issuance of restricted stock	167,000	167	(167)	—	—
Stock-based compensation expense	—	—	5,177,527	—	5,177,527
Net loss	—	—	—	(51,336,831)	(51,336,831)
Balance at December 31, 2020	**29,975,264**	**$ 29,975**	**$ 262,286,008**	**$ (202,172,455)**	**$ 60,143,528**

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year ended December 31,		
	2020	2019	2018
Cash flows from operating activities:			
Net loss	$ (51,336,831)	$ (32,943,583)	$ (39,911,175)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	207,035	133,879	99,572
Stock-based compensation	5,177,527	5,561,895	6,625,743
Changes in operating assets and liabilities:			
Incentive and tax receivables	5,571,383	(11,169,349)	538,984
Prepaid expenses and other assets	(2,981,094)	1,561,780	(1,291,186)
Deferred grant revenue	—	—	(833,975)
Right-of-use assets	(3,027)	(5,307)	—
Accounts payable	(2,145,165)	209,613	1,103,013
Accrued expenses	4,196,132	1,833,096	1,271,673
Net cash used in operating activities	(41,314,040)	(34,817,976)	(32,397,351)
Cash flows from investing activities:			
Purchases of property and equipment	(445,314)	(129,390)	(286,658)
Net cash used in investing activities	(445,314)	(129,390)	(286,658)
Cash flows from financing activities:			
Proceeds from the issuance of common stock	31,707,228	46,907,032	32,500,000
Payment of financing fees and expenses	(853,929)	(1,849,897)	(2,562,495)
Proceeds from the exercise of stock options	—	189,700	—
Net cash provided by financing activities	30,853,299	45,246,835	29,937,505
Net (decrease) increase in cash and cash equivalents	(10,906,055)	10,299,469	(2,746,504)
Cash and cash equivalents at beginning of year	70,063,242	59,763,773	62,510,277
Cash and cash equivalents at end of year	$ 59,157,187	$ 70,063,242	$ 59,763,773
Supplemental disclosures of cash flow information:			
Deferred financing costs included in accounts payable and accrued expenses at end of period	$ 17,275	$ 63,570	$ 60,000
Property and equipment acquired but unpaid at end of period	$ —	$ 15,600	$ 20,350
Reclassification of deferred rent liability to right-of-use assets upon adoption of ASC 842	$ —	$ 12,824	$ —
Right-of-use assets and lease liability recorded upon adoption of ASC 842	$ —	$ 325,683	$ —

See accompanying notes to consolidated financial statements

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

(1) Nature of Business and Liquidity

Zynerba Pharmaceuticals, Inc., together with its subsidiary, Zynerba Pharmaceuticals Pty Ltd ("Zynerba", the "Company", "we"), is a clinical stage specialty pharmaceutical company focused on the development of pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders, including Fragile X syndrome, autism spectrum disorder, 22q11.2 deletion syndrome, and a heterogeneous group of rare and ultra-rare epilepsies known as developmental and epileptic encephalopathies.

The Company has incurred losses and negative cash flows from operations since inception and has an accumulated deficit of $202.2 million as of December 31, 2020. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant revenue from its product candidates currently in development. The Company's primary source of liquidity has been the issuance of equity securities.

In August 2019, the Company entered into a Controlled Equity Offering^{SM} Sales Agreement (the "2019 Sales Agreement") with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., as sales agents (the "Agents"), pursuant to which the Company may sell, from time to time, up to $75.0 million of its common stock. From January 1, 2021 through February 9, 2021, the Company sold and issued 10,244,326 shares of common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $4.22 per share, resulting in gross proceeds of $43.2 million. Net proceeds after deducting commissions and offering expenses were $42.2 million. In 2020, the Company sold and issued 6,596,873 shares of common stock in the open market at a weighted-average selling price of $4.81 per share, for gross proceeds of $31.7 million and net proceeds, after deducting commissions and offering expenses, of $30.7 million. In 2019, the Company sold and issued 13,381 shares of common stock in the open market at a weighted-average selling price of $7.00 per share, for gross and net proceeds of $0.1 million. As of February 9, 2021, the Company utilized the entire $75.0 million under the 2019 Sales Agreement.

Management believes that the Company's cash and cash equivalents as of December 31, 2020, and the net proceeds of $42.2 million in cash generated between January 1, 2021 and February 9, 2021 from sales under the 2019 Sales Agreement, are sufficient to fund operations and capital requirements well into the first half of 2024. Substantial additional financings will be needed by the Company to fund its operations, to complete clinical development of and to commercially develop its product candidates. The Company's ability to raise sufficient additional financing depends on many factors beyond its control, including the current volatility in the capital markets as a result of the COVID-19 pandemic. There is no assurance that such financing will be available when needed or on acceptable terms.

The Company is subject to those risks associated with any clinical stage pharmaceutical company that has substantial expenditures for research and development. There can be no assurance that the Company's research and development projects will be successful, that products developed will obtain necessary regulatory approval, or that any approved product will be commercially viable. In addition, the Company operates in an environment of rapid technological change and is largely dependent on the services of its employees and consultants.

(2) Summary of Significant Accounting Policies

a. Basis of Presentation

The accompanying consolidated financial statements of the Company have been prepared in accordance with U.S. generally accepted accounting principles ("GAAP") and with the instructions to Form 10-K and Article 10 of Regulation S-X.

Certain prior period balances have been reclassified to conform to the current year presentation.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

b. Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities at the date of the financial statements and reported amounts of revenue and expenses during the reporting period. Actual results could differ from such estimates.

c. Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, including cash equivalents, accounts payable and accrued expenses approximate fair value given their short-term nature.

d. Cash and Cash Equivalents

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. As of December 31, 2020 and 2019, the Company invested a portion of its cash balances in money market funds that seek to maintain a stable net asset value. These investments have been included as cash equivalents on the consolidated balance sheets.

e. Incentive and Tax Receivables

The Company's subsidiary, Zynerba Pharmaceuticals Pty Ltd (the "Subsidiary"), is incorporated in Australia. The Subsidiary is eligible to participate in an Australian research and development tax incentive program. As part of this program, the Subsidiary is eligible to receive a cash refund from the Australian Taxation Office ("ATO"), for a percentage of the research and development costs expended by the Subsidiary in Australia. The cash refund is available to eligible companies with an annual aggregate revenue of less than $20.0 million (Australian dollars) during the reimbursable period. The Company estimates the amount of cash refund it expects to receive related to the Australian research and development tax incentive program and records the incentives when it is probable 1) the Company will comply with relevant conditions of the program and 2) the incentive will be received.

Certain research and development expenses incurred with respect to Zygel outside of Australia may also be eligible for the Australian research and development tax incentive program. To receive a cash refund with respect to such expenses incurred outside of Australia, the expenses must have been for eligible research and development activities, as determined by AusIndustry, and the expenditures must have a scientific link to the Australian activities, be unable to be conducted in Australia and be less than the expenditures for activities conducted in Australia, as determined by the ATO. In December 2018, the Company submitted an Advance Overseas Finding ("AOF") application to AusIndustry for a determination that a portion of the Company's activities outside of Australia are eligible research and development activities, which was approved by AusIndustry in July 2019.

As a result of this finding, the Company believes it is eligible to receive a cash refund from the ATO for qualifying expenditures related to its research and development activities outside of Australia in 2018, 2019 and 2020. During the year ended December 31, 2019, the Company recorded $8.3 million as an incentive and tax receivable and recorded a corresponding credit to research and development expense for amounts expected to be received through the AOF for the period January 1, 2018 through December 31, 2019. As of December 31, 2020, incentive and tax receivables included $9.0 million related to the AOF. The increase of $0.7 million was due to unrealized foreign currency gains related to the remeasurement of the Subsidiary's assets and liabilities.

The Company evaluates its eligibility under tax incentive programs as of each balance sheet date based on the most current and relevant data available. If the Company is deemed to be ineligible or unable to receive the Australian research and development tax credit, or the Australian government significantly reduces or eliminates the tax credit, the actual cash refund the Company receives may materially differ from its estimates. In June 2020, the ATO informed the

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

Company that it may not qualify for the AOF program based on their interpretation of certain eligibility requirements. Although the Company continues to believe that it complies with the relevant conditions of the AOF program that were in place when the Company received its original approval from AusIndustry, the Company determined it was no longer probable that the AOF claim would be received. As a result, during the three months ended June 30, 2020, the Company recorded a full reserve against the AOF receivable.

In addition, the Subsidiary incurs Goods and Services Tax ("GST") on services provided by Australian vendors. As an Australian entity, the Subsidiary is entitled to a refund of the GST paid. The Company's estimate of the amount of cash refund it expects to receive related to GST incurred is included in "Incentive and tax receivables" in the accompanying consolidated balance sheets. As of December 31, 2020, incentive and tax receivables included $0.3 million for refundable GST on expenses incurred with Australian vendors during the three months ended December 31, 2020.

