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

FORM 10-K

(Mark One)
☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2022
OR
☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from _____ to _____.

Commission file number: 001-37526

Zynerba Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

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

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

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, par value $0.001 per share	ZYNE	**The Nasdaq Global Market**

Securities registered pursuant to Section 12(g) of the Act:
None

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).
☒ Yes ☐ No

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

Large Accelerated filer ☐	Accelerated filer ☐
	Smaller reporting company ☒
Non-accelerated filer ☒	Emerging growth company ☐

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

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

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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 $47.7 million, based upon the closing price of $1.14 on the Nasdaq Global Market reported for June 30, 2022. 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 22, 2023, the registrant had 53,352,487 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 on Schedule 14A for the 2023 annual meeting of stockholders to be filed no later than 120 days after the end of the registrant's fiscal year ended December 31, 2022.

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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," "could," "continues," "estimate," "expect," "forecast," "intend," "outlook," "plan," "potential," "project," "projection," "should," "seek," "may," "would," "will," "should," "can," "can have," "likely," the negatives thereof and other words and terms of similar meaning.

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

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

- our expectations, projections and estimates regarding expenses, future revenue, capital requirements, incentive and other tax credit eligibility, collectability and timing and availability of and the need for additional financing;
- the results, cost and timing of our preclinical studies and clinical trials, including any delays to such clinical trials relating to enrollment or site initiation, as well as the number of required trials for regulatory approval and the criteria for success in such trials;
- our dependence on third parties in the conduct of our preclinical studies and clinical trials;
- legal and regulatory developments in the United States and foreign countries, including any actions or advice that may affect the design, initiation, timing, continuation, progress or outcome of clinical trials or result in the need for additional clinical trials;
- the results of our preclinical studies and earlier clinical trials of our product candidates may not be predictive of future results and we may not have favorable results in our ongoing or planned clinical trials;
- the difficulties and expenses associated with obtaining and maintaining regulatory approval of our product candidates, and the indication and labeling under any such approval;
- our plans and ability to develop and commercialize our product candidates;
- the successful development of our commercialization capabilities, including sales and marketing capabilities, whether alone or with potential future collaborators;
- the size and growth of the potential markets for our product candidates, the rate and degree of market acceptance of our product candidates and our ability to serve those markets;
- the coverage and reimbursement status for our product candidates from third-party payors;
- the success of competing therapies and products that are or become available;
- our ability to limit our exposure under product liability lawsuits, shareholder class action lawsuits or other litigation;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- legislative developments impacting our industry or the healthcare system broadly, including but not limited to the Inflation Reduction Act of 2022 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, contract laboratories and independent contractors;
- our ability to recruit or retain key scientific, commercial or management personnel or to retain our executive officers;

- our ability to maintain proper functionality and security of our internal computer and information systems and to prevent or avoid cyberattacks, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption;
- the extent to which health epidemics and other outbreaks of communicable diseases, including COVID-19 and higher than normal influenza and respiratory syncytial virus (RSV) rates, could disrupt our operations or materially and adversely affect our business and financial conditions;
- our ability to regain and maintain compliance with the continued listing requirements of The Nasdaq Global Market;
- a deterioration of the credit rating for U.S. long-term sovereign debt, and/or actions and uncertainties surrounding the debt ceiling and the federal budget;
- adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults or non-performance by financial institutions or transactional counterparties, could adversely affect our current and projected business operations and financial condition and results of operations; and
- the extent to which inflation and global instability, including political instability, such as a deterioration in the relationship between the U.S. and China or the conflict between Russia and Ukraine, including any additional resulting sanctions, export controls or other restrictive actions that may be imposed by the U.S. and/or other countries against governmental or other entities in, for example, Russia, may disrupt our business operations and/or our financial condition.

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

RISK FACTOR SUMMARY

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

Risks Related to Our Financial Position and Capital Needs

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

Risks Related to our Business

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

Risks Related to Government Regulation

- The regulatory approval processes of the United States Food and Drug Administration, or FDA, the European Medicines Agency, or the EMA, and other comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.
- We have conducted and are conducting clinical trials for Zygel outside the United States and anticipate conducting additional clinical trials for Zygel outside the United States, and the FDA may not accept data from such trials.
- Zygel may 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.

