**UNITED STATES**
**SECURITIES AND EXCHANGE COMMISSION**
**Washington, D.C. 20549**

# FORM 10-K

(Mark One)
**[X] ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2019.
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 requirement 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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 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 $305.6 million, based upon the closing price on the NASDAQ Global Market reported for June 28, 2019. 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 4, 2020, the registrant had 23,556,181 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 2020 annual meeting of stockholders to be filed no later than 120 days after the end of the registrant's fiscal year ended December 31, 2019.

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## 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, tax credits 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 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 medical affairs and 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; and

- 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.

In light of these risks and uncertainties, expected results or other anticipated events or circumstances discussed in this Report (including the exhibits hereto) might not occur. 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.

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. Other unknown or unpredictable factors also could harm our results. 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.

# 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.

We are currently evaluating Zygel™, a patent-protected transdermal cannabidiol, or CBD, gel for the treatment of FXS, DEE, ASD and 22q. In 2017, we announced results for three Phase 2 clinical trials for Zygel. In April 2018, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with DEE. In September 2019, we completed the first six months of dosing for that study and announced positive top-line results. In July 2018, we initiated what we believe will be a pivotal clinical trial evaluating Zygel in children and adolescent patients with FXS. In the first quarter of 2020, we announced that 212 patients with FXS have been randomized into the trial and enrollment is now complete. We expect to report top-line results late in the second quarter of 2020. In March 2019, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with ASD and completed enrollment in that trial in January 2020. In May 2019, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with 22q. We expect to report top line results for the ASD clinical trial in the second quarter of 2020 and the 22q clinical trial results are now expected in the third quarter of 2020.

Cannabinoids are a class of compounds derived from *Cannabis* plants. The two primary cannabinoids are CBD and Δ9-tetrahydrocannabinol, or THC. CBD is the primary non-euphoric component of *Cannabis*. Clinical and preclinical data suggest that CBD has positive effects on treating behavioral symptoms of FXS, ASD, 22q and seizures in patients with epilepsy.

Zygel is the first and only pharmaceutically-produced CBD formulated as a permeation-enhanced gel for transdermal delivery, and the formulation is patent protected through 2030. Four additional patents are directed to methods of use relating to Zygel, including methods of treating FXS and ASD, and will expire in 2038. In preclinical animal studies, Zygel’s permeation enhancer increased delivery of CBD 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 CBD when delivered transdermally. In addition, an *in vitro* study published in *Cannabis and Cannabinoid Research* in April 2016 demonstrated that CBD 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 CBD is delivered orally and may be avoided with the transdermal delivery of Zygel, which maintains CBD in a neutral pH. Zygel, which is being developed as a clear gel with once- or twice-daily dosing, is targeting treatment of behavioral symptoms of FXS, ASD and 22q and reductions in seizures in patients with DEE. We have been granted orphan drug designation from the FDA for the use of CBD for the treatment of FXS. 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.

In our Phase 1 program, Zygel was demonstrated to be safe and well tolerated, provided a favorable CBD pharmacokinetic profile, and no THC was detected in plasma or urine. As of March 2020, the Zygel safety database across all clinical studies conducted by us includes data from 623 volunteers and patients. Across these clinical studies, Zygel has been well tolerated and consistent with previously reported data.

In April 2018, we initiated the exploratory Phase 2 BELIEVE 1 (Open Label Study to Assess the Safety and Efficacy of Zygel Administered as a Transdermal Gel to Children and Adolescents with Developmental and Epileptic 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 (age three to 17 years) with DEE as classified by the International League Against Epilepsy, or ILAE (Scheffer et al. 2017). Forty-eight patients with confirmed DEE were dosed in this clinical trial. Patients received weight-based initial doses of 250 mg or 500 mg daily and during the maintenance phase patients received up to 1000 mg daily of Zygel. In September 2019, we reported positive top-line results from the BELIEVE 1 trial.

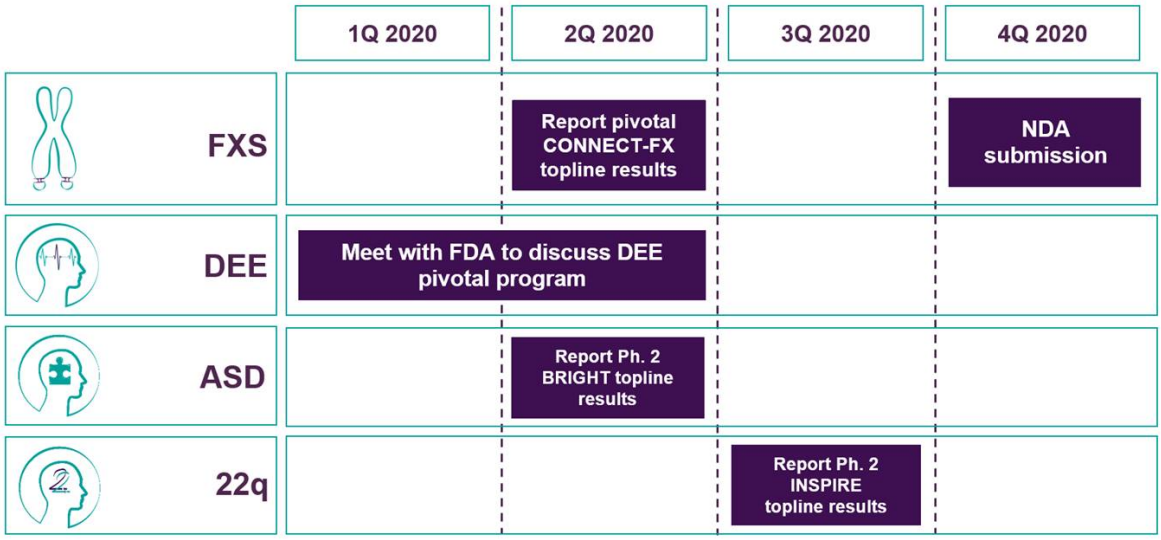
In July 2018, we initiated the pivotal CONNECT-FX (Clinical study of Cannabidiol (CBD) in Children and Adolescents with Fragile X) clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study that will assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the FMR1 gene. In the first quarter of 2020, we announced that 212 patients with FXS have been enrolled at 21 clinical sites in the United States, Australia and New Zealand and enrollment is now complete. The study is being conducted in the United States under an Investigational New Drug, or IND, application opened with the FDA. Patients have been randomized 1:1 to either trial drug or placebo. Randomization was stratified by gender, weight and investigator geographic region. Enrolled patients will receive weight-based doses of 250 mg or 500 mg daily. The primary endpoint is the change from baseline to the end of the treatment period in the Aberrant Behavior Checklist-Community: FXS Specific, or ABC-$C_{FXS,}$ Social Avoidance subscale. Key secondary endpoints are the change from baseline to the end of the treatment period in the ABC-$C_{FXS}$ Irritability subscale score, the ABC-$C_{FXS}$ Socially Unresponsive/Lethargic subscale score and Clinical Global Impression – Improvement, or CGI-I, at the end of the treatment period. Based on discussions with the FDA, we will anchor the CGI-I scale to behavioral symptoms of FXS. Consistent with recent guidance from the FDA on capturing the voice of the patient in drug development, additional qualitative data on the clinical relevance of various FXS behaviors to caregivers and patients will be collected. If we obtain positive results from this trial, we plan to request a meeting with the FDA to determine the acceptability of these data as the basis for an NDA filing. We expect to report top line results from the CONNECT-FX trial late in the second quarter of 2020.

In March 2019, we initiated 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 14-week trial is designed to evaluate the efficacy and safety of Zygel in 37 children and adolescents (ages four through 17) with ASD as confirmed by DSM-5 diagnostic criteria for ASD. The efficacy assessments include the Aberrant Behavior Checklist, or ABC, Parent Rated Anxiety Scale — Autism Spectrum Disorder, Autism Impact Measure, and Clinical Global Impression — Severity and Improvement. Enrollment in this study is complete and we expect to report top line results in the second quarter of 2020. Patients who successfully conclude the 14-week clinical trial are eligible to enroll in a six-month extension study.

In May 2019, we initiated the open-label Phase 2 INSPIRE (Assessing the Impact of Zygel [Transdermal CBD 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 (age six to 17 years). Top line results from this study are now expected in the third quarter of 2020.

***Zygel Clinical Development Timelines***

Our key development programs and expected timelines for the development of Zygel are shown in the chart below:




**CBD Science Overview**

CBD produces multiple effects: CBD is an agonist of the serotonin receptor, or 5-HT1A, a modulator of the cannabinoid receptor system in the human body, or endocannabinoid system, a positive allosteric modulator of GABA-A receptors, a modulator of α3 and α1 glycine receptors, an antagonist of G protein-coupled receptor 55, or GPR-55, a modulator of the equilibrative nucleoside transporter, and regulates the intracellular effects of calcium.

CBD modulates the endocannabinoid system by inhibiting the metabolism (breakdown) of 2-arachidonoylglycerol, 2-AG, and anandamide. This inhibition is thought to result in increased anandamide and 2-AG availability, greater CB1 and CB2 activation, and increased synaptic plasticity. The effect of CBD on the endocannabinoid system is the scientific basis for the use of CBD in the treatment of FXS, ASD and 22q.

CBD 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 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 CBD.

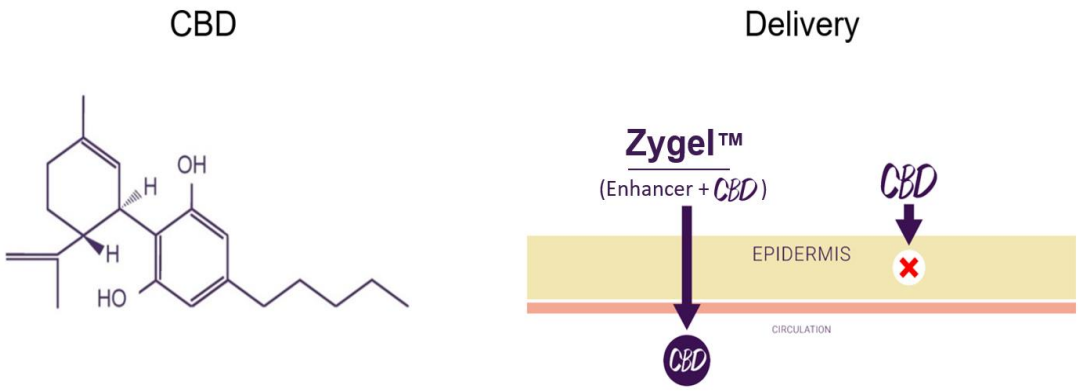
Clinical and preclinical data suggest that CBD has positive effects on treating FXS, ASD and epilepsy. Patients with FXS, ASD and epilepsy share several of the same behavioral symptoms, which may be treatable with CBD. Clinical data also suggest that CBD has a very high therapeutic index. Interest in 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 CBD was approved by the FDA in 2018 for the treatment of two specific epilepsies, Lennox-Gastaut Syndrome, or LGS, and, Dravet Syndrome, or DS. The cannabinoid therapeutics market is expected to grow significantly due to the potential benefits these products may provide over existing therapies.

**Product Candidates**

**Zygel – CBD Transdermal Gel**

Zygel is the first and only pharmaceutically-produced CBD 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 CBD.***




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 CBD 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 CBD through the layers of the skin and into the circulatory system.