Incentive and tax receivables consisted of the following as of December 31, 2020 and 2019:

	December 31, 2020	December 31, 2019
Research and development incentive (non-AOF) for the period 1/1/18 - 12/31/18	$ 3,425,791	$ 3,126,750
Research and development incentive (non-AOF) for the period 1/1/19 - 12/31/19	3,192,056	2,913,417
Research and development incentive (non-AOF) for the period 1/1/20 - 12/31/20	2,127,005	—
Research and development incentive (AOF) for the period 1/1/18 - 12/31/19	9,046,058	8,256,416
Goods and services tax	297,734	317,386
Total incentive and tax receivables before reserve for AOF	18,088,644	14,613,969
Reserve for research and development incentive (AOF) for the period 1/1/18 - 12/31/19	(9,046,058)	—
Total incentive and tax receivables - current assets	$ 9,042,586	$ 14,613,969

As of December 31, 2020, the Company's estimate of the amount of cash refund it expects to receive in 2021 for 2020, 2019 and 2018 eligible spending as part of this incentive program was $8.7 million and was recorded as a current asset.

f. Property and Equipment

Property and equipment are recorded at cost and are depreciated on a straight-line basis over their estimated useful lives. Leasehold improvements are amortized over the estimated useful life of the assets or the remaining lease term at the time the asset is placed into service, whichever is shorter. Repairs and maintenance costs are expensed as incurred. When property and equipment are sold or otherwise disposed of, the cost and related accumulated depreciation are removed from the accounts and the resulting gain or loss is included in other expenses.

g. Impairment of Long-Lived Assets

The Company assesses the recoverability of its long-lived assets, which include property and equipment, whenever significant events or changes in circumstances indicate an impairment may have occurred. If indicators of an impairment exist, projected future undiscounted cash flows associated with the asset are compared to its carrying amount to determine whether the asset's value is recoverable. Any resulting impairment is recorded as a reduction in the carrying value of the related asset in excess of fair value and a charge to operating results. For the years ended December 31, 2020, 2019 and 2018, the Company determined that there was no impairment of its long-lived assets.

h. Research and Development

Research and development costs are expensed as incurred and are primarily comprised of external research and development expenses incurred under arrangements with third parties, such as contract research organizations, contract manufacturing organizations, consultants and employee-related expenses including salaries and benefits. At the end of each reporting period, the Company compares the payments made to each service provider to the estimated progress

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

towards completion of the related project. Factors that the Company considers in preparing these estimates include the number of patients enrolled in studies, milestones achieved and other criteria related to the efforts of its vendors. These estimates will be subject to change as additional information becomes available. Depending on the timing of payments to vendors and estimated services provided, the Company will record net prepaid or accrued expenses related to these costs. Research and development expenses are recorded net of expected refunds of eligible research and development costs paid pursuant to the Australian research and development tax incentive program and GST incurred on services provided by Australian vendors.

The following table summarizes research and development expenses for the years ended December 31, 2020, 2019 and 2018:

	Year ended December 31,		
	2020	2019	2018
Research and development expenses - before R&D incentive	$ 29,437,551	$ 31,549,954	$ 30,631,258
Research and development incentive (non-AOF)	(1,890,252)	(2,895,896)	(3,386,215)
Research and development expenses (before impact of AOF)	27,547,299	28,654,058	27,245,043
AOF - cumulative change in estimate for the period 1/1/18 through 12/31/19	—	(8,270,009)	—
Amounts reserved against AOF refund	8,107,695	—	—
Total research and development expenses	$ 35,654,994	$ 20,384,049	$ 27,245,043

i. Stock-Based Compensation

The Company measures employee and nonemployee stock-based awards at grant-date fair value and records compensation expense on a straight-line basis over the requisite service period of the award.

For restricted stock the Company uses the closing price of the Company's common stock on the date of grant. The Company uses the Black-Scholes option pricing model to estimate the fair value of its stock option awards. Estimating the fair value of stock option awards requires management to apply judgment and make estimates, including the expected volatility of the Company's common stock, the expected term of the Company's stock options and the expected dividend yield. As a result, if factors change and management uses different assumptions, stock-based compensation expense could be materially different for future awards.

The expected term of stock options was estimated using the "simplified method," as the Company has limited historical information to develop reasonable expectations about future exercise patterns and post vesting employment termination behavior for its stock option grants. The simplified method is based on the average of the vesting tranches and the contractual life of each grant. For expected stock price volatility, the Company uses comparable public companies, in addition to the Company's historical volatility, as a basis for its expected volatility to calculate the fair value of option grants. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected term of the option.

j. Revenue Recognition

Grant revenue received is recognized when the related expenditures are incurred. Revenue was entirely related to work performed in connection with grants received in years prior to 2015.

k. Income Taxes

The Company recognizes deferred tax assets and liabilities for temporary differences between the financial reporting basis and the tax basis of the Company's assets and liabilities and the expected benefits of net operating loss carryforwards. The impact of changes in tax rates and laws on deferred taxes, if any, applied during the years in which temporary differences are expected to be settled, is reflected in the consolidated financial statements in the period of

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

enactment. The carrying amount of deferred tax assets is reduced, if necessary, if, based on weight of the evidence, it is more likely than not that some, or all, of the deferred tax assets will not be realized. As of December 31, 2020 and 2019, the Company has concluded that a full valuation allowance is necessary for its net deferred tax assets. The Company has no liability for unrecognized tax benefits or tax-related penalties or interest at December 31, 2020 and does not expect a significant change in the balance of unrecognized tax benefits within the next 12 months.

l. Net Loss Per Share

Basic net loss per share is determined using the weighted average number of shares of common stock outstanding during each period. Diluted net income per share includes the effect, if any, from the potential exercise or conversion of securities, such as restricted stock and stock options, which would result in the issuance of incremental shares of common stock. Basic and dilutive computations of net loss per share are the same in periods in which a net loss exists as the dilutive effects of restricted stock and stock options would be anti-dilutive.

The following potentially dilutive securities outstanding as of December 31, 2020, 2019 and 2018 have been excluded from the computation of diluted weighted average shares outstanding, as their effects on net loss per share for the periods presented would be anti-dilutive:

	December 31,		
	2020	2019	2018
Stock options	4,546,484	3,988,716	3,152,267
Unvested restricted stock	173,800	8,600	10,500
	4,720,284	3,997,316	3,162,767

m. Foreign Currency

The Company has determined the functional currency of its Australian subsidiary to be the U.S. dollar. The Company records remeasurement gains and losses on monetary assets and liabilities, such as incentive and tax receivables and accounts payables, which are not in the functional currency of the operation. These remeasurement gains and losses are recorded in the consolidated statements of operations as they occur.

n. Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one segment.

o. Recently Adopted Accounting Pronouncements

In 2016, the Financial Accounting Standards Board (“FASB”) issued Accounting Standards Update (“ASU”) No. 2016-02, *Leases (Topic 842), Accounting Standards Codification 842* (“ASC 842”), which amends a number of aspects of lease accounting and requires entities to recognize right-of-use assets and lease liabilities on the balance sheet for leases with lease terms of more than 12 months. ASC 842 became effective on January 1, 2019.

As of January 1, 2019, the Company adopted ASC 842 using the modified-retrospective method and recognized right-of-use assets and corresponding lease liability of $325,683, which represented the present value of the remaining lease payments of $350,507, discounted using the Company’s incremental borrowing rate of 11.17%. In addition, the Company eliminated its deferred rent liability and recorded an adjustment to decrease its right-of-use assets by $12,824. The adoption of the standard did not have an impact on the Company’s consolidated statements of cash flows and had no impact on the Company’s consolidated statement of operations.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

(3) Fair Value Measurements

The Company measures certain assets and liabilities at fair value in accordance with Accounting Standards Codification 820 ("ASC 820"), *Fair Value Measurements and Disclosures*. ASC 820 defines fair value as the price that would be received to sell an asset or paid to transfer a liability (the exit price) in an orderly transaction between market participants at the measurement date. The guidance in ASC 820 outlines a valuation framework and creates a fair value hierarchy that serves to increase the consistency and comparability of fair value measurements and the related disclosures. In determining fair value, the Company maximizes the use of quoted prices and observable inputs. Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from independent sources. The fair value hierarchy is broken down into three levels based on the source of inputs as follows:

Level 1 — Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities.

Level 2 — Valuations based on observable inputs and quoted prices in active markets for similar assets and liabilities.

Level 3 — Valuations based on unobservable inputs and models that are supported by little or no market activity.

In accordance with the fair value hierarchy described above, the following table sets forth the Company's financial assets measured at fair value on a recurring basis as of December 31, 2020 and 2019:

	Carrying amount as of December 31, 2020	Fair Value Measurement as of December 31, 2020		
		Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 59,010,328	$ 59,010,328	$ —	$ —
	$ 59,010,328	$ 59,010,328	$ —	$ —

	Carrying amount as of December 31, 2019	Fair Value Measurement as of December 31, 2019		
		Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 69,686,350	$ 69,686,350	$ —	$ —
	$ 69,686,350	$ 69,686,350	$ —	$ —

(4) Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following as of December 31, 2020 and 2019:

	December 31, 2020	December 31, 2019
Prepaid development expenses	$ 866,498	$ 957,814
Prepaid insurance	1,639,687	841,858
Deferred financing costs	—	193,505
Insurance litigation settlement receivable	2,389,250	—
Other current assets	270,966	385,635
Total prepaid expenses and other current assets	$ 5,166,401	$ 2,378,812

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

(5) Property and Equipment

Property and equipment consisted of the following as of December 31, 2020 and 2019:

	Estimated useful life (in years)	December 31, 2020	December 31, 2019
Equipment	2-5	$ 729,489	$ 263,829
Computer equipment	3-5	30,319	30,319
Furniture and fixtures	3-5	311,355	311,355
Leasehold improvements	various	68,881	68,881
Construction in process		42,827	78,773
Total cost		1,182,871	753,157
Less accumulated depreciation		(597,468)	(390,433)
Property and equipment, net		$ 585,403	$ 362,724

Depreciation expense was $207,035, 133,879 and $99,572 for the years ended December 31, 2020, 2019 and 2018 respectively.

(6) Accrued Expenses

Accrued expenses consisted of the following as of December 31, 2020 and 2019:

	December 31, 2020	December 31, 2019
Accrued compensation	$ 1,928,865	$ 2,340,533
Accrued research and development	4,999,881	4,343,322
Accrued litigation settlement expenses	4,000,000	—
Other	352,097	389,651
Total accrued expenses	$ 11,280,843	$ 7,073,506

(7) Stockholders' Equity

Preferred Stock

The Company's board of directors are authorized to issue up to 10.0 million shares of preferred stock, with any rights, preferences and privileges as it may designate. As of December 31, 2020, no shares of preferred stock were issued.

Common Stock

In August 2019, the Company entered into the 2019 Sales Agreement with the Agents pursuant to which the Company may sell, from time to time, up to $75.0 million of its common stock. From January 1, 2021 through February 9, 2021, the Company sold and issued 10,244,326 shares of common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $4.22 per share, resulting in gross proceeds of $43.2 million. Net proceeds after deducting commissions and offering expenses were $42.2 million. In 2020, the Company sold and issued 6,596,873 shares of common stock in the open market at a weighted-average selling price of $4.81 per share, for gross proceeds of $31.7 million and net proceeds, after deducting commissions and offering expenses, of $30.7 million. In 2019, the Company sold and issued 13,381 shares of common stock in the open market at a weighted-average selling price of $7.00 per share, for gross and net proceeds of $0.1 million. As of February 9, 2021, the Company utilized the entire $75.0 million under the 2019 Sales Agreement.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

In 2019, the Company sold and issued 5,521,554 shares of its common stock in the open market at a weighted-average selling price of $8.48 per share, for gross proceeds of $46.8 million and net proceeds, after deducting commissions and offering expenses, of $45.1 million. The last sale under the 2017 Sales Agreement was made on May 16, 2019. From June 2017 through May 16, 2019, the Company has cumulative gross proceeds of $50.0 million from shares sold in the open market under the 2017 Sales Agreement, which has terminated pursuant to its terms.