- Product shipment delays could have a material adverse effect on our business, results of operations and financial condition.
- Increased scrutiny on drug pricing or changes in pricing regulations could restrict the amount that we are able to charge for our product candidates, if approved, which could adversely affect our revenue and results of operations.
- We have been granted orphan drug designation by the FDA and the European Commission, or EC, for the use of cannabidiol for the treatment of Fragile X syndrome, or FXS, and chromosome 22q11.2 deletion syndrome, or 22q, but, if approved, we may be unable to maintain the benefits associated with orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.
- Serious adverse events or other safety risks could require us to abandon development and preclude, delay or limit approval of our product candidates, or limit the scope of any approved label or market acceptance.
- Even though Zygel has received Fast Track designation, the FDA may not approve it at all or any sooner than other product candidates that do not have Fast Track designation.

Risks Related to Our Dependence on Third Parties

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

Risks Related to Our Intellectual Property

- If we are unable to protect our intellectual property rights or if our intellectual property rights are inadequate for our technology and product candidates, our competitive position could be harmed.
- Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.
- We may become subject to claims by third parties either asserting that we or our employees have misappropriated their intellectual property or claiming ownership of what we regard as our own intellectual property.
- We may become involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful and have a material adverse effect on the success of our business.

Risks Related to Ownership of Our Common Stock

- The market price and trading volume of our stock may be volatile.
- We may not be able to regain compliance with the continued listing requirements of The Nasdaq Global Market.
- 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 such an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.
- Our sixth amended and restated certificate of incorporation also provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

General Risks Related to Ownership of Securities

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

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

We are the leader in pharmaceutically-produced transdermal cannabinoid therapies for orphan 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, and chromosome 22q11.2 deletion syndrome, or 22q.

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

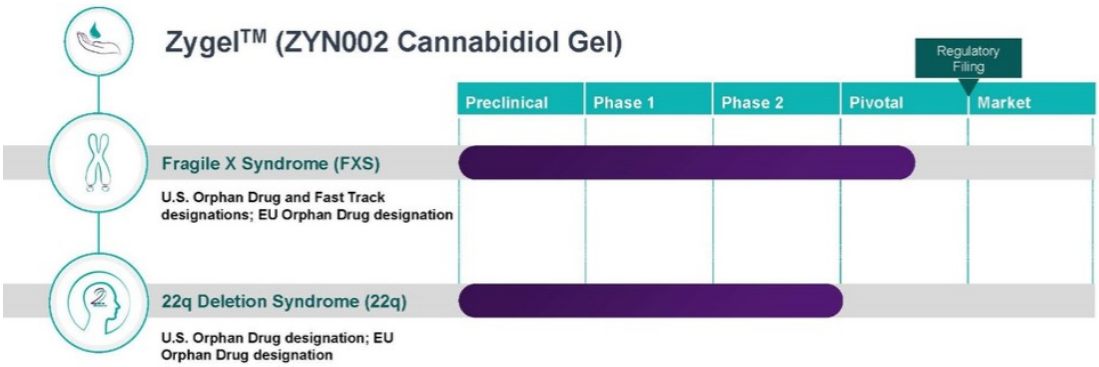
We are currently developing Zygel (also known as ZYN002), the first and only pharmaceutically-produced cannabidiol formulated as a permeation-enhanced gel for transdermal delivery and manufactured without the presence of THC, which is patent protected through 2030. Additional patents expiring between 2026 and 2040 are directed to methods of use relating to Zygel, including methods of treating FXS or 22q.

In preclinical animal studies, Zygel's permeation enhancer increased delivery of cannabidiol through the layers of the skin and into the circulatory system. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism of cannabidiol when delivered transdermally. In addition, an *in vitro* study published in *Cannabis and Cannabinoid Research* in April 2016 demonstrated that cannabidiol is degraded to THC (the major psychoactive cannabinoid in *Cannabis)* in an acidic environment such as the stomach. As a result, we believe such degradation may lead to increased psychoactive effects if cannabidiol is delivered orally. These effects may be avoided with the transdermal delivery of Zygel, which maintains cannabidiol in a neutral pH.