Transdermal delivery allows the CBD 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 Zygel may provide an effective treatment for FXS based on its capacity to interact with the endocannabinoid system, which is compromised in patients with FXS. Specifically, CBD modulates the endocannabinoid system by

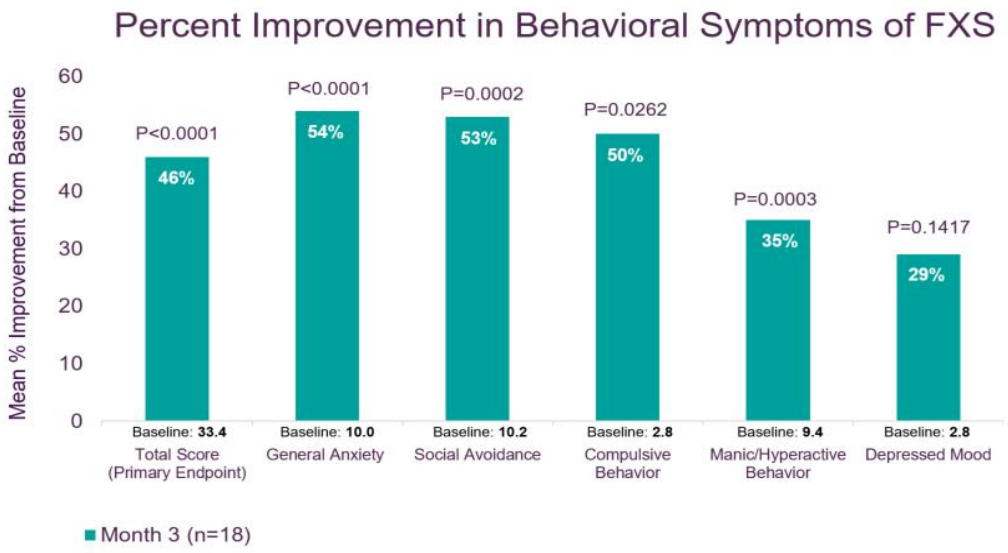
inhibiting the metabolism (breakdown) of 2-AG and anandamide. This inhibition is thought to result in increased anandamide and 2-AG availability, greater $CB_1$ and $CB_2$ activation, and increased synaptic plasticity. This modulation is the scientific basis for the use of CBD in the treatment of FXS. We anticipate Zygel may be used as first line therapy to treat patients suffering from behavioral symptoms of FXS.

*Phase 2 Clinical Trials*

In September 2017, we released 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) aged 6 to 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.

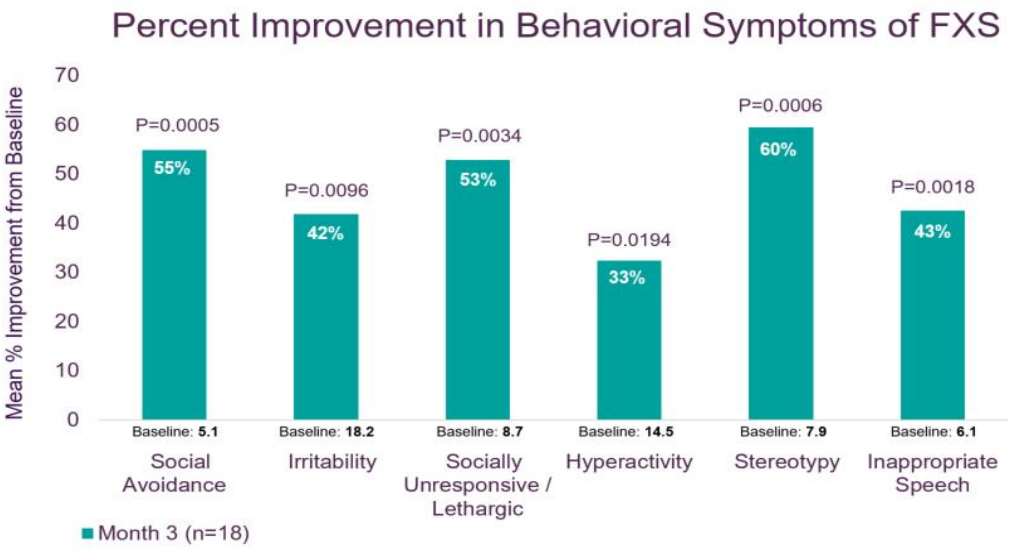
The FAB-C trial successfully met its primary endpoint, achieving a 46% improvement ($p<0.0001$) in the total score of ADAMS at week 12 compared to baseline.

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:

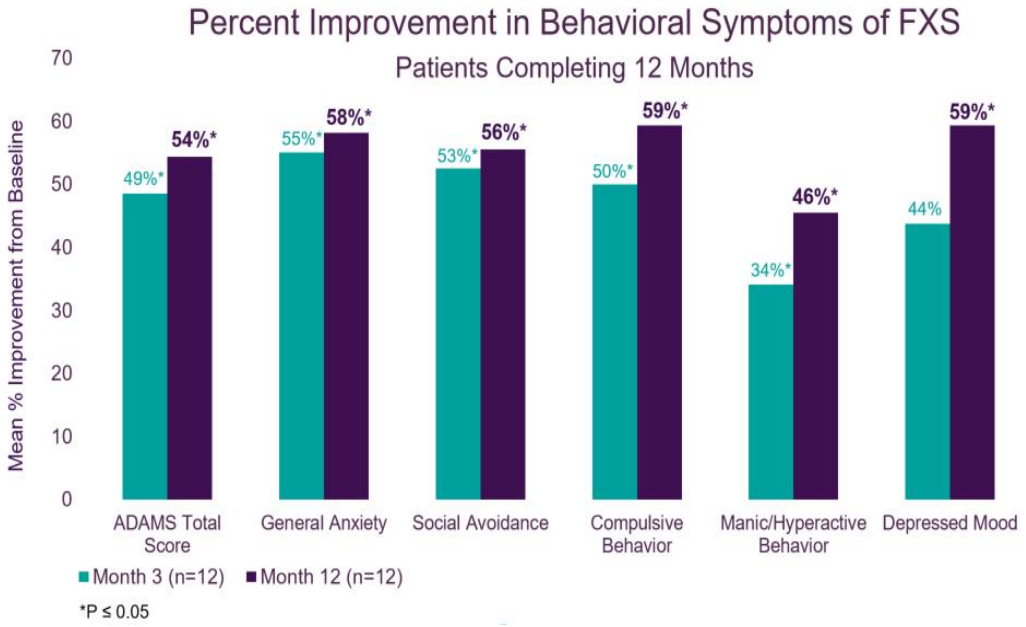


We evaluated multiple other secondary endpoints including a Clinical Global Impression of Improvement, or CGI-I, the Pediatric Anxiety Rating Scale, or PARS-R, Visual Analog Scales for Anxiety, Hyperactivity and Tantrum/Mood Lability, the Vineland Adaptive Behavior III, a Quality of Sleep measurement 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.

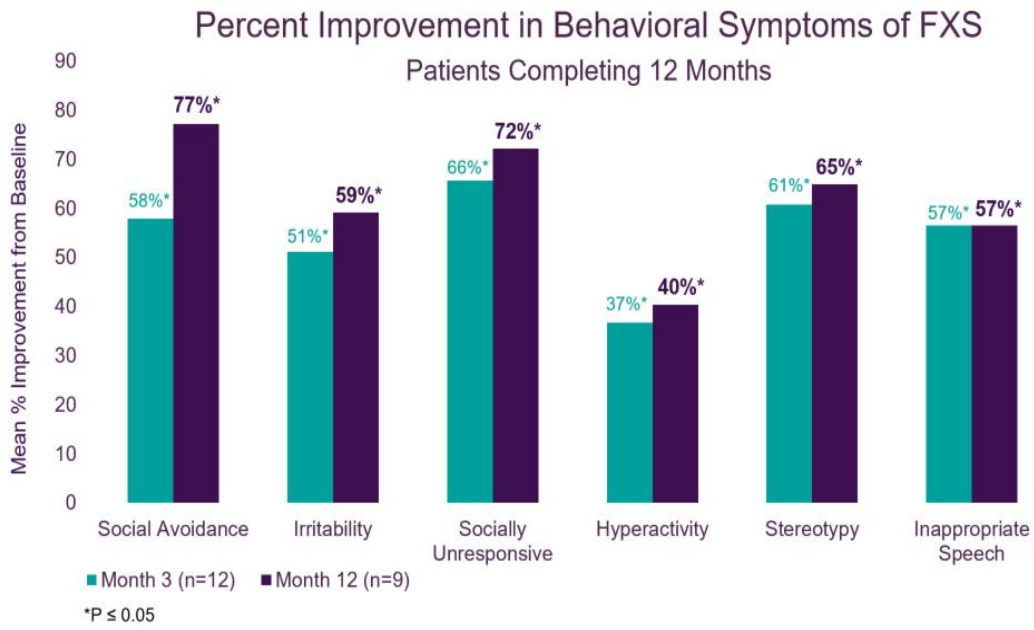
Zygel was shown to be very well tolerated, and the safety profile was consistent with data from earlier clinical trials and our other Phase 2 clinical trials for Zygel. All adverse events were considered mild to moderate and no serious adverse events were reported. No patient experienced drug-related GI events during the 12-week treatment period, and no THC was detected in the plasma. Thirteen of the 18 patients who completed the study have enrolled in the open-label extension and 10 patients are still being treated with Zygel as of March 9, 2020.

In December 2018, we presented new 12-month open label clinical data from the FAB-C trial describing the long-term impact of Zygel on emotional and behavioral symptoms of FXS in a poster presentation at the 57th Annual Meeting of the American College of Neuropsychopharmacology, or ACNP. The statistically significant improvements in the core emotional and behavioral symptoms of FXS versus baseline as measured by the ADAMS and the ABC-$C_{FXS}$ were sustained through 12 months of treatment. In the Social Avoidance subscale of the ABC-$C_{FXS}$, patients completing 12 months of treatment with Zygel experienced a 77% 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. The Social Avoidance subscale of the ABC-$C_{FXS}$ is the primary endpoint of the ongoing pivotal CONNECT-FX study of Zygel. 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 for the ADAMS at 12 months are summarized as follows:



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




In March 2018, we announced the results of a positive meeting held with the FDA regarding our planned development strategy for Zygel in FXS. Based on our dialogue with the FDA, we initiated what we believe will be a single pivotal study mid-year 2018 to support an NDA for Zygel in FXS. We are in agreement with the FDA that the primary and key secondary endpoints for the study should assess observable behaviors in patients with FXS as reported by the caregiver using the validated ABC-$C_{FXS}$. If the pivotal trial meets its endpoints, approval for an indication encompassing the treatment of behavioral symptoms associated with FXS may be granted.

In July 2018, we initiated the pivotal CONNECT-FX (**C**linical study **o**f C**ann**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 that will 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 the first quarter of 2020, we announced that 212 patients with FXS have been enrolled at 21 clinical sites in the United States, Australia and New Zealand and enrollment is now complete.. The study is being conducted in the United States under an IND application opened with the FDA. Patients have been randomized 1:1 to either trial drug or placebo. Randomization was stratified by gender, weight and investigator geographic region. Enrolled patients will receive weight-based doses of 250 mg or 500 mg daily. The primary endpoint is the change from baseline to the end of the treatment period in the ABC-$C_{FXS}$ Social Avoidance subscale. Key secondary endpoints are the change from baseline to the end of the treatment period in the ABC-$C_{FXS}$ Irritability subscale score and the ABC-$C_{FXS}$ Socially Unresponsive/Lethargic subscale score, and CGI-I at the end of the treatment period. Based on discussions with the FDA, we will anchor the CGI-I scale to behavioral symptoms of FXS. Consistent with recent guidance from the FDA on capturing the voice of the patient in drug development, additional qualitative data on the clinical relevance of various FXS behaviors to caregivers and patients will be collected.

As intended and prospectively designed, the trial has enrolled a more severely affected population than that enrolled in the previously completed Phase 2 FAB-C trial as measured by baseline behavioral symptoms, enabling the study to potentially demonstrate the anticipated full range of efficacy of Zygel in several behavioral domains. The ABC-$C_{FXS}$ mean baseline scores for patients randomized in the CONNECT FX trial in comparison to the FAB-C trial are as follows (higher baseline scores denote more severe behaviors):

- Social Avoidance subscale (primary endpoint): 7.2 in CONNECT-FX vs 5.1 in FAB-C;
- Irritability subscale (key secondary endpoint): 28.1 in CONNECT-FX vs 18.2 in FAB-C;
- Socially Unresponsive/Lethargic subscale (key secondary endpoint): 13.2 in CONNECT-FX vs 8.7 in FAB-C;
- Hyperactivity subscale: 18.4 in CONNECT-FX vs 14.5 in FAB-C;
- Stereotypy subscale: 9.4 in CONNECT-FX vs 7.9 in FAB-C; and
- Inappropriate Speech subscale: 6.9 in CONNECT-FX vs 6.1 in FAB-C.

During screening, caregivers of patients in the trial were informed that their participating child may have the opportunity to receive Zygel in an open label extension trial following the child's compliant completion of CONNECT-FX, regardless of their child's perceived response or actual blinded drug assignment in CONNECT-FX. As of March 9, 2020, 97% of the 163 patients who have completed the CONNECT-FX trial have enrolled in the open label extension trial.

Of the 212 patients randomized, 159 (75%) are male and the mean age in the study is 9.7 years.

We expect to disclose top line results of the trial late in the second quarter of 2020. If the results are positive, we expect to meet with the FDA to determine acceptability of the data as a basis for a New Drug Application, or NDA, for Zygel in FXS in the second half of 2020.