In July 2018, the Company completed a follow-on public offering, selling 4,062,500 shares of its common stock at an offering price of $8.00 per share, resulting in gross proceeds of $32.5 million. Net proceeds received after deducting underwriting discounts and commissions and offering expenses were $29.9 million.

(8) Stock-Based Compensation

The Company maintains the Amended and Restated 2014 Omnibus Incentive Compensation Plan, as amended (the "2014 Plan"), which allows for the granting of incentive stock options, nonqualified stock options, stock appreciation rights, stock awards, stock units, performance units and other stock-based awards to employees, officers, non-employee directors, consultants, and advisors. In addition, the 2014 Plan provides selected executive employees with the opportunity to receive bonus awards that are considered qualified performance-based compensation. The 2014 Plan is subject to automatic annual increases in the number of shares authorized for issuance under the 2014 Plan on the first trading day of January each year equal to the lesser of 1.5 million shares or 10% of the number of shares of common stock outstanding on the last trading day of December of the preceding year. As of January 1, 2021, the number of shares of common stock that may be issued under the 2014 Plan was automatically increased by 1.5 million shares, increasing the total number of shares of common stock available for issuance under the 2014 Plan to 9,304,869 shares. As of December 31, 2020, 2,543,009 shares were available for future issuance under the 2014 Plan.

Options issued under the 2014 Plan have a contractual life of 10 years and may be exercisable in cash or as otherwise determined by the board of directors. The Company has granted options to employees and non-employee directors. Stock options granted to employees primarily vest 25% upon the first anniversary of the grant date and the balance of unvested options vests in quarterly installments over the remaining three years. Stock options granted annually to non-employee directors vest on the earlier of the one-year anniversary of the grant date, or the date of the Company's next annual stockholders' meeting that occurs after the grant date. The Company's non-employee director compensation policy enables directors to receive stock options in lieu of quarterly cash payments. Any option granted to the directors in lieu of cash compensation vests in full on the grant date. The Company records forfeitures as they occur.

During 2018, the Company granted 83,280 performance-based stock options to certain employees. During 2019, the Company granted 5,000 performance-based restricted stock awards. Vesting of the performance-based options and restricted stock awards is dependent on meeting certain performance conditions, which relate to the Company's research and development progress, which were established by the Company's board of directors. The Company's board of directors determines if the performance conditions have been met. Stock-based compensation expense for these performance-based grants are recorded when management estimates that the vesting of these shares is probable based on the status of the Company's research and development programs and other relevant factors. For the years ended December 31, 2020, 2019 and 2018, none of the performance-based metrics were deemed probable of achievement. Any change in these estimates will result in a cumulative adjustment in the period in which the estimate is changed, so that as of the end of a period, the cumulative compensation expense recognized for an award or grant equals the amount that would be recognized on a straight-line basis as if the current estimates had been utilized since the beginning of the service period. During the fourth quarter of 2020, the Company's board of directors determined that the performance criteria was not achieved on the 83,280 performance-based stock option issued during 2018 and these options were forfeited and returned to the pool of outstanding options. As of December 31, 2020, the aggregate estimated grant date fair values of the restricted stock awards for which the satisfaction of the related-performance conditions have not been deemed probable was $24,850.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

During 2020, the Company granted 194,000 restricted stock awards that contain both performance-based and service-based conditions. These awards vest on the earlier of: (a) meeting the performance condition or (b) service provided for one-year from the grant date. Awards with both performance and service conditions are being expensed over the service period, with an acceleration of the remaining compensation expense, if the performance-based criteria is met before the end of the service condition.

During the years ended December 31, 2020, 2019 and 2018, the Company recorded $5,177,527, $5,561,895 and $6,625,743, respectively, in stock-based compensation expense related to its stock option grants and restricted stock awards, as follows:

	Stock Option Grants			Restricted stock awards		
	2020	2019	2018	2020	2019	2018
Research and development	$ 2,053,675	$ 2,348,205	$ 2,884,689	$ 141,213	$ 23,793	$ 202,809
General and administrative	2,922,620	3,189,897	3,491,432	60,019	—	46,813
	$ 4,976,295	$ 5,538,102	$ 6,376,121	$ 201,232	$ 23,793	$ 249,622

The following table summarizes the Company's stock option activity:

	Number of Shares	Weighted-Average Exercise Price	Weighted-Average Contractual Life (in Years)	Aggregate Intrinsic Value
Outstanding as of December 31, 2018	3,152,267	$ 12.16		
Granted	960,432	6.07		
Exercised	(40,983)	4.63		
Forfeited	(83,000)	9.48		
Outstanding as of December 31, 2019	3,988,716	10.83		
Granted	840,480	5.09		
Forfeited	(282,712)	10.93		
Outstanding as of December 31, 2020	4,546,484	9.76	6.73	$ —
Exercisable as of December 31, 2020	3,071,471	11.43	5.87	$ —
Vested and expected to vest as of December 31, 2020	4,546,484	$ 9.76		

The weighted-average grant date fair value of options granted during the years ended December 31, 2020, 2019 and 2018 was $3.58, $4.22 and $7.84, respectively.

The fair values of stock options granted were calculated using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year ended December 31,		
	2020	2019	2018
Weighted-average risk-free interest rate	1.27%	2.36%	2.53%
Expected term of options (in years)	6.18	6.16	6.12
Expected stock price volatility	82.00%	79.85%	78.09%
Expected dividend yield	0%	0%	0%

As of December 31, 2020, there was $5.0 million of unrecognized stock-based compensation expense related to stock options, which is expected to be recognized over a weighted-average period of 2.20 years.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

The following table summarizes the restricted stock award activity under the 2014 Plan:

	Shares	Weighted Average Grant Date Fair Value
Unvested as of December 31, 2018	10,500	11.86
Granted	8,600	4.42
Vested	(10,500)	11.86
Unvested as of December 31, 2019	8,600	$ 4.42
Granted	199,000	3.58
Forfeited	(32,000)	3.53
Vested	(1,800)	3.65
Unvested as of December 31, 2020	173,800	$ 3.64

As of December 31, 2020, excluding performance-based restricted stock awards that have not been deemed probable, there was $0.4 million of unrecognized stock-based compensation expense related to unvested restricted stock awards, which is expected to be recognized over a weighted-average period of 0.70 years. The Company expects that all 168,800 of the unvested, non-performance based, restricted stock awards will vest.

(9) Operating Lease Obligations

The Company adopted ASC 842 prospectively using the modified-retrospective method and elected the package of transition practical expedients that does not require reassessment of: (1) whether any existing or expired contracts are or contain leases, (2) lease classification and (3) initial direct costs. In addition, the Company has elected other available practical expedients to not separate lease and nonlease components, which consist principally of common area maintenance charges, and to exclude leases with an initial term of 12 months or less.

The Company leases its headquarters where it occupies 10,877 square feet of office space. On November 11, 2019, the Company extended its original five-year lease for one additional year until May 31, 2021. The Company's lease contains variable lease costs that do not depend on a rate or index and consist primarily of common area maintenance, taxes, and insurance charges. As the implicit rate was not readily determinable for the Company's lease, the Company used an estimated incremental borrowing rate, or discount rate, to determine the initial present value of the lease payments. The discount rate for the lease was calculated using a synthetic credit rating model.

As of January 1, 2019, the Company recognized a lease liability of $325,683 and a right-of-use asset of $312,859, which was recorded net of a pre-existing deferred rent liability of $12,824. As of November 11, 2019, the effective date of the lease modification, the Company remeasured the lease liability for the remaining portion of the lease and adjusted the lease liability to $392,822 and right-of-use assets to $386,609, which was recorded net of a deferred rent liability of $6,213. As of December 31, 2020, the Company's right-of-use asset, net of amortization, was $105,199.

Other operating lease information as of December 31, 2020:

Weighted-average remaining lease term - operating leases	0.4 years
Weighted-average discount rate - operating leases	6.6 %

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

The following is a maturity analysis of the annual undiscounted cash flows of the operating lease liabilities as of December 31, 2020 and 2019:

Year ended:	December 31, 2020	December 31, 2019
December 31, 2020	$ —	$ 259,864
December 31, 2021	111,506	111,506
Total minimum lease payments	111,506	371,370
Less: imputed lease interest	(1,817)	(18,004)
Total lease liabilities	$ 109,689	$ 353,366

Lease expense for the year ended December 31, 2020 and 2019 was comprised of the following:

	Year ended December 31,	
	2020	2019
Operating lease expense	$ 256,837	$ 241,443
Variable lease expense	58,697	58,697
Total lease expense	$ 315,534	$ 300,140

Cash payments related to operating leases for the years ended December 31, 2020 and 2019 were $318,561 and $246,750, respectively.

In March 2021, the Company extended its lease for office space until May 31, 2024.

(10) Defined Contribution Retirement Plan

The Company offers a tax-qualified defined contribution retirement plan, which we refer to as our 401(k) plan, to eligible employees, including our current named executive officers. Our 401(k) plan permits eligible employees to defer their annual eligible compensation subject to the limitations imposed by the Internal Revenue Service. The Company may, but is not required to, make discretionary employer matching contributions on behalf of eligible employees under this plan. On January 1, 2018, the Company commenced making an employer match of 33% for the first 6% of employee contributions. Employer matching contributions vest immediately. During the years ended December 31, 2020, 2019 and 2018, the Company's contributions to the plan was $111,846, $107,419 and $84,276, respectively.