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

*DEE Overview*

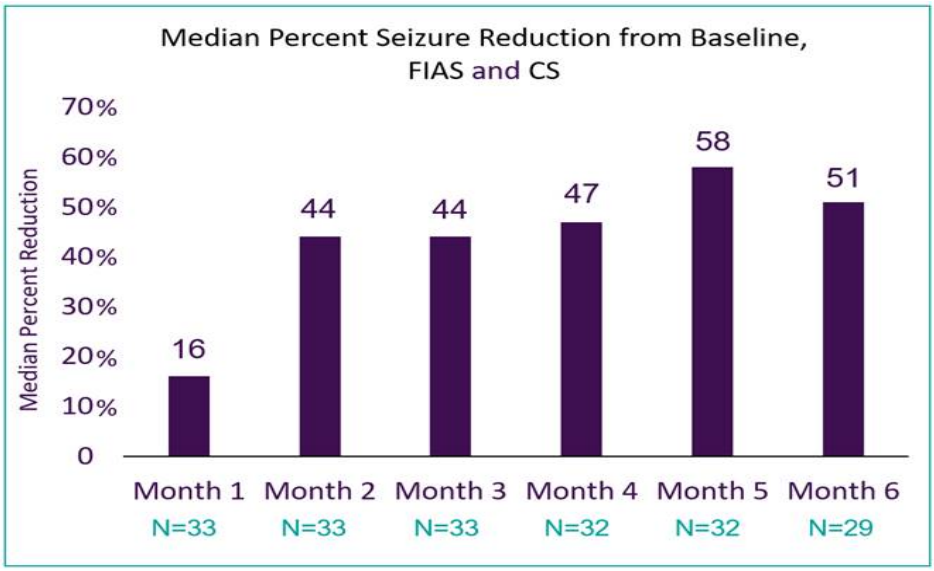
DEE is a category of rare and ultra-rare severe brain disorders that manifest with seizures or EEG abnormalities that are associated with delay or regression in cognition and/or behavior. This category includes a number of epilepsy syndromes, including DS, LGS, Doose, and Ohtahara (early infantile epileptic 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 CBD 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 CBD 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 CBD, in the United States only for the treatment of DS and LGS.

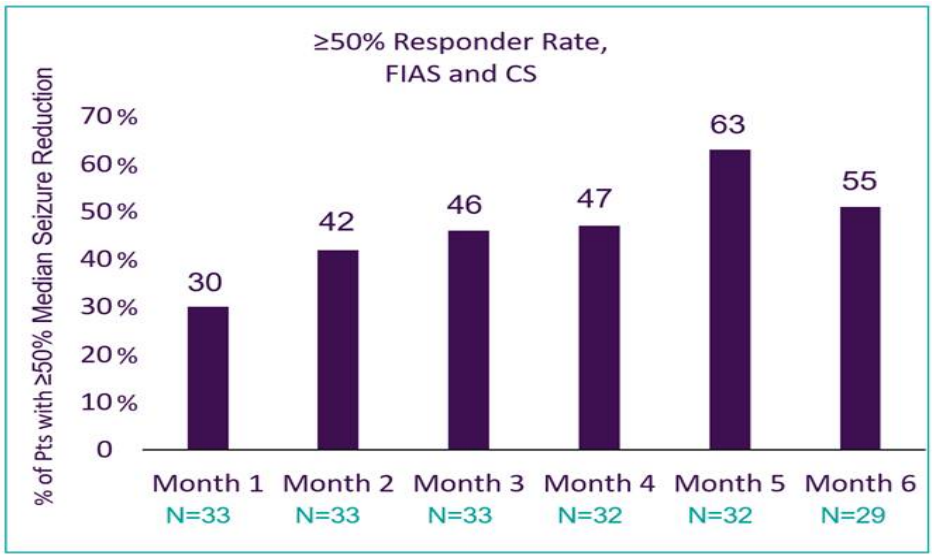
*Phase 2 Clinical Trial in Children and Adolescents with DEE*

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 (age three to 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 intent-to-treat population, or mITT. 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 convulsive seizures (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.




Fifty-five percent (55%) of patients with FIAS and/or convulsive seizures experienced a ≥50% median reduction in seizures at month six of treatment with Zygel.



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 SAE's 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).

We intend to meet with the FDA in the first half of 2020 to discuss the clinical path forward in DEE.

***Development of Zygel for Treatment of ASD***

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 CBD. Exogenous CBD may modulate the endocannabinoid system and improve certain autism-related behaviors.

In March 2019, we initiated the Phase 2 BRIGHT (An Open-La**b**el Tole**r**abi**l**ity and Efficacy Study of ZYN002 Administered as a Transdermal **G**el to C**h**ildren and Adolescen**t**s with Autism Spectrum Disorder) trial. The study will assess the safety, tolerability and efficacy of Zygel for the treatment of pediatric and adolescent patients with ASD. The 14-week trial is designed to evaluate the efficacy and safety of Zygel in children and adolescents (ages four through 17) with ASD as confirmed by DSM-5 diagnostic criteria for ASD. The efficacy assessments include the ABC, Parent Rated Anxiety Scale — Autism Spectrum Disorder, Autism Impact Measure, and Clinical Global Impression — Severity and Improvement. In January 2020, we completed enrollment in the BRIGHT clinical trial. Using the Autism Diagnostic Observation Schedule (ADOS-2) which is administered at baseline by a qualified clinician, 94% of the 37 enrolled patients had moderate-to-severe symptoms of ASD at baseline. The mean baseline ABC-C Irritability subscale score of 30.0 further supports the severity of the enrolled patient population. Thirty-four (92%) are male. The mean age of these patients is 9.2 years. We expect to report top line results from this study in the second quarter of 2020.

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

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.

CBD 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.

In May 2019, we initiated the open-label Phase 2 INSPIRE (Assessing the Impact of Zygel [Transdermal CBD Gel] on Pediatric Behavioral and Emotional Symptoms of 22q11.2 Deletion Syndrome) 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 in approximately 20 children and adolescents (ages six through 17) with genetically-confirmed 22q. The efficacy assessments include the Aberrant Behavior Checklist-Community, or ABC-C, ADAMS, the Qualitative Caregiver Reported Behavioral Problem Survey and Clinical Global Impression — Severity and Improvement. We now expect to report top line results in the third quarter of 2020.

***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 CBD 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. CBD 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 CBD PK profile, and no THC was detected in plasma or urine.

Prior to December 2018, we were also evaluating Zygel in a Phase 2 program in adult patients with refractory epileptic focal seizures (formerly known as complex partial seizures). In December 2018, we announced that we postponed the initiation of additional studies in adult refractory focal seizures until after reporting data from the four childhood neuropsychiatric studies (FXS, DEE, ASD and 22q).

**ZYN001**

Our pipeline includes ZYN001, a pro-drug of THC. In July 2018, we decided to pause the development of ZYN001 and focus our development efforts and investments on our development programs for Zygel.

**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 4, 2020, we owned a total of fourteen issued U.S. utility 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 applications.

***Zygel***

Our Zygel patent portfolio currently consists of six issued patents in the United States, and six pending United States patent applications. There are seven issued patents in Canada, France, Germany, Ireland, Japan, Switzerland, and the United Kingdom, and four 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 a contract manufacturer.

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 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 studying Zygel in pediatric and adolescent patients with FXS, DEE, ASD and 22q.

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 and other patients who experience general anxiety, social anxiety and other chronic conditions may benefit from different types of anti-anxiety medications. We are aware that Neuren Pharmaceuticals, Confluence Pharmaceuticals, Ovid Therapeutics and Tetra Discovery Partners among others are developing compounds for the treatment of FXS.

Within epilepsy, we intend to treat pediatric and adolescent 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 has received approval from the FDA to market Epidiolex, a sesame oil liquid formulation of highly concentrated plant extracted CBD, in the United States for the treatment of DS and LGS and has also received marketing authorization from the European Medicines Agency or EMA to market Epidiolex (under the trade name *Epidyolex®)* for use as adjunctive therapy of seizures associated with DS and LGS, in conjunction with clobazam. GW is also studying Epidiolex in patients with Tuberous Sclerosis Complex and Rett Syndrome and is studying additional cannabinoids, including cannabidivarin, or CBDV, for adult patients with focal seizures, autism spectrum disorders and Rett Syndrome. Chilion Group Holdings US, Inc., or Chilion, has acquired Insys Therapeutics, Inc., or Insys, CBD and THC formulations. Insys was developing a synthetic CBD oral solution compound for the potential treatment of childhood absence epilepsy, infantile spasms and Prader-Willi syndrome.

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 are aware that GW is studying CBDV for use in patients with ASD. Chilion, through their acquisition of Insys's CBD formulations may also be considering CBD for use in ASD.

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 CBD, THC or any other cannabinoid in this patient population.

We are also aware of other companies that are working on non-cannabinoid treatments for indications similar to those with Zygel, including Confluence Pharmaceuticals with acamprosate for FXS; Tetra Discovery Partners 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 and TAK-935/OV935, a Cholesterol 24S-hydroxylase Inhibitor, for DEE; Marinus Pharmaceuticals with ganaxolone for pediatric refractory epilepsies; Zogenix with fenfluramine hydrochloride (ZX-008) for LGS and DS; Roche with RO5285119 for ASD; and Janssen with JNJ-42165279 for ASD, among others.

**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 EMA and the European Commission 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 CBD 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 a 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 DEA prior to commercialization. This step is required if the drug has a potential for abuse and is not currently controlled (scheduled) by 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. In advance of commencing our CONNECT FX pivotal trial at sites in the United States, we received the required approval from the DEA.

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 completed several Phase 1 and Phase 2 clinical trials and have three ongoing Phase 2 clinical trials for Zygel in Australia and New Zealand. We also have one ongoing pivotal clinical trial for Zygel in Australia, New Zealand and the United States.

In Australia, the approval process for commencing Phase 1 and 2 clinical trials resides with the Human Research Ethics Committee, or HREC. Prior to commencing a clinical trial, a sponsor must submit to the HREC a study protocol, an investigator brochure and a template informed consent for such clinical trial. The HREC approval process generally takes four to eight weeks.

Once a study is approved by the HREC, a Clinical Trial Notification, or CTN, is submitted to the Australian Government Department of Health, Therapeutic Goods Administration, or TGA. The CTN is a notification that the HREC has approved the safety, efficacy and ethical acceptability of the trial, approved the trial protocol and evaluated the scientific merit of the trial. The TGA sends the clinical trial site a written acknowledgement of the clinical trial, allowing the clinical trial to begin. TGA response time to acknowledge a clinical trial is approximately two weeks from receipt of the CTN from the clinical trial site.

***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 exceeding $2,942,000 for fiscal year 2020. The applicant under an approved new drug application is also subject to an annual program fee, currently exceeding $325,000 per product for fiscal year 2020. 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. The FDA will initially review the NDA for completeness before it accepts the NDA for filing. The FDA has 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 will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with 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 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 CBD 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 CBD. Absent guidance to the contrary from 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 manufactures in the United States and Canada to manufacture the API for Zygel and contract manufactures in the United Kingdom and Australia to manufacture the drug product for our clinical trials. We are conducting a pivotal clinical trial 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 28 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

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 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 January 20, 2017, the President signed an executive order directing federal agencies to exercise existing authorities to reduce burdens associated with the Affordable Care Act pending further action by Congress. In April 2018, the Centers for Medicare & Medicaid Services, or CMS, issued a final rule and guidance documents which changed requirements for health plans sold through the Affordable Care Act marketplaces for 2019. These changes include, for example, (i) turning over responsibility for ensuring that marketplace plans have enough health care providers in their networks to the states that rely on the federal HealthCare.gov exchange; (ii) allowing states to alter aspects of the essential health benefits required of health plans sold through the federal and state insurance marketplaces; (iii) eliminating certain Small Business Health Options Program, or SHOP, regulatory requirements; and (iv) outlining criteria by which insurers may reduce the percentage of income allocated to patient care. The U.S. Department of Labor issued a final rule in June 2018 to expand the availability of association health plans available to small business owners and self-employed individuals, beginning on September 1, 2018. These association health plans will not be required to provide the essential health benefits mandated by the Affordable Care Act. These and other regulations may impact coverage of certain health care services.

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.

***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, effective January 1, 2021, 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 the United Kingdom, 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.

**Employees**

As of March 4, 2020, we had 28 full-time employees. In addition to our full-time employees, we contract with third-parties for the conduct of certain preclinical, manufacturing, accounting and administrative activities. We have no collective bargaining agreements with our employees and none are represented by labor unions.