(11) Income Taxes

The Company's U.S. and foreign loss before income taxes are set forth below:

	Year ended December 31,		
	2020	2019	2018
United States	$ (40,407,933)	$ (26,052,255)	$ (34,308,847)
Foreign	(10,928,898)	(6,891,328)	(5,602,328)
Total	$ (51,336,831)	$ (32,943,583)	$ (39,911,175)

The Company had $129.7 million and $96.0 million of federal net operating loss carryforwards and $3.7 million and $2.6 million of U.S. research tax credit carryforwards as of December 31, 2020 and 2019, respectively. The U.S. federal net operating loss carryforwards and research tax credit carryforwards begin to expire in 2028 and 2027, respectively. The Company has $129.6 million and $103.8 million of state net operating loss carryforwards as of December 31, 2020 and 2019, respectively. The state net operating loss carryforwards begin to expire in 2028. As of December 31, 2020 and 2019, the Company had $16.7 million and $1.0 million, respectively, of Australia net operating loss carryforwards, which have an indefinite life.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

The Tax Reform Act of 1986 (the Act) provides for limitation on the use of net operating loss and research and development tax credit carryforwards following certain ownership changes (as defined by the Act) that could limit the Company's ability to utilize these carryforwards. The Company may have experienced various ownership changes, as defined by the Act, as a result of past financings. Accordingly, the Company's ability to utilize the aforementioned carryforwards may be limited. Additionally, U.S. tax laws limit the time during which these carryforwards may be applied against future taxes; therefore, the Company may not be able to take full advantage of these carryforwards for federal income tax purposes.

The components of the net deferred income tax asset as of December 31, 2020 and 2019 are as follows:

	December 31, 2020	December 31, 2019
Deferred tax assets:		
Net operating loss carry forwards	$ 42,172,547	$ 27,661,926
Research and development credit carry forwards	3,803,776	2,666,036
Stock-based compensation	7,514,754	6,046,848
Property and equipment	3,969	—
Other	1,019,725	650,018
Gross deferred tax assets	54,514,771	37,024,828
Deferred tax liabilities:		
Property and equipment	—	(28,926)
Gross deferred tax liabilities	—	(28,926)
Less valuation allowance	(54,514,771)	(36,995,902)
Net deferred tax asset	$ —	$ —

On March 27, 2020, in response to COVID-19 and its detrimental impact to the global economy, President Trump signed the CARES Act into law, which provides a stimulus to the U.S. economy in the form of various individual and business assistance programs as well as temporary changes to existing tax law. The changes to the provision in business tax laws include a five-year net operating loss carryback for the 2018, 2019 and 2020 tax years, a deferral of the employer's portion of the social security tax, and an increase in the interest expense limitation under Section 163(j) from 30% to 50% for the 2019 and 2020 tax years, among other things. The Act did not have a material impact on the Company's income taxes. The Company will continue to monitor.

On December 21, 2020, Congress approved the Consolidated Appropriations Act, 2021 (the "Appropriations Act"), which was signed into law by the President on December 27, 2020. The Appropriations Act funds the federal government to the end of the fiscal year and provides further COVID-19 economic relief. Some of the business provisions included in the Appropriations Act are additional Paycheck Protection Program (PPP) loans, clarification of the deductibility of business expenses that were paid for with PPP funds, expansion of the employee retention credit, and temporary full deduction for business expenses for food and beverages provided by a restaurant. The Appropriations Act did not have a material impact on the Company's income taxes. The Company will continue to monitor for additional legislation related to COVID-19 and its impact on our results of operations.

In assessing the realizability of deferred tax assets, the Company considers whether it is more-likely-than-not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during the periods in which the temporary differences representing net future deductible amounts become deductible. After consideration of all the evidence, both positive and negative, the Company has recorded a full valuation allowance against its net deferred tax assets as of December 31, 2020 and 2019, respectively, because the Company has determined that is it more likely than not that these assets will not be fully realized due to historic net operating losses incurred. The valuation allowance increased by $17.5 million and $5.1 million during the years ended December 31, 2020 and 2019, respectively, due primarily to the generation of net operating loss carryforwards during those years.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

The Company does not have unrecognized tax benefits as of December 31, 2020 and 2019, respectively. The Company recognizes interest and penalties accrued on any unrecognized tax benefits as a component of income tax expense.

A reconciliation of income tax expense (benefit) at the statutory federal income tax rate and income taxes as reflected in the financial statements is as follows:

	Year ended December 31,		
	2020	2019	2018
Federal income tax benefit at statutory rate	21.0 %	21.0 %	21.0 %
State income tax, net of federal benefit	6.4	4.2	6.8
Foreign tax rate differential	—	0.1	0.3
Nondeductible research and development expenses	(4.6)	(4.3)	(2.2)
Other permanent differences	0.2	—	—
Research and development credit benefit	2.2	1.0	1.4
Adjustment of prior years' income taxes	(0.1)	(6.6)	—
Rate change from 2017 Tax Cuts and Jobs Act	—	—	0.3
Change in valuation allowance	(25.1)	(15.4)	(27.6)
Effective income tax rate	— %	— %	— %

The Company and its subsidiaries are subject to income taxes in the U.S. federal jurisdiction, various state jurisdictions and Australia. The Company’s 2011 to 2020 tax years remain open and subject to examination.

(12) Commitments and Contingencies

a. Federal Grants

There was $86,000 in grant revenue recognized during the year ended December 31, 2018. Previous grants received were recorded as deferred revenue and recognized as revenue as the designated preclinical study progressed and amounts were earned.

b. Leases

The Company is a party to a noncancelable operating lease for office space, under a long-term lease arrangement. As of December 31, 2020, future minimum lease commitment for the Company’s noncancelable lease was $135,963. Total lease expense for the years ended December 31, 2020, 2019 and 2018 was $315,534, $300,140 and $264,648 respectively. In March 2021, the Company extended its operating lease for an additional three years until May 31, 2024.

c. Employment Agreements

The Company has entered into employment contracts and subsequent amendments with its officers and certain employees that provide for severance and continuation of benefits in the event of termination of employment either by the Company without cause or by the employee for good reason, both as defined in the agreements. In addition, in the event of termination of employment following a change in control, as defined in the employment contracts, either by the Company without cause or by the employee for good reason, any unvested portion of the employee’s stock options and/or restricted stock awards become immediately vested.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

d. Litigation

Liabilities for loss contingencies arising from claims, assessments, litigation, fines, penalties, and other sources are recorded when it is probable that a liability has been incurred and the amount can be reasonably estimated. Legal fees are expensed as incurred.

On October 23, 2019, a putative class action complaint was filed against the Company and certain of its current officers in the United States District Court for the Eastern District of Pennsylvania, with an amended complaint filed on March 9, 2020. This action was purportedly brought on behalf of a putative class of Zynerba investors who purchased the Company's publicly traded securities between March 11, 2019 and September 17, 2019. The complaint alleges that Defendants made certain material misstatements and omissions relating to product candidate Zygel ("ZYN002") in alleged violation of Section 10(b) of the Exchange Act, Rule 10b-5 promulgated thereunder, and Section 20(a) of the Exchange Act. Specifically, plaintiff claims that Defendants made false statements or failed to disclose that: (i) Zygel was proving unsafe and not well-tolerated in the BELIEVE 1 clinical trial; (ii) that the foregoing created a foreseeable, heightened risk that Zynerba would fail to secure the necessary regulatory approvals for commercializing Zygel for the treatment of developmental and epileptic encephalopathies in children and adolescents, and (iii) as a result the Company's public statements and public filings were materially false and misleading to investors. The Company's motion to dismiss the plaintiffs' complaint was denied on November 25, 2020. The Company and the individual defendants have recently reached an agreement in principle to settle this action that is subject to the preliminary approval and final approval of the court.

With respect to the foregoing matter, the Company has previously incurred and expensed fees and expenses in an amount less than its insurance policy deductible of $2.0 million. The Company's insurers have undertaken to cover the amount of the settlement payment in excess of the remainder of the insurance policy deductible, if the proposed settlement is finally approved by the Court. As of December 31, 2020, the Company has accrued both the amount of the settlement payment under the agreement in principle, and a corresponding insurance receivable from its insurers.

The Company and the individual defendants have denied, and continue to deny, that they have committed any violations of law or breaches of duty as alleged in these lawsuits and make no admission of liability or any form of wrongdoing.

On April 24, 2020, a stockholder derivative complaint, captioned Philip Quartararo v. Armando Anido, et al., was filed against the Company, its current and former directors (Armando Anido, John P. Butler, Warren D. Cooper, William J. Federici, Thomas L. Harrison, Daniel L. Kisner, Kenneth I. Moch, and Pamela Stephenson), and its Chief Financial Officer, James E. Fickenscher. The complaint generally alleges breach of fiduciary duty, corporate waste and violations of Section 14 (a) of the Exchange Act in connection with the Company's disclosures around the BELIEVE I clinical trial. These proceedings are currently stayed by agreement of the parties.

On December 4, 2020 a stockholder derivative complaint, captioned Dmitry Itkis, derivatively on behalf of Zynerba Pharmaceuticals, Inc. v. Armando Anido, et al. was filed against the Company, its current and former directors (Armando Anido, John P. Butler, Warren D. Cooper, William J. Federici, Thomas L. Harrison, Daniel L. Kisner, Kenneth I. Moch, and Pamela Stephenson), and its Chief Financial Officer, James E. Fickenscher. The complaint generally alleges breach of fiduciary duty, corporate waste and violations of Section 14 (a) of the Exchange Act in connection with the Company's disclosures around the BELIEVE I clinical trial. These proceedings are currently stayed by agreement of the parties.

We believe that the claims asserted in the foregoing stockholder derivative suits are without merit, and we intend to defend these actions vigorously. There is no assurance, however, that we will be successful in the defense of these lawsuits, or any associated appeals. These lawsuits are in the early stages and, at this time, no assessment can be made as to their likely outcome or whether the outcome will be material to us.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED

(13) Quarterly Financial Data (unaudited)

The following information has been derived from unaudited consolidated financial statements that, in the opinion of management, include all recurring adjustments necessary for a fair statement of such information.

	2020			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Operating expenses:				
Research and development	$ 6,882,793	$ 17,349,841 [2]	$ 5,805,948	$ 5,616,412
General and administrative	3,916,569	4,492,034	3,425,831	4,573,114
Total operating expenses	10,799,362	21,841,875	9,231,779	10,189,526
Loss from operations	(10,799,362)	(21,841,875)	(9,231,779)	(10,189,526)
Other income (expense):				
Interest income	201,684	26,601	10,781	4,926
Foreign exchange loss	(1,740,151)	1,482,513	172,467	566,890
Total other income (expense)	(1,538,467)	1,509,114	183,248	571,816
Net loss	$ (12,337,829)	$ (20,332,761)	$ (9,048,531)	$ (9,617,710)
Net loss per share basic and diluted	$ (0.53)	$ (0.78)	$ (0.31)	$ (0.33)
Basic and diluted weighted average shares outstanding	23,399,438	26,100,264	29,243,375	29,299,233

	2019			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Operating expenses:				
Research and development	$ 6,306,712	$ 8,223,783	$ (1,604,399)[1]	$ 7,457,953
General and administrative	3,159,657	3,287,276	3,530,617	3,958,211
Total operating expenses	9,466,369	11,511,059	1,926,218	11,416,164
Loss from operations	(9,466,369)	(11,511,059)	(1,926,218)	(11,416,164)
Other income (expense):				
Interest income	350,951	439,201	436,846	295,140
Foreign exchange loss	(31,599)	(63,327)	(457,018)	406,033
Total other income (expense)	319,352	375,874	(20,172)	701,173
Net loss	$ (9,147,017)	$ (11,135,185)	$ (1,946,390)	$ (10,714,991)
Net loss per share basic and diluted	$ (0.47)	$ (0.50)	$ (0.08)	$ (0.46)
Basic and diluted weighted average shares outstanding	19,452,088	22,116,758	23,186,410	23,191,428

(1) During the three months ended September 30, 2019, the Company recorded $8.3 million as an incentive and tax receivable and recorded a corresponding credit to research and development expense for amounts expected to be received through the AOF for the period January 1, 2018 through September 30, 2019.
(2) During the three months ended June 30, 2020, the Company recorded a full reserve of $8.1 million against the AOF receivable, which was originally recorded during the three months ended September 30, 2019.

Per share amounts are calculated using the weighted average number of common shares outstanding for each period presented. As such, the sum of the quarterly per share amounts above will not necessarily equal the per share amounts for the fiscal year.

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2020. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the rules and forms, promulgated by the SEC. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as of December 31, 2020, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's annual report on internal control over financial reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is a process designed to provide reasonable assurance of the reliability of financial reporting and of the preparation of financial statements for external reporting purposes, in accordance with U.S. generally accepted accounting principles.

Internal control over financial reporting includes policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect transactions and disposition of assets; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. generally accepted accounting principles, and that receipts and expenditures are being made only in accordance with the authorization of its management and directors; and (3) provide reasonable assurance regarding the prevention or timely detection of unauthorized acquisition, use, or disposition of our assets that could have a material effect on its financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of the effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies and procedures included in such controls may deteriorate.

Our management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2020. In making this assessment, management used the criteria established by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in *Internal Control – Integrated Framework (2013)*. These criteria are in the areas of control environment, risk assessment, control activities, information and communication, and monitoring. Management's assessment included extensive documentation, evaluating and testing the design and operating effectiveness of its internal controls over financial reporting.

Based on the Management's processes and assessment, as described above, management has concluded that, as of December 31, 2020, our internal control over financial reporting was effective.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting during the quarter ended December 31, 2020 that has materially affected, or is 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

The information required by this item is incorporated herein by reference to the material under the captions "Board of Directors, Executive Officers and Corporate Governance," and "Security Ownership of Certain Beneficial Owners and Management – Section 16(a) Beneficial Ownership Reporting Compliance" in our proxy statement for the 2021 annual meeting of stockholders to be filed no later than 120 days after the end of our fiscal year ended December 31, 2020 (the "2021 Proxy Statement").

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference to the material under the captions "Board of Directors, Executive Officers and Corporate Governance," "Director Compensation" and "Executive Compensation" in our 2021 Proxy Statement.

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

The following table contains information about our equity compensation plans as of December 31, 2020.

Equity Compensation Plan Information

Plan Category	Number of securities to be issued upon exercise of outstanding options	Weighted-average exercise price of outstanding options	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a))
Equity compensation plans approved by security holders	4,396,484	$ 9.75	2,543,009
Equity compensation plans not approved by security holders	150,000 (1)	10.23	— (2)
Total	4,546,484	$ 9.76	2,543,009

(1) Reflects option grants that were "inducement grants" as defined in Nasdaq Listing Rule 5635(c)(4).

(2) Our board of directors has not established any specific number of shares that could be issued without shareholder approval. Inducement grants to new key employees are determined on a case-by-case basis. Other than possible inducement grants, we expect that all equity awards will be made under stockholder-approved plan.

Please see note (8) to our audited financial statements for a description of our Amended and Restated 2014 Omnibus Incentive Compensation Plan.

The other information required by this item is incorporated herein by reference to the material under the caption "Security Ownership of Certain Beneficial Owners and Management" in our 2021 Proxy Statement.

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

The information required by this item is incorporated herein by reference to the material under the captions “Certain Relationships and Related Party Transactions,” “Board of Directors, Executive Officers and Corporate Governance – Policies and Procedures for Related Party Transactions” and “Board of Directors, Executive Officers and Corporate Governance – Our Board” in our 2021 Proxy Statement.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated herein by reference to the material under the captions “Independent Auditors and Related Fees” in our 2021 Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Financial Statements.

The Consolidated Financial Statements and related Notes thereto as set forth under Item 8 of this Report are incorporated herein by reference.

(a)(2) Financial Statement Schedules.

No financial statement schedules are provided because the information called for is not required or is shown either in the financial statements or the notes thereto.

(a)(3) Exhibits:

The following exhibits are filed with this report or incorporated by reference:

Exhibit No.	Exhibit Description
3.1	Sixth Amended and Restated Certificate of Incorporation of Zynerba Pharmaceuticals, Inc., effective August 10, 2015. Incorporated herein by reference to Exhibit 3.1 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 10, 2015.
3.2	Amended and Restated By-laws of Zynerba Pharmaceuticals, Inc., effective August 10, 2015. Incorporated herein by reference to Exhibit 3.2 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 10, 2015.
4.1	Form of Common Stock Certificate. Incorporated herein by reference to Exhibit 4.1 to the registrant's Registration Statement on Form S-1/A (File No. 333-205355) filed on July 31, 2015.
4.2	Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934 (filed herewith).
10.1(A)+	Employment Agreement dated September 4, 2014, by and between the registrant and Armando Anido. Incorporated herein by reference to Exhibit 10.2(A) to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.1(B)+	Amendment to the Employment Agreement, dated October 2, 2014, by and between the registrant and Armando Anido. Incorporated herein by reference to Exhibit 10.2(B) to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.1(C)+	Amendment to the Employment Agreement, dated August 30, 2019, by and between the registrant and Armando Anido. Incorporated herein by reference to Exhibit 10.2 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 30, 2019.
10.2(A)+	Employment Agreement dated October 2, 2014, by and between the registrant and Terri B. Sebree. Incorporated herein by reference to Exhibit 10.3 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.2(B)+	Amendment to the Employment Agreement, dated August 30, 2019, by and between the registrant and Terri B. Sebree. Incorporated herein by reference to Exhibit 10.4 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 30, 2019.
10.3(A)+	Employment Agreement dated October 2, 2014, by and between the registrant and Suzanne M. Hanlon. Incorporated herein by reference to Exhibit 10.4 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.3(B)+	Amendment to the Employment Agreement, dated August 30, 2019, by and between the registrant and Suzanne M. Hanlon. Incorporated herein by reference to Exhibit 10.5 to the registrant's Quarterly Report on Form 10-Q for the period ended September 30, 2019 (File No. 001-37526) filed on November 6, 2019.
10.4(A)+	Employment Agreement dated August 11, 2016, by and between the registrant and James E. Fickenscher. Incorporated herein by reference to Exhibit 10.2 to the registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2016 (File No. 001-37526) filed on November 14, 2016.
10.4(B)+	Amendment to the Employment Agreement, dated August 30, 2019, by and between the registrant and James E. Fickenscher. Incorporated herein by reference to Exhibit 10.3 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 30, 2019.
10.5(A)+	Employment Agreement dated January 18, 2017, by and between the registrant and Brian Rosenberger. Incorporated herein by reference to Exhibit 10.7 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2016 (File No. 001-37526) filed on March 27, 2017.
10.5(B)+	Amendment to the Employment Agreement, dated August 30, 2019, by and between the registrant and Brian Rosenberger. Incorporated herein by reference to Exhibit 10.6 to the registrant's Quarterly Report on Form 10-Q for the period ended September 30, 2019 (File No. 001-37526) filed on November 6, 2019.
10.6	Grant no. 5RC2DA028984-02 dated September 17, 2010, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.13 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.7	Grant no. 1R43DA032161-01 dated July 14, 2011, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.14 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.