**Implications of Being an Emerging Growth Company**

We are an “emerging growth company,” as defined in Section 2(a) of the Securities Act of 1933, as amended, or the Securities Act, as modified by the Jumpstart Our Business Startups Act of 2012, or JOBS Act. For as long as we remain an “emerging growth company”, we may take advantage of certain exemptions from various disclosure and reporting

requirements that are applicable to other public companies that are not “emerging growth companies” including, but not limited to:

- an exemption from the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act of 2002;
- reduced disclosure obligations regarding executive compensation, including no Compensation Disclosure and Analysis;
- an exemption from any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements; and
- an exemption from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We will remain an “emerging growth company” until the earliest of (1) December 31, 2020, and (2) the date on which we have , during the previous three-year period, issued more than $1.0 billion in non-convertible debt securities.

We have elected to take advantage of certain of the reduced disclosure obligations in this Report and may elect to take advantage of other reduced reporting requirements in future filings. As a result, the information that we provide to our stockholders may be different than you might receive from other public reporting companies in which you hold equity interests.

The JOBS Act provides that an “emerging growth company” can take advantage of an extended transition period for complying with new or revised accounting standards. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we are subject to the same new or revised accounting standards as other public companies that are not “emerging growth companies.”

**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

*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 specialty 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, 2019, 2018 and 2017 were approximately $32.9 million, $39.9 million and $32.0 million, respectively. As of December 31, 2019, we had an accumulated deficit of $150.8 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, 2019, we had approximately $70.1 million in cash and cash equivalents. We believe that current cash and cash equivalents and the proceeds anticipated from the AOF (as defined below) are sufficient to fund operations and capital requirements beyond the expected NDA submission and potential approval of Zygel for the treatment of FXS and into the second half of 2021. 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 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 concession 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. In June 2018, the Australian Federal Government proposed certain changes to the Research and Development Tax Incentive program which may reduce the amount of cash refunds our Australian subsidiary receives under the program. In

February 2019, an Australian senate committee placed these proposals on hold, effectively deferring any decision until after the May 2019 Australian federal elections. In December 2019, these proposals were reintroduced with proposed changes, including, among others, a higher research and development spending threshold, fixing of the rate of the refundable R&D tax offset to 13.5% and a cap on refunds at A$4 million a year.

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. However, 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.

In addition, in July 2019, the Australian government’s Department of Industry, Innovation and Science, or AusIndustry, responded to an Advance Overseas Finding, or AOF, application submitted by us to allow certain research and development expenses incurred with respect to Zygel outside of Australia to be eligible for the Australian research and development tax incentive program. As a result of this finding, we are eligible to receive a cash refund from the Australian Taxation Office for the qualifying research and development costs expended outside of Australia in 2018, 2019 and 2020, which we estimate will be approximately $8.3 million. The AOF determination is binding on the Australian Tax Office with respect to the eligibility of the activities, but not the eligibility of particular expenditures. While we expect that the Australian Tax Office will approve our reimbursed expenditures for refund, there can be no assurance that all expenditures will be approved for refund.

***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, 2019, we had U.S. net operating loss, or NOL, carryforwards of approximately $96.0 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, 2019, 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 have no marketed products. We have reported top line results from four Phase 2 clinical trials with Zygel and Zygel is currently being evaluated in one ongoing pivotal clinical trial and an open label extension of that pivotal trial and three ongoing Phase 2 clinical trials. 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. 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 clinical trials of Zygel for the treatment of behavioral 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 undo reliance on early data.

***Even if Zygel advances through pre-clinical studies and clinical trials, 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 28 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 pre-clinical studies and clinical trials, we will need to expand our development, regulatory 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;
- 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 could be identified in our ongoing toxicology studies;
- 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. For example, based on our intention to concentrate our focus on rare and near-rare neuropsychiatric disorders, we have postponed development in adult refractory epileptic focal seizures. 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.

***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 four Phase 2 clinical trials, which were conducted in Australia and New Zealand. We also have two ongoing Phase 2 clinical trials in Australia and New Zealand and have initiated what we believe will be a pivotal clinical trial for FXS in Australia, New Zealand and the United States. We anticipate that we will conduct additional clinical trials for Zygel in countries outside the United States, including Australia and New Zealand, 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.

***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. The virus has now spread to several other countries, including the United States, and could materially and adversely impact our operations or those of our third party partners. 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 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, but 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, hemp containing THC levels greater than 0.3 percent remains a Schedule I illegal drug.

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 CBD as a pharmaceutical product, and any product containing CBD 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 CBD, for the treatment of seizures associated with Lennox-Gastaut and Dravet syndrome, for patients two years 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 CBD 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 CBD, 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 CBD and the DEA scheduled Epidiolex to Schedule V. 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 manufactures in the United States and Canada to manufacture the API for Zygel and contract manufactures in the United Kingdom and Australia to manufacture the drug product for our clinical trials. For Zygel, we have completed a Phase 1 clinical trial in the United States, have completed several Phase 1 and Phase 2 clinical trials in Australia and New Zealand and have three ongoing Phase 2 clinical trials in Australia and New Zealand. We also have one pivotal trial which is ongoing in Australia, New Zealand and the United States and we anticipate conducting additional clinical trials for Zygel in patients with FXS, DEE, ASD and 22q in the United States, Australia and New Zealand. 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 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 countries worldwide, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. 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.

***Healthcare legislation, including potentially unfavorable pricing regulations or other healthcare reform initiatives, may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates.***

In the United States there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities or affect our ability to profitably sell any product candidates for which we obtain marketing approval.

The Affordable Care Act, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug products. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on pharmaceutical and medical device manufacturers, and impose additional health policy reforms, any of which could negatively impact our business. The Affordable Care Act also closes the Medicare coverage gap for drugs, also known as the donut hole, by requiring pharmaceutical manufacturers to pay a higher percentage of drug costs for Medicare

patients while they are in the coverage gap. These payments were scheduled to increase each year up to 2020, when the amount beneficiaries would be expected to pay for prescriptions while they were in the gap was reduced to 25 percent of the cost. The two year budget deal signed into law in February 2018 by President Trump accelerated the closure by one year. Rather than accelerating the planned increase in insurers' liability, the legislation instead increases the required manufacturer discount from 50 percent to 70 percent indefinitely.

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 to Congress proposals in spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reduction to several government programs. This 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 legislation extended the 2% reduction, on average, to 2025.

We expect that 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, new payment methodologies 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 products. We expect continued significant focus on health care and drug pricing legislation through the November 2020 U.S. presidential election and beyond.

Finally, 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. Further legislative changes to and regulatory changes under the Affordable Care Act remain possible. It is unknown what form any such changes or any law proposed to replace the Affordable Care Act would take, and how or whether it may affect our business in the future.

***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 several recent U.S. Congressional inquiries and hearings with respect to pharmaceutical drug pricing practices, including in connection with the investigation of specific price increase by several pharmaceutical companies. Additionally, several states have recently 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 CBD for the treatment of FXS, 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.

***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, can 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.

***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 will 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 will result in a significant reduction in the cost of products to consumers. The Secretary of Health and Human Services has so far declined to approve a reimportation plan. Proponents of drug reimportation, including certain state legislatures, may attempt to pass legislation that would directly allow reimportation under certain circumstances. Legislation or regulations allowing the reimportation of drugs, if enacted, 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.

***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 achieving such amendments to the laws and regulations 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 CBD 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.

We are aware of multiple companies that are working in the Cannabis therapeutic area, including pharmaceutical companies such as GW, which markets Epidiolex in the United States (Epidyolex in the EU), a sesame oil liquid formulation of highly purified CBD extract, as a treatment for DS and LGS and which is also under investigation for Tuberous Sclerosis Complex and Rett Syndrome and Sativex, a botanical CBD/THC combination oral mucosal spray for the treatment of spasticity due to multiple sclerosis, which has already been approved in more than 25 foreign countries, and which is also in development in in schizophrenia and other neurological conditions; Chilion, which acquired rights to CBD and THC assets from Insys, including Syndros®, its dronabinol oral solution, which is a schedule II cannabinoid product, for anorexia associated with weight loss in patients with AIDS and chemotherapy-induced nausea and vomiting, or CINV, in patients with cancer whose response to conventional antiemetics is inadequate.Chilion, as part of their acquisition of Insys's CBD and THC assets, acquired an orally administered liquid formulation of its synthetic CBD compound as a potential treatment for childhood absence epilepsy, infantile spasms and Prader-Willi syndrome; along with several other companies in early stage discovery, preclinical and clinical development utilizing CBD, THC and/or other cannabinoids.

We are also aware of other companies that are working on non-cannabinoid treatments for indications similar to those with Zygel, including Confluence Pharmaceuticals with acamprosate for FXS; Tetra Discovery Partners 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 and TAK-935/OV935, a Cholesterol 24S-hydroxylase Inhibitor, for DEE; Marinus Pharmaceuticals with ganaxolone for pediatric refractory epilepsies; Zogenix with fenfluramine hydrochloride (ZX-008) for LGS and DS; Roche with RO5285119 for ASD; and Janssen with JNJ-42165279 for ASD, among others.

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.***

On October 23, 2019, a putative class action complaint was filed against us and certain of our officers in the United States District Court for the Eastern District of Pennsylvania. This action was purportedly brought on behalf of a putative class of our investors who purchased our publicly traded securities between March 11, 2019 and September 17, 2019. The Complaint alleges that we and our executives violated federal securities laws concerning certain material misstatements and omissions relating to product candidate Zygel.

We believe that the lawsuit is without merit and intend to vigorously defend against it. The lawsuit is in the early stages and, at this time, no assessment can be made as to its likely outcome or whether the outcome will be material to us. This

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
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 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 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 CBD to a patient where the CBD 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 CBD 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 CBD 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 our DEE program 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 a 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 2016 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. 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, including in recent months. 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. For example, on October 23, 2019, a putative class action complaint was filed against us and certain of our officers in the United States District Court for the Eastern District of Pennsylvania. This action was purportedly brought on behalf of a putative class of our investors who purchased our publicly traded securities between March 11, 2019 and September 17, 2019. While we believe that the lawsuit is without merit and intend to vigorously defend against it, the lawsuit is in the early stages and, at this time, no assessment can be made as to its likely outcome or whether the outcome will be material to us. 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 37.2% of our voting stock at March 4, 2020. 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.

***We will no longer be an emerging growth company beginning on December 31, 2020 after which we will not be able to take advantage of the reduced disclosure requirements applicable to emerging growth companies.***

We are an "emerging growth company," as defined in the JOBS Act, and we have taken advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a non-binding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We expect to cease to be an emerging growth company as of December 31, 2020.

As a result, we will need to comply with the independent auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act beginning with our annual report on Form 10-K for the year ending December 31, 2020, will be

required to hold a say-on-pay vote and a say-on-frequency vote at our 2021 annual meeting of stockholders, and will no longer be entitled to provide the reduced executive compensation disclosures permitted by emerging growth companies in our annual report on the Form 10-K and proxy statement for the year ending December 31, 2020 (unless we are able to do so as a smaller reporting company). We expect that our transition from "emerging growth company" will require additional attention from management and will result in increased costs to us, which could include higher legal fees, accounting fees and fees associated with investor relations activities, among others.

***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 reviews, 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 directors and officers liability insurance coverage. 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.

***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, including under our current Controlled Equity Offering Sales Agreement℠ with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., or the 2019 Sales Agreement. 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 4, 2020, there were 2,547,297 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.

**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 pursuant to a lease which expires on May 31, 2021.

**Item 3. Legal Proceedings**

On October 23, 2019, a putative class action complaint was filed against us and certain of our current officers in the United States District Court for the Eastern District of Pennsylvania. This action was purportedly brought on behalf of a putative class of our investors who purchased our publicly traded securities between March 11, 2019 and September 17, 2019. The Complaint alleges that we and our executives violated federal securities laws concerning certain material misstatements and omissions relating to product candidate Zygel. Specifically, the complaint alleges that we 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.

We believe that the claims asserted are without merit, and we intend to defend this action vigorously. The lawsuit is in the early stages and, at this time, no assessment can be made as to its likely outcome or whether the outcome will be material to us.