10.8	Grant no. 1RC2DA028984-01 dated September 30, 2009, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.15 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.9	Grant no. 1RC2DA028984-01, revised award letter dated June 9, 2011, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.16 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.10(A)+	Amended and Restated 2014 Omnibus Incentive Compensation Plan. Incorporated herein by reference to Exhibit 10.19(A) to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.10(B)+	Form of Amendment to Amended and Restated 2014 Omnibus Incentive Compensation Plan. Incorporated herein by reference to Exhibit 10.19(B) to the registrant's Registration Statement on Form S-1/A (File No. 333-205355) filed on July 23, 2015.
10.10(C)+	Form of Incentive Stock Option Grant under Amended and Restated 2014 Omnibus Incentive Compensation Plan. Incorporated herein by reference to Exhibit 10.19(C) to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.10(D)+	Form of Nonqualified Stock Option Grant under Amended and Restated 2014 Omnibus Incentive Compensation Plan. Incorporated herein by reference to Exhibit 10.19(D) to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.10(E)+	Form of Restricted Stock Grant Agreement under Amended and Restated 2014 Omnibus Incentive Compensation Plan. Incorporated herein by reference to Exhibit 10.19(E) to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.11+	Form of Award Agreement for Inducement Awards. Incorporated herein by reference to Exhibit 10.17 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2016 (File No. 001-37526) filed on March 27, 2017.
10.12+	Zynerba Pharmaceuticals, Inc. Non-Employee Director Compensation Policy. Incorporated herein by reference to Exhibit 10.18 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2016 (File No. 001-37526) filed on March 27, 2017.
10.13+	Form of Indemnification Agreement for directors and officers. Incorporated herein by reference to Exhibit 10.20 to the registrant's Registration Statement on Form S-1/A (File No. 333-205355) filed on July 23, 2015.
10.14	Grant no. 5RC2DA028984-02, revised award letter dated May 9, 2012, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.24 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.15	Lease Agreement dated February 12, 2015 by and between Provco Devon, L.L.C. and the registrant. Incorporated herein by reference to Exhibit 10.26 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.16	Lease Amendment dated December 1, 2016, by and between Provco Devon, L.L.C. and the registrant. Incorporated herein by reference to Exhibit 10.26 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2016 (File No. 001-37526) filed on March 27, 2017.
10.17	Open Market Sale Agreement dated June 9, 2017, by and between Jefferies LLC and the registrant. Incorporated herein by reference to Exhibit 1.2 to the registrant's Registration Statement on Form S-3 (File No. 333-218638) filed on June 9, 2017.
10.18	Lease amendment No. 2 dated February 9, 2018, by and between Provco Devon, L.L.C. and the registrant. Incorporated herein by reference to Exhibit 10.19 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2017 (File No. 001-37526) filed on March 12, 2018.
10.19	Controlled Equity Offering℠ Sales Agreement, dated August 30, 2019, by and among the registrant, Cantor Fitzgerald & Co., Canaccord Genuity LLC, H.C. Wainwright & Co., LLC, and Ladenburg Thalmann & Co. Inc. Incorporated herein by reference to Exhibit 10.1 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 30, 2019.
10.20	Lease amendment No. 3 dated November 19, 2019, by and between Provco Devon, L.L.C. and the registrant (filed herewith)

10.21	Lease amendment No. 4 dated March 1, 2021, by and between Provco Devon, L.L.C. and the registrant (filed herewith)
21.1	List of subsidiaries of the registrant (filed herewith).
23.1	Consent of independent registered public accounting firm (filed herewith).
31.1	Certifying Statement of the Chief Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (filed herewith).
31.2	Certifying Statement of the Chief Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (filed herewith).
32.1	Certifying Statement of the Chief Executive Officer pursuant to Section 1350 of Title 18 of the United States Code (furnished herewith).
32.2	Certifying Statement of the Chief Financial Officer pursuant to Section 1350 of Title 18 of the United States Code (furnished herewith).
101 INS	Inline XBRL Instance Document (filed herewith).
101 SCH	Inline XBRL Taxonomy Extension Schema Document (filed herewith).
101 CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document (filed herewith).
101 DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document (filed herewith).
101 LAB	Inline XBRL Taxonomy Extension Label Linkbase Document (filed herewith).
101 PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document (filed herewith).
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

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.

Date: March 10, 2021

ZYNERBA PHARMACEUTICALS, INC.

By: /s/ Armando Anido
Armando Anido
Chairman 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 and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Armando Anido Armando Anido	Chairman and Chief Executive Officer (Principal Executive Officer)	March 10, 2021
/s/ James E. Fickenscher James E. Fickenscher	Chief Financial Officer (Principal Financial and Accounting Officer)	March 10, 2021
/s/ John P. Butler John P. Butler	Director	March 10, 2021
/s/ Warren D. Cooper, MB, BS, BSc, MFPM Warren D. Cooper, MB, BS, BSc, MFPM	Director	March 10, 2021
/s/ William J. Federici William J. Federici	Director	March 10, 2021
/s/ Daniel L. Kisner, MD Daniel L. Kisner, MD	Director	March 10, 2021
/s/ Kenneth I. Moch Kenneth I. Moch	Director	March 10, 2021
/s/ Pamela Stephenson Pamela Stephenson	Director	March 10, 2021

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

Zynerba Pharmaceuticals, Inc. (the "Company") has one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). The Company's common stock, $0.001 par value per share ("Common Stock") is registered under Section 12(b) of the Exchange Act. The following description of our Common Stock is a summary and does not purport to be complete. It is subject to and qualified in its entirety by reference to our sixth amended and restated certificate of incorporation ("Certificate of Incorporation") and amended and restated bylaws ("Bylaws"), each of which is incorporated by reference as an exhibit to the Annual Report on Form 10-K of which this Exhibit 4.2 is a part. We encourage you to read our Certificate of Incorporation, Bylaws and the applicable provisions of Delaware General Corporation Law ("DGCL"), for additional information.

References to "Zynerba," "we," "our" and the "Company" herein are, unless the context otherwise indicates, only to Zynerba Pharmaceuticals, Inc. and not to any of its subsidiaries.

Common Stock

Authorized Capital Stock. Our authorized capital stock consists of 210,000,000 shares, 200,000,000 of which are designated as Common Stock and 10,000,000 of which are designated as preferred stock with a par value of $0.001 (the "Preferred Stock"). Shares of our Common Stock have the following rights, preferences and privileges:

Voting Rights. Each share of our Common Stock is entitled to one vote in each matter submitted to a vote at a meeting of stockholders including in all elections for directors; stockholders are not entitled to cumulative voting in the election for directors. Our stockholders may vote either in person or by proxy. Certain matters identified in our charter and our bylaws, including amending certain provisions of our charter, such as the provisions relating to preferred stock, stockholder action, bylaw amendment, director removal and director liability, require the approval of 66 2/3% of our issued and outstanding Common Stock. Our directors shall be elected by a plurality of votes cast. All other questions shall be decided by a majority of votes cast.

Dividends. Our board of directors may authorize, and we may make, distributions to our common stockholders, subject to any restriction in our charter and to those limitations prescribed by law. However, we have never paid cash dividends on our Common Stock or any other securities. We anticipate that we will retain all of our future earnings, if any, for use in the expansion and operation of our business and do not anticipate paying cash dividends in the foreseeable future.

No Preemptive or Similar Rights. Holders of our Common Stock have no preemptive rights and have no other rights to subscribe for additional securities under Delaware law. Nor does our Common Stock have any conversion rights or rights of redemption (or, if any such rights have been granted in relation to our Common Stock, any such rights have been waived).

Transfer Agent and Registrar. The transfer agent and registrar for our Common Stock is American Stock Transfer and Trust Company, LLC.

Listing. Our Common Stock is listed on the Nasdaq Global Market under the symbol "ZYNE."

Preferred Stock

Our Board has the authority, subject to limitations prescribed by Delaware law and without further action by our stockholders, to issue up to 10,000,000 shares of Preferred Stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the designation, powers, preferences and other rights and privileges of the shares of each wholly unissued series and any qualifications, limitations or restrictions thereon, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding. Our Board may authorize the issuance of Preferred Stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our Common Stock. The issuance of Preferred Stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in our control and may adversely affect the market price of the Common Stock and the voting and other rights of the holders of our Common Stock.

Delaware Anti-Takeover Law and Provisions of Our Certificate of Incorporation and Bylaws

Some provisions of Delaware law and our charter and bylaws contain provisions that could make the following transactions more difficult: acquisition of us by means of a tender offer; acquisition of us by means of a proxy contest or otherwise; or removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult

to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions that might result in a premium over the market price for our shares.

These provisions, summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless prior to the date of the transaction the interested stockholder attained such status with the approval of our board of directors or unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and the sale of 10% or more of our assets. In general, an "interested stockholder" is any entity or person beneficially owning (currently or within the prior three years) 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Undesignated Preferred Stock

Our board of directors may issue up to 10 million shares of Preferred Stock, with any rights, preferences and privileges as it may designate.

Board Size and Vacancies

All vacancies on our board of directors, including as a result of newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if the number of directors then in office constitutes less than a quorum and the authorized number of directors may be changed only by the resolution of our board of directors.

Elimination of Stockholder Action by Written Consent

Any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and may not be taken by written consent.

Requirements for Advance Notification of Stockholder Nominations and Proposals

Stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide advance notice in writing, and our bylaws specify requirements as to the form and content of a stockholder's notice.

Special Stockholder Meetings

Our bylaws provide that special meetings of our stockholders may be called only by the board of directors or by such person or persons requested by a majority of the board of directors to call such meetings.

Choice of Forum

Our bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum in which we and our directors may be sued by our stockholders. This provision does not apply to any claims arising under the Securities Act or the Exchange Act, or any claim in which exclusive jurisdiction is vested in a court or forum other than the Court of Chancery or for which the Court of Chancery does not have subject matter jurisdiction. Although our bylaws contain the exclusive forum described above, it is possible that a court could find that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

Amendment of Charter Provisions

Our certificate of incorporation and bylaws can only be amended to remove or revise the anti-takeover measures discussed above upon consent of 66 2/3% of the outstanding capital stock.

LEASE AMENDMENT #3

THIS LEASE AMENDMENT #3 (“Amendment #3”) is entered into as of the 11th day of November 2019, by and between PROVCO DEVON, L.L.C., a Pennsylvania limited liability company (hereinafter called the "Landlord"), and ZYNERBA PHARMACEUTICALS, INC. a Delaware corporation (hereinafter referred to as "Tenant"). The following statements are a material part of the Amendment:

WITNESSETH:

WHEREAS, Landlord and Tenant entered into a written Lease Agreement (the “Lease”) dated February 12, 2015 for that certain premises in known as Suite 300, The World Activity Building, 80 West Lancaster Avenue, Devon, PA 19333 (the “Premises”);

WHEREAS, on or about December 1, 2016, the parties amended the Lease (“Amendment #1”) expanding the size of the Premises;

WHEREAS, on or about February 9, 2018, the parties further amended the Lease to further expand the Premises (“Amendment #2”);

WHEREAS, Landlord and Tenant desire to further amend the Lease as hereinafter provided;

NOW, THEREFORE, in consideration of the mutual agreements, covenants and representations herein contained and those contained in the Lease and in reliance thereon, the parties intending to be legally bound hereby mutually agree as follows:

1. The Term of the Lease shall be extended to May 31, 2021.

2. From June 1, 2020-May 31, 2021, Tenant shall pay to Landlord, as annual base rent for the Premises, the sum of $326,310.00 per year, payable on the first day of each month during the Lease Year at the rate of $27,192.50 per month or $30.00 per rentable square foot.