**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 4, 2020, there were 31 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**

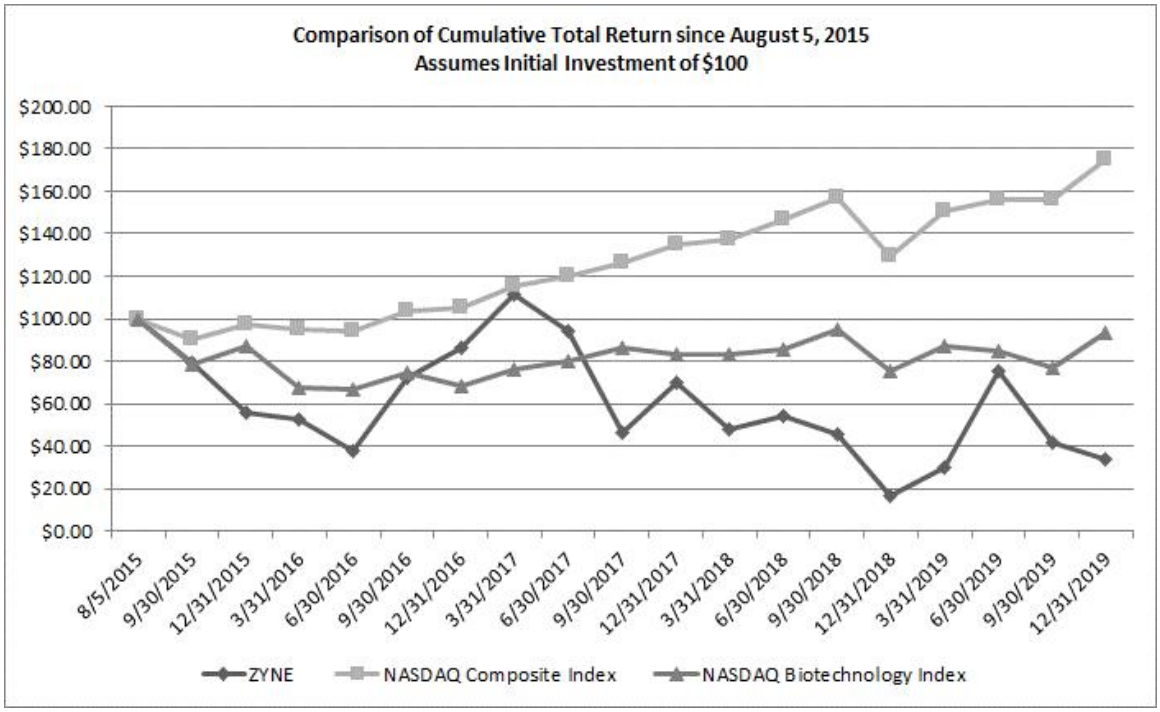
None.

**Performance Graph**

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

The following graph illustrates a comparison of the total cumulative stockholder return for our common stock since August 5, 2015, which is the first trading day for our stock, to two indices: the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes an initial investment of $100 on August 5, 2015, in our common stock, the

stocks comprising the Nasdaq Composite Index, and the stocks comprising the Nasdaq Biotechnology Index. Historical stockholder return is not necessarily indicative of the performance to be expected for any future periods.



## 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, 2019, 2018 and 2017 and the selected consolidated balance sheet data as of December 31, 2019 and 2018 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, 2016 and 2015 and the selected consolidated balance sheet data as of December 31, 2017, 2016 and 2015 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, | | | | |
|---|---|---|---|---|---|
| | 2019 | 2018 | 2017 | 2016 | 2015 |
| Revenue | $ — | $ 86,000 | $ — | $ 7,250 | $ 278,900 |
| Operating expenses: | | | | | |
| Research and development | 20,384,049 | 27,245,043 | 22,806,107 | 16,784,626 | 7,445,669 |
| General and administrative | 13,935,761 | 13,238,787 | 10,016,902 | 6,430,252 | 5,364,390 |
| Total operating expenses | 34,319,810 | 40,483,830 | 32,823,009 | 23,214,878 | 12,810,059 |
| Loss from operations | (34,319,810) | (40,397,830) | (32,823,009) | (23,207,628) | (12,531,159) |
| Other income (expense): | | | | | |
| Interest income | 1,522,138 | 961,323 | 519,554 | 80,222 | 7,352 |
| Foreign exchange (loss) gain | (145,911) | (474,668) | 291,151 | (189,497) | — |
| Loss on disposal of equipment | — | — | — | (99,147) | — |
| Total other income (expense) | 1,376,227 | 486,655 | 810,705 | (208,422) | 7,352 |
| Loss before income taxes | (32,943,583) | (39,911,175) | (32,012,304) | (23,416,050) | (12,523,807) |
| Income tax (benefit) expense | — | — | — | (27,543) | 27,543 |
| Net loss | $ (32,943,583) | $ (39,911,175) | $ (32,012,304) | $ (23,388,507) | $ (12,551,350) |
| Per share information: | | | | | |
| Net loss per share basic and diluted [1] | $ (1.50) | $ (2.61) | $ (2.48) | $ (2.58) | $ (2.82) |
| Basic and diluted weighted average shares outstanding | 22,000,203 | 15,308,886 | 12,914,814 | 9,070,232 | 4,457,719 |

(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, | | | | |
|---|---|---|---|---|---|
| | 2019 | 2018 | 2017 | 2016 | 2015 |
| BALANCE SHEET DATA: | | | | | |
| Cash and cash equivalents | $ 70,063,242 | $ 59,763,773 | $ 62,510,277 | $ 30,965,791 | $ 41,513,060 |
| Total assets | 87,764,596 | 67,327,443 | 69,054,309 | 36,554,274 | 43,643,541 |
| Total liabilities | 12,167,853 | 9,725,782 | 8,104,721 | 6,966,966 | 3,937,617 |
| Total stockholders' equity | 75,596,743 | 57,601,661 | 60,949,588 | 29,587,308 | 39,705,924 |

## 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.

We are currently evaluating Zygel™, a patent-protected transdermal cannabidiol, or CBD, gel for the treatment of FXS, DEE, ASD and 22q. In 2017, we announced results for three Phase 2 clinical trials for Zygel. In April 2018, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with DEE. In September 2019, we completed the first six months of dosing for that study and announced positive top-line results. In July 2018, we initiated what we believe will be a pivotal clinical trial evaluating Zygel in children and adolescent patients with FXS. In the first quarter of 2020, we announced that 212 patients with FXS have been randomized into the trial and enrollment is now complete. We expect to report top-line results late in the second quarter of 2020. In March 2019, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with ASD and completed enrollment in that trial in January 2020. In May 2019, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with 22q. We expect to report top line results for the ASD clinical trial in the second quarter of 2020 and the 22q clinical trial results are now expected in the third quarter of 2020.

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

Zygel is the first and only pharmaceutically-produced CBD formulated as a permeation-enhanced gel for transdermal delivery, and the formulation is patent protected through 2030. Four additional patents are directed to methods of use relating to Zygel, including methods of treating FXS and ASD, and will expire in 2038. In preclinical animal studies, Zygel's permeation enhancer increased delivery of CBD 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 CBD when delivered transdermally. In addition, an *in vitro* study published in *Cannabis and Cannabinoid Research* in April 2016 demonstrated that CBD 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 CBD is delivered orally and may be avoided with the transdermal delivery of Zygel, which maintains CBD in a neutral pH. Zygel, which is being developed as a clear gel with once- or twice-daily dosing, is targeting treatment of behavioral symptoms of FXS, ASD and 22q and reductions in seizures in patients with DEE. We have been granted orphan drug designation from the FDA for the use of CBD for the treatment of FXS. 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

In April 2018, we initiated the exploratory Phase 2 BELIEVE 1 (Open Label Study to Assess the Safety and Efficacy of Zygel Administered as a Transdermal Gel to Children and Adolescents with Developmental and Epileptic 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 (age three to 17 years) with DEE as classified by the International League Against Epilepsy, or ILAE (Scheffer et al. 2017). In September 2019, we reported positive top-line results from the BELIEVE 1 trial.

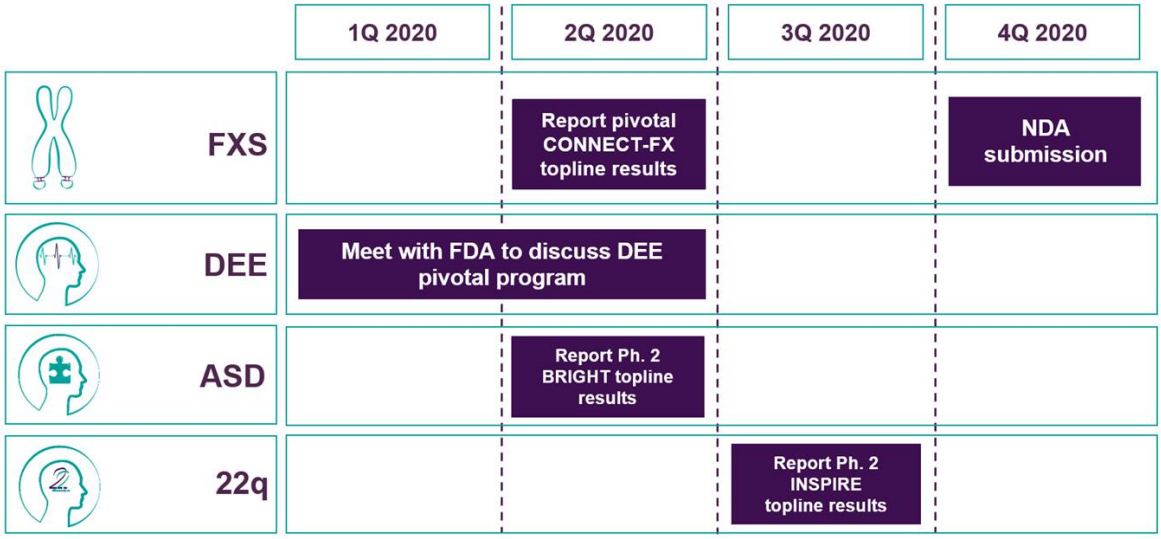
In July 2018, we initiated the pivotal CONNECT-FX (Clinical study of Cannabidiol (CBD) in Children and Adolescents with Fragile X) clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study that will assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the FMR1 gene. In the first quarter of 2020, we announced that 212 patients with FXS have been enrolled at 21 clinical sites in the United States, Australia and New Zealand and enrollment is now complete. We expect to report top-line results late in the second quarter of 2020.

In March 2019, we initiated 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. We have enrolled 37 patients in the BRIGHT clinical trial and enrollment is now complete. We expect to report top line results from this study in the second quarter of 2020.

In May 2019, we initiated the open-label Phase 2 INSPIRE (Assessing the Impact of Zygel [Transdermal CBD 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 (age six to 17 years). Top line results from this study are now expected in the third quarter of 2020.

***Zygel Clinical Development Timelines***

Our key development programs and expected timelines for the development of Zygel are shown in the chart below:




We have never been profitable and have incurred net losses since inception. Our net losses were $32.9 million, $39.9 million and $32.0 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of

December 31, 2019, our accumulated deficit was $150.8 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. In July 2019, the Australian government's Department of Industry, Innovation and Science, or AusIndustry, responded to an Advance Overseas Finding, or AOF, application submitted by Zynerba that will allow certain research and development expenses incurred with respect to Zygel™ outside of Australia to be eligible for the Australian research and development tax incentive program. As a result of this finding, we are eligible to receive a cash refund from the Australian Taxation Office for the qualifying research and development costs expended outside of Australia in 2018, 2019 and 2020. During the year ended December 31, 2019, we recorded an $8.3 million credit to research and development expenses for amounts expected to be received through the AOF for the period January 1, 2018 through December 31, 2019. Although the AOF approval extends into 2020, management believes that substantially all qualifying amounts have been recorded as of December 31, 2019.

For the years ended December 31, 2019, 2018 and 2017, we incurred research and development expenses of $20.4 million, $27.2 million and $22.8 million, respectively, which were net of $11.2 million, $3.4 million and $3.8 million, respectively, associated with the Australian research and development tax incentive program.

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

| | Year ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Research and development expenses - before R&D incentive | $ 31,549,954 | $ 30,631,258 | $ 26,584,938 |
| Research and development incentive (non-AOF) | (2,895,896) | (3,386,215) | (3,778,831) |
| Research and development expenses (before impact of AOF) | 28,654,058 | 27,245,043 | 22,806,107 |
| AOF - cumulative change in estimate for the period 1/1/18 through 12/31/19 | (8,270,009) | — | — |
| Total research and development expenses | $ 20,384,049 | $ 27,245,043 | $ 22,806,107 |

Excluding the reduction of research and development expenses from the AOF, we expect research and development expenses to increase in 2020 as compared to 2019 as we continue to advance our clinical trials and prepare for a potential NDA filing for Zygel in FXS. 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, 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 (Loss) Gain* — Foreign exchange (loss) gain relates to the effect of exchange rates on transactions incurred by the Subsidiary.

*Income Taxes* — The 2017 Tax Cuts and Jobs Act, which became effective in 2018, resulted in significant changes to the U.S. corporate income tax system. These changes included a federal statutory rate reduction from 34% to 21%, the elimination or reduction of certain domestic deductions and credits and limitations on the deductibility of interest

expense and executive compensation. The 2017 Tax Cuts and Jobs Act also transitioned international taxation from a worldwide system to a modified territorial system and included base erosion prevention measures on non-U.S. earnings, which has the effect of subjecting certain earnings of our foreign subsidiaries to U.S. taxation as global intangible low-taxed income (GILTI). The 2017 Tax Cuts and Jobs Act also included a one-time mandatory deemed repatriation tax on accumulated foreign subsidiaries' previously untaxed foreign earnings.

We recognized the provisional tax impacts related to the revaluation of the deferred tax assets and liabilities and included these amounts in our consolidated financial statements for the year ended December 31, 2017. In regard to the change in the federal income tax rate as it related to our deferred tax assets and liabilities as of December 31, 2017, we decreased our related deferred tax assets by $8.7 million along with a corresponding offset against the valuation allowance for these deferred tax assets. We completed the accounting for the impacts of the 2017 Tax Cuts and Jobs Act in the fourth quarter of 2018, which did not result in any material adjustments to the provisional estimates.

As of December 31, 2019, we had $96.0 million of federal operating loss carryforwards and $2.6 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, 2019 and 2018, 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 policies are 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, 2019 and December 31, 2018***

| | Year Ended December 31, | | Increase (Decrease) | |
|---|---|---|---|---|
| | 2019 | 2018 | $ | % |
| Revenue | $ — | $ 86,000 | $ (86,000) | — % |
| Operating expenses: | | | | |
| Research and development | 20,384,049 | 27,245,043 | (6,860,994) | (25)% |
| General and administrative | 13,935,761 | 13,238,787 | 696,974 | 5 % |
| Total operating expenses | 34,319,810 | 40,483,830 | (6,164,020) | (15)% |
| Loss from operations | (34,319,810) | (40,397,830) | 6,078,020 | (15)% |
| Other income | 1,376,227 | 486,655 | 889,572 | 183 % |
| Net loss | $ (32,943,583) | $ (39,911,175) | $ 6,967,592 | (17)% |

*Revenue*

Revenue in 2018 was related to services rendered for our ZYN001 program in connection with grants received prior to 2015. Grants received were recorded as deferred revenue and recognized as revenue as the designated preclinical study progressed and amounts were earned.

*Research and Development Expenses*

Excluding the $8.3 million reduction in research and development expenses for amounts expected to be received through the AOF for the period January 1, 2018 through December 31, 2019, research and development expenses increased by $1.4 million, or 5%, to $28.7 million for the year ended December 31, 2019 from $27.2 million for the year ended December 31, 2018. The increase was primarily related to increased manufacturing and clinical trial costs related to our Zygel program; partially offset by a decrease in non-clinical trial costs related to our Zygel program and decreases in employee-related costs and stock-based compensation expense.

*General and Administrative Expenses*

General and administrative expenses increased by $0.7 million, or 5%, to $13.9 million for the year ended December 31, 2019 from $13.2 million for the year ended December 31, 2018. The increase was primarily related to increased employee-related costs and an increase in directors and officers liability insurance; partially offset by decreases in stock-based compensation expense and lower costs associated with the recruiting of new employees.

*Other Income*

During the years ended December 31, 2019 and 2018, we recognized $1.5 million and $1.0 million, respectively, in interest income. The increase in interest income was related both to a higher amount of invested cash resulting from the receipt of $45.1 million in net proceeds from the sale of our shares of common stock under the Open Market Sales Agreement, or the 2017 Sales Agreement, with Jefferies LLC, or Jefferies, during the first half of 2019 and to a higher average interest rate earned on our investments. During the years ended December 31, 2019 and 2018, we recognized foreign currency losses of $0.1 million and $0.5 million, respectively. Foreign currency gains and losses are due primarily to the remeasurement of the Subsidiary's assets and liabilities that 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 IPO in 2015, sales under our "at-the-market" offering, and our follow-on public offerings) 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, 2019, our principal sources of liquidity were our cash and cash equivalents of $70.1 million. Our working capital was $75.0 million as of December 31, 2019.

Management believes that current cash and cash equivalents and the proceeds anticipated from the AOF are sufficient to fund operations and capital requirements beyond the expected NDA submission and potential approval of Zygel for the treatment of FXS and into the second half of 2021. 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.

*Equity Financings*

On August 30, 2019, we entered into a Controlled Equity Offering 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 December 12, 2019 through March 4, 2020, we have sold and issued 353,171 shares of our common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $5.22 per share, resulting in gross proceeds of $1.8 million. Net proceeds after deducting commissions and offering expenses were $1.6 million. As of December 31, 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, for gross and net proceeds of $0.1 million. From January 1, 2020 through March 4, 2020, we sold and issued 339,790 shares of our common stock in the open market at a weighted average selling price of $5.15 per share, for gross proceeds of $1.7 million and net proceeds, after deducting commissions and offering expenses, of $1.5 million.

In June 2017, we entered into the 2017 Sales Agreement with Jefferies, pursuant to which we sold $50.0 million of our common stock. In the first quarter of 2019, we sold and issued 3,439,523 shares of common stock under the 2017 Sales Agreement with Jefferies in the open market at a weighted average selling price of $5.44 per share, resulting in gross proceeds of $18.7 million. Net proceeds received after deducting commissions and offering expenses were $18.1 million. In the second quarter of 2019, we sold and issued 2,082,031 shares of common stock under the 2017 Sales Agreement with Jefferies in the open market at a weighted average selling price of $13.50 per share, resulting in gross proceeds of $28.1 million. Net proceeds received after deducting commissions and offering expenses were $27.0 million. The last sale under the 2017 Sales Agreement was made on May 16, 2019. From June 2017 through May 16, 2019, we have cumulative gross proceeds of $50.0 million from shares sold in the open market under the 2017 Sales Agreement, which was terminated pursuant to its terms.

In July 2018, we completed a follow-on public offering, selling 4,062,500 shares of our 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.

*Debt*

We had no debt outstanding as of December 31, 2019 or 2018.

*Future Capital Requirements*

During the year ended December 31, 2019, net cash used in operating activities was $34.8 million, and our accumulated deficit as of December 31, 2019 was $150.8 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 continue 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 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;
- our ability to limit our exposure under product liability lawsuits, shareholder class action lawsuits or other litigation;
- 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 independently commercialize our products.

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*

*Years Ended December 31, 2019 and December 31, 2018* — The following table summarizes our cash flows from operating, investing and financing activities for the years ended December 31, 2019 and December 31, 2018.

| | Year Ended December 31, | |
|---|---|---|
| | 2019 | 2018 |
| **Statement of Cash Flows Data:** | | |
| Total net cash (used in) provided by: | | |
| Operating activities | $ (34,817,976) | $ (32,397,351) |
| Investing activities | (129,390) | (286,658) |
| Financing activities | 45,246,835 | 29,937,505 |
| Net increase (decrease) in cash and cash equivalents | $ 10,299,469 | $ (2,746,504) |

*Operating Activities*

For the year ended December 31, 2019, cash used in operating activities was $34.8 million, compared to $32.4 million for the year ended December 31, 2018. The increase from 2018 was primarily the result of the increased research and development expenses related to clinical trial costs of our Zygel program, excluding amounts expected to be received from the Australian research and development tax incentive program.

Excluding the cash anticipated to be received from the July 2019 AOF application, we expect cash used in operating activities to increase in 2020 as compared to 2019, as we continue to advance our clinical trials and prepare for a potential NDA filing and commercialization of Zygel in FXS.

*Investing Activities*

For the year ended December 31, 2019, cash used in investing activities primarily represented the cost of expenditures made for manufacturing equipment. For the year ended December 31, 2018, cash used in investing activities represented the cost of expenditures made for manufacturing equipment and furniture and fixtures and leasehold improvements associated with our corporate headquarters.

*Financing Activities*

Cash provided by financing activities for the year ended December 31, 2019 consisted primarily of $45.1 million in net proceeds from sales of our shares of common stock under the 2017 Sales Agreement with Jefferies and $0.1 million under the 2019 Sales Agreement. Cash provided by financing activities for the year ended December 31, 2018 consisted primarily of $29.9 million in net proceeds from sales of our shares of common stock under a follow-on public offering.

**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.

**Contractual Obligations**

The following table summarizes our contractual obligations as of December 31, 2019:

| | Payments Due by Period | | | | |
|---|---|---|---|---|---|
| | Total | 2020 | 2021 and 2022 | 2023 and 2024 | 2025 and Thereafter |
| Operating lease obligations | $ 454,524 | $ 318,561 | $ 135,963 | - | $ - |

**Accounting Pronouncements**

For descriptions of recently issued accounting pronouncements, see “Note 2 – Summary of Significant Accounting Policies – 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, 2019, we had cash and cash equivalents of $70.1 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 and Canada and to conduct clinical trials for our product candidates in 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. Accordingly, we do not believe our foreign currency exchange rate risk is significant due to the limited extent of our operations in foreign currencies; however, 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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| Consolidated Statements of Stockholders' Equity for the years ended December 31, 2017, 2018 and 2019 | 94 |
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## 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, 2019 and 2018, the related consolidated statements of operations, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2019, 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, 2019 and 2018, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2019, 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.

/s/ KPMG LLP

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

Philadelphia, Pennsylvania
March 10, 2020

**ZYNERBA PHARMACEUTICALS, INC.**
**CONSOLIDATED BALANCE SHEETS**

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 70,063,242 | $ 59,763,773 |
| Incentive and tax receivables | 14,613,969 | 3,444,620 |
| Prepaid expenses and other current assets | 2,378,812 | 3,747,087 |
| Total current assets | 87,056,023 | 66,955,480 |
| Property and equipment, net | 362,724 | 371,963 |
| Right-of-use assets | 345,849 | — |
| Total assets | $ 87,764,596 | $ 67,327,443 |
| **Liabilities and Stockholders' Equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 4,740,981 | $ 4,461,567 |
| Accrued expenses | 7,073,506 | 5,264,215 |
| Lease liabilities | 243,677 | — |
| Total current liabilities | 12,058,164 | 9,725,782 |
| Lease liabilities, long-term | 109,689 | — |
| Total liabilities | 12,167,853 | 9,725,782 |
| 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; 23,211,391 shares issued and outstanding at December 31, 2019 and 17,626,873 shares issued and outstanding at December 31, 2018 | 23,211 | 17,627 |
| Additional paid-in capital | 226,409,156 | 175,476,075 |
| Accumulated deficit | (150,835,624) | (117,892,041) |
| Total stockholders' equity | 75,596,743 | 57,601,661 |
| Total liabilities and stockholders' equity | $ 87,764,596 | $ 67,327,443 |

See accompanying notes to consolidated financial statements.

**ZYNERBA PHARMACEUTICALS, INC.**
**CONSOLIDATED STATEMENTS OF OPERATIONS**

| | Year ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Revenue | $ — | $ 86,000 | $ — |
| Operating expenses: | | | |
| Research and development | 20,384,049 | 27,245,043 | 22,806,107 |
| General and administrative | 13,935,761 | 13,238,787 | 10,016,902 |
| Total operating expenses | 34,319,810 | 40,483,830 | 32,823,009 |
| Loss from operations | (34,319,810) | (40,397,830) | (32,823,009) |
| Other income (expense): | | | |
| Interest income | 1,522,138 | 961,323 | 519,554 |
| Foreign exchange (loss) gain | (145,911) | (474,668) | 291,151 |
| Total other income | 1,376,227 | 486,655 | 810,705 |
| Net loss | $ (32,943,583) | $ (39,911,175) | $ (32,012,304) |
| | | | |
| Net loss per share basic and diluted | $ (1.50) | $ (2.61) | $ (2.48) |
| Basic and diluted weighted average shares outstanding | 22,000,203 | 15,308,886 | 12,914,814 |

See accompanying notes to consolidated financial statements.