3. Except as modified herein, the parties hereto agree that all the terms and conditions of the Lease, Amendment #1 and Amendment #2 shall remain in full force and effect and are hereby ratified and confirmed including that the Landlord May Confess Judgment as follows:

CONFESSION OF JUDGMENT.

THE FOLLOWING PARAGRAPHS SET FORTH WARRANTS OF AUTHORITY FOR AN ATTORNEY TO CONFESS JUDGMENT AGAINST TENANT, IN GRANTING THIS RIGHT TO CONFESS JUDGMENT AGAINST TENANT, TENANT HEREBY KNOWINGLY, INTENTIONALLY, VOLUNTARILY AND IRREVOCABLY AND, ON THE ADVICE OF THE SEPARATE COUNSEL OF TENANT, UNCONDITIONALLY WAIVES ANY AND ALL RIGHTS TENANT HAD OR MAY HAVE TO PRIOR NOTICE AND AN OPPORTUNITY FOR HEARING UNDER THE RESPECTIVE CONSTITUTIONS AND LAWS OF THE UNITED STATES AND THE COMMONWEALTH OF PENNSYLVANIA.

(i) CONFESSIONS OF JUDGMENT/EJECTMENT. TENANT HEREBY KNOWINGLY, INTENTIONALLY, VOLUNTARILY AND IRREVOCABLY AGREES THAT, IN THE EVENT THAT, AND WHEN THIS LEASE SHALL BE DETERMINED BY TERM, COVENANT, LIMITATION OR CONDITION BROKEN, AS AFORESAID, DURING THE TERM, AND ALSO WHEN AND AS SOON AS THE TERM, AS SAME MAY HAVE BEEN EXTENDED FROM TIME TO TIME, HEREBY CREATED SHALL HAVE EXPIRED OR BE

TERMINATED, IT SHALL BE LAWFUL FOR ANY ATTORNEY, AS ATTORNEY FOR TENANT TO CONFESS JUDGMENT IN EJECTMENT IN ANY COMPETENT COURT AGAINST TENANT AND ALL PERSONS CLAIMING UNDER TENANT FOR THE RECOVERY BY LANDLORD OF POSSESSION OF THE LEASED PREMISES, WITHOUT ANY LIABILITY ON THE PART OF THE SAID ATTORNEY, FOR WHICH THIS LEASE SHALL BE A SUFFICIENT WARRANT; WHEREUPON, IF LANDLORD SO DESIRES, A WRIT OF POSSESSION WITH CLAUSES FOR COSTS MAY ISSUE FORTHWITH WITH OR WITHOUT ANY PRIOR WRIT OR PROCEEDING WHATSOEVER. IF FOR ANY REASON AFTER SUCH ACTION HAS BEEN COMMENCED, THE SAME SHALL BE DETERMINED AND THE POSSESSION OF THE LEASED PREMISES REMAINS IN OR IS RESTORED TO TENANT, THE LANDLORD SHALL HAVE THE RIGHT IN THE EVENT OF ANY SUBSEQUENT DEFAULT OR DEFAULTS TO CONFESS JUDGMENT IN EJECTMENT AGAINST TENANT IN THE MANNER AND FORM HEREINBEFORE SET FORTH, TO RECOVER POSSESSION OF THE LEASED PREMISES FOR SUCH SUBSEQUENT DEFAULT, NO SUCH DETERMINATION OF THIS LEASE NOR RECOVERING POSSESSION OF THE LEASED PREMISES SHALL DEPRIVE LANDLORD OF ANY REMEDIES OR ACTION AGAINST TENANT FOR RENT OR FOR DAMAGES DUE OR TO BECOME DUE FOR THE BREACH OF ANY CONDITION OR COVENANT; NOR THE RESORT TO ANY WAIVER OF THE RIGHT TO INSIST UPON THE FORFEITURE, AND TO OBTAIN POSSESSION IN THE MANNER PROVIDED HEREIN.

(ii) AFFIDAVIT OF DEFAULT. In any action to confess judgment in ejectment, Landlord shall first cause to be filed in such action an affidavit made by Landlord or someone acting for Landlord setting forth the facts necessary to authorize the entry of judgment, of which facts such affidavit shall be conclusive evidence and if a true copy of the Lease (and of the truth of the copy such affidavit shall be sufficient evidence) be filed in such action, it shall not be necessary to file the original as a warrant of attorney, any rule of Court, custom or practice to the contrary notwithstanding.

(iii) TENANT WAIVER. TENANT SPECIFICALLY ACKNOWLEDGES THAT TENANT HAS KNOWINGLY, INTENTIONALLY, VOLUNTARILY AND IRREVOCABLY WAIVED CERTAIN DUE PROCESS RIGHTS TO A PREJUDGMENT HEARING RELATING SOLELY TO THE POSSESSION OF THE LEASED PREMSIES BY AGREEING TO THE TERMS OF THIS PARAGRAPH REGARDING CONFESSION OF JUDGMENT, TENANT FURTHER SPECIFICALLY AGREES THAT IN THE EVENT OF DEFAULT, LANDLORD MAY PURSUE MULTIPLE REMEDIES INCLUDING OBTAINING POSSESSION OF THE LEASED PREMISES PURSUANT TO A JUDGMENT BY CONFESSION AND ALSO OBTAINING A MONEY JUDGMENT FOR PAST DUE AND ACCELERATED AMOUNTS AND EXECUTING UPON SUCH JUDGMENT. FURTHERMORE, TENANT SPECIFICALLY WAIVES ANY CLAIM AGAINST LANDLORD AND LANDLORD'S COUNSEL FOR VIOLATION OF TENANT'S CONSTITUTIONAL RIGHTS IN THE EVENT THAT JUDGMENT IS CONFESSED PURSUANT TO THIS PARAGRAPH.

(iv) In view of the commercial nature of the relationship between the parties hereto and the fact that the parties hereto may have adverse interests, the parties agree that there is no expectation that Landlord shall have any duty under any provision of Chapter 56 of the Pennsylvania Decedents, Estates and Fiduciaries Code (20 Pa. C.S.A. § 5601, et seq.) (including, without limitation, 20 Pa. C.S.A. § 5601.3(a)(1)) to act in the best interest of Tenant hereunder, and it is agreed that Landlord shall have no such duty. Further, Landlord and Tenant hereby agree that all duties owed by an agent as specified under 20 Pa.C.S.A. § 5601.3(b) (as the term "agent" is used therein) are irrevocably waived.

4. This Amendment #3 shall be governed by and construed in accordance with the laws of the Commonwealth of Pennsylvania.

5. This Amendment #3 can be executed in any number of counterparts, each of which shall be deemed an original.

6. To the extent there are any conflicts or inconsistencies between the Lease, Amendment #1, Amendment #2 and this Amendment #3, this Amendment #3 and the rights and obligations herein shall govern. All other terms and provisions of the previous agreements between the parties shall remain unaffected by this Amendment #3.

IN WITNESS WHEREOF, the Landlord and Tenant hereto have executed this Amendment #3 as of the date first written above.

LANDLORD:

WITNESS

Provco Devon, L.L.C.

_____

By: /s/ Gerald N. Holtz
Its: Vice President

TENANT:

WITNESS

Zynerba Pharmaceuticals, Inc.

_____

By: /s/ James E. Fickenscher
Its: Chief Financial Officer

COMMONWEALTH OF PENNSYLVANIA
COUNTY OF CHESTER

On this the 11th day of November, 2019, before me, a Notary Public in and for the Commonwealth of Pennsylvania, the undersigned officer, personally appeared James E. Fickenscher who acknowledged himself to be the Chief Financial Officer of Zynerba Pharmaceuticals, Inc., and who, being authorized to do so, executed the foregoing instrument for the purposes therein contained, by signing their names thereto.

IN WITNESS WHEREOF, I hereunto set my hand and official seal.

[SEAL] /s/ Janice Liberato
Notary Public

COMMONWEALTH OF PENNSYLVANIA
COUNTY OF DELAWARE

On this the 11th day of November, 2019, before me, a Notary Public in and for the Commonwealth of Pennsylvania, the undersigned officer, personally appeared Gerald N. Holtz who acknowledged himself to be the Vice President of Provco Devon, L.L.C. and who, being authorized to do so, executed the foregoing instrument for the purposes therein contained, by signing their names thereto.

IN WITNESS WHEREOF, I hereunto set my hand and official seal.

[SEAL] /s/ Willys K. Silvers
Notary Public

LEASE AMENDMENT #4

THIS LEASE AMENDMENT #4 (“Amendment #4”) is entered into as of the 1st day of March 2021, by and between PROVCO DEVON, L.L.C., a Pennsylvania limited liability company (hereinafter called the "Landlord"), and ZYNERBA PHARMACEUTICALS, INC. a Delaware corporation (hereinafter referred to as "Tenant"). The following statements are a material part of the Amendment:

WITNESSETH:

WHEREAS, Landlord and Tenant entered into a written Lease Agreement (the “Lease”) dated February 12, 2015 for that certain premises in known as Suite 300, The World Activity Building, 80 West Lancaster Avenue, Devon, PA 19333 (the “Premises”);

WHEREAS, on or about December 1, 2016, the parties amended the Lease (“Amendment #1”) expanding the size of the Premises;

WHEREAS, on or about February 9, 2018, the parties further amended the Lease to further expand the Premises (“Amendment #2”);

WHEREAS, on or about November 11, 2019, the parties further amended the Lease (“Amendment #3”);

WHEREAS, Landlord and Tenant desire to further amend the Lease as hereinafter provided;

NOW, THEREFORE, in consideration of the mutual agreements, covenants and representations herein contained and those contained in the Lease and in reliance thereon, the parties intending to be legally bound hereby mutually agree as follows:

1. The Term of the Lease shall be extended to May 31, 2024.

2. From June 1, 2021-May 31, 2024, Tenant shall pay to Landlord, as annual base rent for the Premises, the sum of $299,117.50 per year, payable on the first day of each month during the Lease Year at the rate of $24,926.46 per month or $27.50 per rentable square foot.