**ZYNERBA PHARMACEUTICALS, INC.**
**CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY**
**YEARS ENDED DECEMBER 31, 2017, 2018 and 2019**

| | Common stock | | Additional paid-capital | Accumulated deficit | Total stockholders' equity |
|---|---|---|---|---|---|
| | Shares | Amount | | | |
| **Balance at December 31, 2016** | **9,994,825** | **$ 9,995** | **$ 75,545,875** | **$ (45,968,562)** | **$ 29,587,308** |
| Issuance of common stock, net of issuance costs | 3,516,594 | 3,517 | 57,289,524 | — | 57,293,041 |
| Exercise of stock options | 42,454 | 42 | 434,649 | — | 434,691 |
| Stock-based compensation expense | — | — | 5,646,852 | — | 5,646,852 |
| Net loss | — | — | — | (32,012,304) | (32,012,304) |
| **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** |

See accompanying notes to consolidated financial statements.

**ZYNERBA PHARMACEUTICALS, INC.**
**CONSOLIDATED STATEMENTS OF CASH FLOWS**

| | Year ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Cash flows from operating activities: | | | |
| Net loss | $ (32,943,583) | $ (39,911,175) | $ (32,012,304) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | | |
| Depreciation | 133,879 | 99,572 | 94,211 |
| Stock-based compensation | 5,561,895 | 6,625,743 | 5,646,852 |
| Changes in operating assets and liabilities: | | | |
| Incentive and tax receivables | (11,169,349) | 538,984 | (369,661) |
| Prepaid expenses and other assets | 1,561,780 | (1,291,186) | (324,304) |
| Deferred grant revenue | — | (833,975) | — |
| Right-of-use assets | (5,307) | — | — |
| Accounts payable | 209,613 | 1,103,013 | 1,492,171 |
| Accrued expenses | 1,833,096 | 1,271,673 | (369,416) |
| Net cash used in operating activities | (34,817,976) | (32,397,351) | (25,842,451) |
| Cash flows from investing activities: | | | |
| Purchases of property and equipment | (129,390) | (286,658) | (115,356) |
| Net cash used in investing activities | (129,390) | (286,658) | (115,356) |
| Cash flows from financing activities: | | | |
| Proceeds from the issuance of common stock, net of issuance costs | 45,187,070 | 29,937,505 | 57,293,041 |
| Payment of deferred financing costs | (129,935) | — | (225,439) |
| Proceeds from the exercise of stock options | 189,700 | — | 434,691 |
| Net cash provided by financing activities | 45,246,835 | 29,937,505 | 57,502,293 |
| Net increase (decrease) in cash and cash equivalents | 10,299,469 | (2,746,504) | 31,544,486 |
| Cash and cash equivalents at beginning of year | 59,763,773 | 62,510,277 | 30,965,791 |
| Cash and cash equivalents at end of year | $ 70,063,242 | $ 59,763,773 | $ 62,510,277 |
| | | | |
| Supplemental disclosures of cash flow information: | | | |
| Deferred financing costs included in accounts payable and accrued expenses | $ 63,570 | $ 60,000 | $ 15,000 |
| Changes in property and equipment acquired but not paid | $ 4,750 | $ 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 was incorporated on January 31, 2007 under the laws of the State of Delaware as AllTranz, Inc. and changed its name to Zynerba Pharmaceuticals, Inc. in August 2014.

The Company has incurred losses and negative cash flows from operations since inception and has an accumulated deficit of $150.8 million as of December 31, 2019. 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.

On August 30, 2019, the Company entered into a Controlled Equity Offering 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 December 12, 2019 through March 4, 2020, the Company has sold and issued 353,171 shares of its common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $5.22 per share, resulting in gross proceeds of $1.8 million. Net proceeds after deducting commissions and offering expenses were $1.6 million. As of December 31, 2019, the Company sold and issued 13,381 shares of its common stock in the open market at a weighted-average selling price of $7.00, for gross and net proceeds of $0.1 million. From January 1, 2020 through March 4, 2020, the Company sold and issued 339,790 shares of its common stock in the open market at a weighted average selling price of $5.15 per share, for gross proceeds of $1.7 million and net proceeds, after deducting commissions and offering expenses, of $1.5 million.

In June 2017, the Company entered into an Open Market Sales Agreement (the "2017 Sales Agreement") with Jefferies LLC, ("Jefferies") pursuant to which the Company sold $50.0 million of its common stock. In the first quarter of 2019, the Company sold and issued 3,439,523 shares of common stock under the 2017 Sales Agreement with Jefferies in the open market at a weighted average selling price of $5.44 per share, resulting in gross proceeds of $18.7 million. Net proceeds received after deducting commissions and offering expenses were $18.1 million. In the second quarter of 2019, the Company sold and issued 2,082,031 shares of common stock under the 2017 Sales Agreement with Jefferies in the open market at a weighted average selling price of $13.50 per share, resulting in gross proceeds of $28.1 million. Net proceeds received after deducting commissions and offering expenses were $27.0 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 was 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.

In July 2019, the Australian government's Department of Industry, Innovation and Science ("AusIndustry") responded to an Advance Overseas Finding ("AOF") application submitted by Zynerba that will allow certain research and development expenses incurred with respect to the Company's product candidate Zygel™ outside of Australia to be eligible for the Australian research and development tax incentive program. As a result of this finding, the Company is eligible to receive a cash refund from the Australian Taxation Office for the qualifying research and development costs expended 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

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

development expense for amounts expected to be received through the AOF for the period January 1, 2018 through December 31, 2019. Although the AOF approval extends into 2020, management believes that substantially all qualifying amounts have been recorded as of December 31, 2019.

Management believes that current cash and cash equivalents and the proceeds anticipated from the AOF are sufficient to fund operations and capital requirements into the second half of 2021. 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. 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.

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, 2019 and 2018, 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 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’s estimate of the amount of cash refund it expects to receive related to the Australian research and development tax incentive program is included in “Incentive and tax receivables” in the accompanying consolidated

balance sheets. As of December 31, 2019, the Company's estimate of the amount of cash refund it expects to receive in 2020 for both 2019 and 2018 eligible spending as part of this incentive program was $6.0 million and was recorded as a current asset.

In July 2019, AusIndustry responded to an AOF application submitted by Zynerba that will allow certain research and development expenses incurred with respect to Zygel outside of Australia to be eligible for the Australian research and development tax incentive program. As a result of this finding, the Company is eligible to receive a cash refund from the Australian Taxation Office for the qualifying research and development costs expended 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, 2019, incentive and tax receivables included $8.3 million related to the AOF.

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, 2019, incentive and tax receivables included $0.3 million for refundable GST on expenses incurred with Australian vendors during the three months ended December 31, 2019.

Incentive and tax receivables consisted of the following as of December 31, 2019 and 2018:

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| Research and development incentive (non-AOF) for the period 1/1/18 - 12/31/18 | $ 3,126,750 | $ 3,149,546 |
| Research and development incentive (non-AOF) for the period 1/1/19 - 12/31/19 | 2,913,417 | — |
| Research and development incentive (AOF) for the period 1/1/18 - 12/31/19 | 8,256,416 | — |
| Goods and services tax | 317,386 | 295,074 |
| Total incentive and tax receivables | $ 14,613,969 | $ 3,444,620 |

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, 2019, 2018 and 2017, 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 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 Company incurred research and development expenses of $20.4 million, $27.2 million and $22.8 million for the years ended December 31, 2019, 2018 and 2017, respectively, which were net of $11.2 million, $3.4 million, and $3.8 million, respectively, associated with the Australian research and development tax incentive program.

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. Stock-based awards issued to non-employees, if any, are revalued until the award vests.

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 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 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, 2019 and 2018, 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, 2019 and does not expect a significant change in the balance of unrecognized tax benefits within the next 12 months.

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

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, 2019, 2018 and 2017 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, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Stock options | 3,988,716 | 3,152,267 | 2,386,538 |
| Unvested restricted stock | 8,600 | 10,500 | 108,730 |
| | 3,997,316 | 3,162,767 | 2,495,268 |

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. 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. In July 2018, the FASB issued ASU No. 2018-11, *Leases (Topic 842): Targeted Improvements* (“ASU 2018-11”), which offered a transition option to entities adopting ASC 842. Under ASU 2018-11, entities can elect to apply ASC 842 using a modified-retrospective adoption approach resulting in a cumulative effect adjustment, if any, to retained earnings at the beginning of the year in which the new lease standard is adopted, rather than adjustments to the earliest comparative period presented in their financial statements.

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. In addition, the Company eliminated its deferred rent liability and recorded an adjustment to decrease its right-of-use asset 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, 2019 and 2018:

| | 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 | $ — | $ — |

| | Carrying amount as of December 31, 2018 | Fair Value Measurement as of December 31, 2018 | | |
|---|---|---|---|---|
| | | Level 1 | Level 2 | Level 3 |
| Cash equivalents (money market accounts) | $ 59,554,458 | $ 59,554,458 | $ — | $ — |
| | $ 59,554,458 | $ 59,554,458 | $ — | $ — |

**(4) Prepaid Expenses and Other Current Assets**

Prepaid expenses and other current assets consisted of the following as of December 31, 2019 and 2018:

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| Prepaid development expenses | $ 957,814 | $ 2,671,815 |
| Prepaid insurance | 841,858 | 393,451 |
| Deferred financing costs | 193,505 | 255,754 |
| Other current assets | 385,635 | 426,067 |
| Total prepaid expenses and other current assets | $ 2,378,812 | $ 3,747,087 |

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

**(5) Property and Equipment**

Property and equipment consisted of the following as of December 31, 2019 and 2018:

| | Estimated useful life (in years) | December 31, 2019 | December 31, 2018 |
|---|---|---|---|
| Equipment | 2-5 | $ 263,829 | $ 178,001 |
| Computer equipment | 3-5 | 30,319 | 30,319 |
| Furniture and fixtures | 3-5 | 311,355 | 300,407 |
| Leasehold improvements | various | 68,881 | 68,881 |
| Construction in process | | 78,773 | 57,015 |
| Total cost | | 753,157 | 634,623 |
| Less accumulated depreciation | | (390,433) | (262,660) |
| Property and equipment, net | | $ 362,724 | $ 371,963 |

Depreciation expense was $133,879, $99,572 and $94,211 for the years ended December 31, 2019, 2018 and 2017 respectively.

**(6) Accrued Expenses**

Accrued expenses consisted of the following as of December 31, 2019 and 2018:

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| Accrued compensation | $ 2,340,533 | $ 2,188,801 |
| Accrued research and development | 4,343,322 | 1,928,305 |
| Grants payable | — | 747,926 |
| Other | 389,651 | 399,183 |
| Total accrued expenses | $ 7,073,506 | $ 5,264,215 |

**(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, 2019, no shares of preferred stock were issued.

***Common Stock***

On August 30, 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 December 12, 2019 through March 4, 2020, the Company has sold and issued 353,171 shares of its common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $5.22 per share, resulting in gross proceeds of $1.8 million. Net proceeds after deducting commissions and offering expenses were $1.6 million. As of December 31, 2019, the Company sold and issued 13,381 shares of its common stock in the open market at a weighted-average selling price of $7.00, for gross and net proceeds of $0.1 million. From January 1, 2020 through March 4, 2020, the Company sold and issued 339,790 shares of its common stock in the open market at a weighted average selling price of $5.15 per share, for gross proceeds of $1.7 million and net proceeds, after deducting commissions and offering expenses, of $1.5 million.

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

In the first quarter of 2019, the Company sold and issued 3,439,523 shares of common stock under the 2017 Sales Agreement with Jefferies in the open market at a weighted average selling price of $5.44 per share, resulting in gross proceeds of $18.7 million. Net proceeds received after deducting commissions and offering expenses were $18.1 million. In the second quarter of 2019, the Company sold and issued 2,082,031 shares of common stock under the 2017 Sales Agreement with Jefferies in the open market at a weighted average selling price of $13.50 per share, resulting in gross proceeds of $28.1 million. Net proceeds received after deducting commissions and offering expenses were $27.0 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 was 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.

In June 2017, the Company terminated the 2016 Sales Agreement and entered into the 2017 Sales Agreement with Jefferies pursuant to which the Company may sell, from time to time, up to $50.0 million of its common stock. During 2017, the Company sold and issued 296,594 shares of common stock in the open market at a weighted average selling price of $10.74 per share, for gross proceeds of $3.2 million. Net proceeds after deducting commissions and offering expenses were $3.0 million.

In the first quarter of 2017, the Company completed an additional follow-on public offering, selling 3,220,000 shares at an offering price of $18.00 per share resulting in gross proceeds of $58.0 million. Net proceeds received after deducting underwriting and commissions and offering expenses were $54.2 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, 2020, 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 number of shares of common stock available for issuance under the 2014 Plan to 7,804,869 shares. As of December 31, 2019, 1,767,777 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 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. These performance options have a 10-year life and an exercise price equal to the fair value of the Company’s stock at the grant date. 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

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

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, 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. As of December 31, 2019, the aggregate estimated grant date fair values of options and restricted stock awards for which the satisfaction of the related-performance conditions have not been deemed probable were $663,484 and $24,850, respectively.

During the years ended December 31, 2019, 2018 and 2017, the Company recorded $5,561,895, $6,625,743 and $5,646,852, respectively, in stock-based compensation expense related to its stock option grants and restricted stock awards, as follows:

| | Stock Option Grants | | | Restricted stock awards | | |
|---|---|---|---|---|---|---|
| | 2019 | 2018 | 2017 | 2019 | 2018 | 2017 |
| Research and development | $ 2,348,205 | $ 2,884,689 | $ 2,127,386 | $ 23,793 | $ 202,809 | $ 157,480 |
| General and administrative | 3,189,897 | 3,491,432 | 3,279,626 | — | 46,813 | 82,360 |
| | $ 5,538,102 | $ 6,376,121 | $ 5,407,012 | $ 23,793 | $ 249,622 | $ 239,840 |

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, 2017 | 2,386,538 | $ 12.53 | | |
| Granted | 875,416 | 11.34 | | |
| Expired | (109,687) | 9.20 | | |
| 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 | 7.20 | $ 2,668,248 |
| Exercisable as of December 31, 2019 | 2,439,217 | 11.98 | 6.29 | $ 1,047,743 |
| Vested and expected to vest as of December 31, 2019 | 3,905,436 | $ 10.81 | | |

The weighted-average grant date fair value of options granted during the years ended December 31, 2019, 2018 and 2017 was $4.22, $7.84 and $12.95, 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, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Weighted-average risk-free interest rate | 2.36% | 2.53% | 2.11% |
| Expected term of options (in years) | 6.16 | 6.12 | 6.12 |
| Expected stock price volatility | 79.85% | 78.09% | 77.00% |
| Expected dividend yield | 0% | 0% | 0% |

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**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED**

As of December 31, 2019, excluding performance-based stock options that have not been deemed probable, there was $7.4 million of unrecognized stock-based compensation expense related to stock options, which is expected to be recognized over a weighted-average period of 2.09 years.

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, 2017 | 108,730 | $ 1.65 |
| Granted | 10,500 | 11.86 |
| Vested | (108,730) | 1.65 |
| 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 |

As of December 31, 2019, excluding performance-based restricted stock awards that have not been deemed probable, there was $6,984 of unrecognized stock-based compensation expense related to unvested restricted stock awards, which is expected to be recognized over a weighted-average period of 1.07 years. The Company expects that all 3,600 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, 2019, the Company's right-of-use asset, net of amortization, was $345,849.

Other operating lease information as of December 31, 2019:

| | |
|---|---|
| Weighted-average remaining lease term - operating leases | 1.4 years |
| Weighted-average discount rate - operating leases | 6.6 % |

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**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, 2019:

| Year ended: | |
|---|---|
| December 31, 2020 | $ 259,864 |
| December 31, 2021 | 111,506 |
| Total minimum lease payments | 371,370 |
| Less: imputed lease interest | (18,004) |
| Total lease liabilities | $ 353,366 |

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

| | |
|---|---|
| Operating lease expense | $ 241,443 |
| Variable lease expense | 58,697 |
| Total lease expense | $ 300,140 |

Cash payments related to operating leases for the year ended December 31, 2019 were $246,750.

**(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, 2019 and 2018, the Company's contributions to the plan was $107,419 and $84,276, respectively, and no contributions were made during the year ended December 31, 2017.

**(11) Income Taxes**

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

| | Year ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| United States | $ (26,052,255) | $ (34,308,847) | $ (27,051,148) |
| Foreign | (6,891,328) | (5,602,328) | (4,961,156) |
| Total | $ (32,943,583) | $ (39,911,175) | $ (32,012,304) |

The Company had $96.0 million and $84.0 million of federal net operating loss carryforwards and $2.6 million and $2.3 million of research tax credit carryforwards as of December 31, 2019 and 2018, 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 $103.8 million and $84.1 million of state net operating loss carryforwards as of December 31, 2019 and 2018, respectively. The state net operating loss carryforwards begin to expire in 2028 and 2027, respectively. As of December 31, 2019 and 2018, the Company had $1.0 million and $1.2 million, respectively, of Australia net operating loss carryforwards, which have an indefinite life.

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

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

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, 2019 and 2018 are as follows:

| | December 31, 2019 | December 31, 2018 |
|---|---|---|
| Deferred tax assets: | | |
| Net operating loss carry forwards | $ 27,661,926 | $ 24,399,299 |
| Research and development credit carry forwards | 2,666,036 | 2,291,226 |
| Stock-based compensation | 6,046,848 | 4,575,617 |
| Other | 650,018 | 706,745 |
| Gross deferred tax assets | 37,024,828 | 31,972,887 |
| Deferred tax liabilities: | | |
| Property and equipment | (28,926) | (59,524) |
| Gross deferred tax liabilities | (28,926) | (59,524) |
| Less valuation allowance | (36,995,902) | (31,913,363) |
| Net deferred tax asset | $ — | $ — |

The 2017 Tax Cuts and Jobs Act, which became effective in 2018, resulted in significant changes to the U.S. corporate income tax system. These changes included a federal statutory rate reduction from 34% to 21%, the elimination or reduction of certain domestic deductions and credits and limitations on the deductibility of interest expense and executive compensation. The 2017 Tax Cuts and Jobs Act also transitioned international taxation from a worldwide system to a modified territorial system and included base erosion prevention measures on non-U.S. earnings, which has the effect of subjecting certain earnings of our foreign subsidiaries to U.S. taxation as global intangible low-taxed income (GILTI). The 2017 Tax Cuts and Jobs Act also includes a one-time mandatory deemed repatriation tax on accumulated foreign subsidiaries' previously untaxed foreign earnings.

On December 22, 2017, the SEC staff issued Staff Accounting Bulletin, or SAB, No. 118 to address the application of U.S. GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the Tax Cuts and Jobs Act. The Company recognized the provisional tax impacts related to the revaluation of the deferred tax assets and liabilities and included these amounts in its consolidated financial statements for the year ended December 31, 2017. In regard to the change in the federal income tax rate as it related to our deferred tax assets and liabilities as of December 31, 2017, we decreased our related deferred tax assets by $8.7 million along with a corresponding offset against the valuation allowance for these deferred tax assets. The Company completed the accounting for the impacts of the 2017 Tax Cuts and Jobs Act as allowed under SAB No. 118 in the fourth quarter of 2018, which did not result in any material adjustments to the provisional estimates.

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, 2019 and 2018, 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 $5.1 million and $11.1 million during the years ended December 31, 2019 and 2018, respectively, due primarily to the generation of net operating loss carryforwards during those years.

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**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS–CONTINUED**

The Company does not have unrecognized tax benefits as of December 31, 2019 and 2018, 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, | | |
|---|---|---|---|
| | 2019 | 2018 | 2017 |
| Federal income tax benefit at statutory rate | 21.0 % | 21.0 % | 34.0 % |
| State income tax, net of federal benefit | 4.2 | 6.8 | 6.5 |
| Foreign tax rate differential | 0.1 | 0.3 | — |
| Nondeductible research and development expenses | (4.3) | (2.2) | (5.1) |
| Other permanent differences | — | — | (0.1) |
| Research and development credit benefit | 1.0 | 1.4 | 1.3 |
| Adjustment of prior years' income taxes | (6.6) | — | — |
| Rate change from 2017 Tax Cuts and Jobs Act | — | 0.3 | (27.3) |
| Change in valuation allowance | (15.4) | (27.6) | (9.3) |
| 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 2019 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 noncancelable operating leases for office space, under long-term lease arrangements that expire in 2021. As of December 31, 2019, future minimum lease commitments for all noncancelable leases were $318,561 and $135,963 for the years ending December 31, 2020 and 2021, respectively. Total lease expense for the years ended December 31, 2019, 2018 and 2017 was $300,140, $264,648 and $189,775 respectively.

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 become immediately vested.

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.

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

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. 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 Securities Exchange Act of 1934 ("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.

We believe that the claims asserted are without merit, and we intend to defend this action vigorously. The lawsuit is in the early stages and, at this time, no assessment can be made as to its likely outcome or whether the outcome will be material to us. Legal fees are expensed as incurred.

**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.

| | 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 |

| | 2018 | | | |
|---|---|---|---|---|
| | First Quarter | Second Quarter | Third Quarter | Fourth Quarter |
| Revenue | $ — | $ — | $ — | $ 86,000 |
| Operating expenses: | | | | |
| Research and development | 8,975,513 | 8,533,466 | 4,859,902 | 4,876,162 |
| General and administrative | 3,420,623 | 3,436,340 | 3,125,780 | 3,256,044 |
| Total operating expenses | 12,396,136 | 11,969,806 | 7,985,682 | 8,132,206 |
| Loss from operations | (12,396,136) | (11,969,806) | (7,985,682) | (8,046,206) |
| Other income (expense): | | | | |
| Interest income | 175,184 | 186,304 | 278,214 | 321,621 |
| Foreign exchange loss | (85,382) | (223,731) | (99,897) | (65,658) |
| Total other income (expense) | 89,802 | (37,427) | 178,317 | 255,963 |
| Net loss | $ (12,306,334) | $ (12,007,233) | $ (7,807,365) | $ (7,790,243) |
| | | | | |
| Net loss per share basic and diluted | $ (0.91) | $ (0.89) | $ (0.47) | $ (0.44) |
| Basic and diluted weighted average shares outstanding | 13,467,694 | 13,504,485 | 16,587,353 | 17,616,373 |

(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.

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, 2019. 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, 2019, 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, 2019. 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, 2019, 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, 2019 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 2020 annual meeting of stockholders to be filed no later than 120 days after the end of our fiscal year ended December 31, 2019 (the "2020 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 2020 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, 2019.

**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 | 3,838,716 | $ | 10.85 | 1,767,777 |
| Equity compensation plans not approved by security holders | 150,000 (1) | | 10.23 | — (2) |
| Total | 3,988,716 | $ | 10.83 | 1,767,777 |

(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 2020 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 2020 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 2020 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. |
| 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 | XBRL Instance Document (filed herewith). |
| 101 SCH | XBRL Taxonomy Extension Schema Document (filed herewith). |
| 101 CAL | XBRL Taxonomy Extension Calculation Linkbase Document (filed herewith). |
| 101 DEF | XBRL Taxonomy Extension Definition Linkbase Document (filed herewith). |
| 101 LAB | XBRL Taxonomy Extension Label Linkbase Document (filed herewith). |
| 101 PRE | XBRL Taxonomy Extension Presentation Linkbase Document (filed herewith). |

**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, 2020

**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<br>Armando Anido | Chairman and Chief Executive Officer<br>(Principal Executive Officer) | March 10, 2020 |
| /s/ James E. Fickenscher<br>James E. Fickenscher | Chief Financial Officer<br>(Principal Financial and Accounting Officer) | March 10, 2020 |
| /s/ John P. Butler<br>John P. Butler | Director | March 10, 2020 |
| /s/ Warren D. Cooper, MB, BS, BSc, MFPM<br>Warren D. Cooper, MB, BS, BSc, MFPM | Director | March 10, 2020 |
| /s/ William J. Federici<br>William J. Federici | Director | March 10, 2020 |
| /s/ Daniel L. Kisner, MD<br>Daniel L. Kisner, MD | Director | March 10, 2020 |
| /s/ Kenneth I. Moch<br>Kenneth I. Moch | Director | March 10 2020 |
| /s/ Pamela Stephenson<br>Pamela Stephenson | Director | March 10, 2020 |

# 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.

**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. 333-230182, 333-223597, 333-216968, 333-216967, and 333-207973) of Zynerba Pharmaceuticals, Inc. of our report dated March 10, 2020, with respect to the consolidated balance sheets of Zynerba Pharmaceuticals, Inc. as of December 31, 2019 and 2018, the related consolidated statements of operations, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2019, and the related notes, which report appears in the December 31, 2019 annual report on Form 10-K of Zynerba Pharmaceuticals, Inc.

/s/ KPMG LLP

Philadelphia, Pennsylvania
March 10, 2020

**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, 2020

**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, 2020

**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, 2019 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, 2020

**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, 2019 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, 2020