3. Except as modified herein, the parties hereto agree that all the terms and conditions of the Lease, Amendment #1, Amendment #2 and Amendment #3 shall remain in full force and effect and are hereby ratified and confirmed including that the Landlord May Confess Judgment as follows:

CONFESSION OF JUDGMENT.

THE FOLLOWING PARAGRAPHS SET FORTH WARRANTS OF AUTHORITY FOR AN ATTORNEY TO CONFESS JUDGMENT AGAINST TENANT, IN GRANTING THIS RIGHT TO CONFESS JUDGMENT AGAINST TENANT, TENANT HEREBY KNOWINGLY, INTENTIONALLY, VOLUNTARILY AND IRREVOCABLY AND, ON THE ADVICE OF THE SEPARATE COUNSEL OF TENANT, UNCONDITIONALLY WAIVES ANY AND ALL RIGHTS TENANT HAD OR MAY HAVE TO PRIOR NOTICE AND AN OPPORTUNITY FOR HEARING UNDER THE RESPECTIVE CONSTITUTIONS AND LAWS OF THE UNITED STATES AND THE COMMONWEALTH OF PENNSYLVANIA.

(i) CONFESSIONS OF JUDGMENT/EJECTMENT. TENANT HEREBY KNOWINGLY, INTENTIONALLY, VOLUNTARILY AND IRREVOCABLY AGREES THAT, IN THE EVENT THAT, AND WHEN THIS LEASE SHALL BE DETERMINED BY TERM,

COVENANT, LIMITATION OR CONDITION BROKEN, AS AFORESAID, DURING THE TERM, AND ALSO WHEN AND AS SOON AS THE TERM, AS SAME MAY HAVE BEEN EXTENDED FROM TIME TO TIME, HEREBY CREATED SHALL HAVE EXPIRED OR BE TERMINATED, IT SHALL BE LAWFUL FOR ANY ATTORNEY, AS ATTORNEY FOR TENANT TO CONFESS JUDGMENT IN EJECTMENT IN ANY COMPETENT COURT AGAINST TENANT AND ALL PERSONS CLAIMING UNDER TENANT FOR THE RECOVERY BY LANDLORD OF POSSESSION OF THE LEASED PREMISES, WITHOUT ANY LIABILITY ON THE PART OF THE SAID ATTORNEY, FOR WHICH THIS LEASE SHALL BE A SUFFICIENT WARRANT; WHEREUPON, IF LANDLORD SO DESIRES, A WRIT OF POSSESSION WITH CLAUSES FOR COSTS MAY ISSUE FORTHWITH WITH OR WITHOUT ANY PRIOR WRIT OR PROCEEDING WHATSOEVER. IF FOR ANY REASON AFTER SUCH ACTION HAS BEEN COMMENCED, THE SAME SHALL BE DETERMINED AND THE POSSESSION OF THE LEASED PREMISES REMAINS IN OR IS RESTORED TO TENANT, THE LANDLORD SHALL HAVE THE RIGHT IN THE EVENT OF ANY SUBSEQUENT DEFAULT OR DEFAULTS TO CONFESS JUDGMENT IN EJECTMENT AGAINST TENANT IN THE MANNER AND FORM HEREINBEFORE SET FORTH, TO RECOVER POSSESSION OF THE LEASED PREMISES FOR SUCH SUBSEQUENT DEFAULT, NO SUCH DETERMINATION OF THIS LEASE NOR RECOVERING POSSESSION OF THE LEASED PREMISES SHALL DEPRIVE LANDLORD OF ANY REMEDIES OR ACTION AGAINST TENANT FOR RENT OR FOR DAMAGES DUE OR TO BECOME DUE FOR THE BREACH OF ANY CONDITION OR COVENANT; NOR THE RESORT TO ANY WAIVER OF THE RIGHT TO INSIST UPON THE FORFEITURE, AND TO OBTAIN POSSESSION IN THE MANNER PROVIDED HEREIN.

(ii) AFFIDAVIT OF DEFAULT. In any action to confess judgment in ejectment, Landlord shall first cause to be filed in such action an affidavit made by Landlord or someone acting for Landlord setting forth the facts necessary to authorize the entry of judgment, of which facts such affidavit shall be conclusive evidence and if a true copy of the Lease (and of the truth of the copy such affidavit shall be sufficient evidence) be filed in such action, it shall not be necessary to file the original as a warrant of attorney, any rule of Court, custom or practice to the contrary notwithstanding.

(iii) TENANT WAIVER. TENANT SPECIFICALLY ACKNOWLEDGES THAT TENANT HAS KNOWINGLY, INTENTIONALLY, VOLUNTARILY AND IRREVOCABLY WAIVED CERTAIN DUE PROCESS RIGHTS TO A PREJUDGMENT HEARING RELATING SOLELY TO THE POSSESSION OF THE LEASED PREMSIES BY AGREEING TO THE TERMS OF THIS PARAGRAPH REGARDING CONFESSION OF JUDGMENT, TENANT FURTHER SPECIFICALLY AGREES THAT IN THE EVENT OF DEFAULT, LANDLORD MAY PURSUE MULTIPLE REMEDIES INCLUDING OBTAINING POSSESSION OF THE LEASED PREMISES PURSUANT TO A JUDGMENT BY CONFESSION AND ALSO OBTAINING A MONEY JUDGMENT FOR PAST DUE AND ACCELERATED AMOUNTS AND EXECUTING UPON SUCH JUDGMENT. FURTHERMORE, TENANT SPECIFICALLY WAIVES ANY CLAIM AGAINST LANDLORD AND LANDLORD'S COUNSEL FOR VIOLATION OF TENANT'S CONSTITUTIONAL RIGHTS IN THE EVENT THAT JUDGMENT IS CONFESSED PURSUANT TO THIS PARAGRAPH.

(iv) In view of the commercial nature of the relationship between the parties hereto and the fact that the parties hereto may have adverse interests, the parties agree that there is no expectation that Landlord shall have any duty under any provision of Chapter 56 of the Pennsylvania Decedents, Estates and Fiduciaries Code (20 Pa. C.S.A. § 5601, et seq.) (including, without limitation, 20 Pa. C.S.A. § 5601.3(a)(1)) to act in the best interest of Tenant hereunder, and it is agreed that Landlord shall have no such duty. Further, Landlord and Tenant hereby agree that all duties owed by an agent as specified under 20 Pa.C.S.A. § 5601.3(b) (as the term "agent" is used therein) are irrevocably waived.

4. This Amendment #4 shall be governed by and construed in accordance with the laws of the Commonwealth of Pennsylvania.

5. This Amendment #4 can be executed in any number of counterparts, each of which shall be deemed an original.

6. To the extent there are any conflicts or inconsistencies between the Lease, Amendment #1, Amendment #2, Amendment #3 and this Amendment #4, this Amendment #4 and the rights and obligations herein shall govern. All other terms and provisions of the previous agreements between the parties shall remain unaffected by this Amendment #4.

IN WITNESS WHEREOF, the Landlord and Tenant hereto have executed this Amendment #4 as of the date first written above.

LANDLORD:

WITNESS

Provco Devon, L.L.C.

_____

By: /s/ Kent Silvers
Its: Vice President

TENANT:

WITNESS

Zynerba Pharmaceuticals, Inc.

_____

By: /s/ James E. Fickenscher
Its: Chief Financial Officer

COMMONWEALTH OF PENNSYLVANIA
COUNTY OF CHESTER

On this the 1st day of March, 2021, before me, a Notary Public in and for the Commonwealth of Pennsylvania, the undersigned officer, personally appeared James E. Fickenscher who acknowledged himself to be the CFO of Zynerba Pharmaceuticals, Inc., and who, being authorized to do so, executed the foregoing instrument for the purposes therein contained, by signing their names thereto.

IN WITNESS WHEREOF, I hereunto set my hand and official seal.

[SEAL]

/s/ Patricia LePera
Notary Public

Exhibit 21.1

Subsidiaries of Zynerba Pharmaceuticals, Inc.

Subsidiary	Jurisdiction of Incorporation
Zynerba Pharmaceuticals Pty Ltd	Australia

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

The Board of Directors
Zynerba Pharmaceuticals, Inc.:

We consent to the incorporation by reference in the registration statements on Form S-3 (Nos. 333-233038, 333-218638, and 333-213430) and Form S-8 (Nos. 333-237051, 333-230182, 333-223597, 333-216968, 333-216967, and 333-207973) of Zynerba Pharmaceuticals, Inc. of our report dated March 10, 2021, with respect to the consolidated balance sheets of Zynerba Pharmaceuticals, Inc. and subsidiary as of December 31, 2020 and 2019, the related consolidated statements of operations, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2020, and the related notes, which report appears in the December 31, 2020 annual report on Form 10-K of Zynerba Pharmaceuticals, Inc.

/s/ KPMG LLP

Philadelphia, Pennsylvania
March 10, 2021

Exhibit 31.1

CERTIFICATION

I, Armando Anido, certify that:

1. I have reviewed this annual report on Form 10-K of Zynerba Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

By: /s/ Armando Anido
Name: Armando Anido
Title: Chairman and Chief Executive Officer

Dated: March 10, 2021

Exhibit 31.2

CERTIFICATION

I, James E. Fickenscher, certify that:

1. I have reviewed this annual report on Form 10-K of Zynerba Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

By: /s/ James E. Fickenscher
Name: James E. Fickenscher
Title: Chief Financial Officer and Treasurer

Dated: March 10, 2021

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Zynerba Pharmaceuticals, Inc. (the "Company") on Form 10-K for the fiscal year ended December 31, 2020 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Armando Anido, Chairman and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Armando Anido
Armando Anido
Chairman and Chief Executive Officer

Dated: March 10, 2021

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Zynerba Pharmaceuticals, Inc. (the "Company") on Form 10-K for the fiscal year ended December 31, 2020 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, James E. Fickenscher, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ James E. Fickenscher
James E. Fickenscher
Chief Financial Officer

Dated: March 10, 2021