Zygel is being developed as a clear gel and is targeting treatment of behavioral symptoms of FXS and 22q. We have received orphan drug designations from the United States Food and Drug Administration, or FDA, for cannabidiol, the active ingredient in Zygel, for the treatment of FXS and 22q. During the first quarter of 2022, we received orphan drug designation from the European Commission for cannabidiol, the active ingredient in Zygel, for the treatment of FXS, followed by orphan drug designation for treatment of 22q in November 2022. 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.

Clinical Development Programs

Our clinical programs for Zygel include ongoing and planned clinical trials evaluating Zygel in the treatment of behavioral symptoms of FXS and 22q.



The Zygel safety database across all clinical studies conducted by us includes data from more than 900 volunteers and patients. Across these clinical studies, Zygel has been generally well-tolerated to date, with a safety profile that has been consistent across our Phase 2 and Phase 3 clinical trials.

FXS

CONNECT-FX Trial

In June 2020, we announced results of our CONNECT-FX clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study designed to assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the *FMR1* gene. While Zygel did not achieve statistical significance versus placebo in the primary endpoint of improvement in the Social Avoidance subscale of the Aberrant Behavior Checklist - Community FXS, or ABC-C_{FXS}, a pre-planned ad hoc analysis of the most severely impacted patients in the trial, as defined by patients having at least 90% methylation (“highly methylated”) of the impacted *FMR1* gene, demonstrated that those patients receiving Zygel achieved statistical significance in the primary endpoint of improvement at 12 weeks of treatment in the Social Avoidance subscale of the ABC-C_{FXS} compared to placebo. We performed a subsequent analysis of the CONNECT-FX population within those patients having 100% or complete methylation of the impacted *FMR1* gene, which demonstrated that these patients having complete methylation and receiving Zygel similarly achieved statistical significance in the primary endpoint of improvement at 12 weeks of treatment in the Social Avoidance subscale of the ABC-C_{FXS} compared to placebo.

RECONNECT Trial

In September 2021, we initiated our RECONNECT (A Randomized, Double-Blind, Placebo-Controlled, Multiple-Center, Efficacy and Safety Study of ZYN002 Administered as a Transdermal Gel to Children, Adolescents, and Young Adults with Fragile X Syndrome) trial, a pivotal, multi-national, confirmatory Phase 3 trial of Zygel in patients with FXS. The trial is designed to confirm the positive results observed in patients having 100% or complete methylation of the impacted *FMR1* gene in our CONNECT-FX trial.

RECONNECT is an 18-week trial that is expected to enroll approximately 200 patients, aged three through 22 years, at approximately 29 clinical sites in the United States, Australia, the United Kingdom and Ireland. Approximately 160 of the patients enrolled will have complete (100%) methylation of their *FMR1* gene and approximately 40 patients will

have partial methylation of their *FMR1* gene. Patients will be randomized 1:1 to either Zygel or placebo. Randomization will be stratified by gender, methylation status and weight.

The primary endpoint for the trial will be the change from baseline to the end of the treatment period in the ABC-C_{FXS} Social Avoidance subscale in patients who have complete methylation of their *FMR1* gene. The ABC-C_{FXS} Social Avoidance subscale is the same primary endpoint used in the CONNECT-FX trial.

Key secondary efficacy endpoints include: (i) the change from baseline to the end of the treatment period in the ABC-C_{FXS} Irritability subscale in patients who have complete methylation of their *FMR1* gene; (ii) the percent of patients with any improvement on the Caregiver Global Impression of Change, or CaGI-C, at the end of the treatment period for Social Interactions among patients with complete methylation of the *FMR1* gene; (iii) the percent of patients rated as improved on the Clinical Global Impression- Improvement, or CGI-I, scale among patients with complete methylation (100%) of the *FMR1* gene; and (iv) the change from baseline to the end of the treatment period in the ABC-C_{FXS} Social Avoidance subscale among all randomized patients (complete and partial methylation of the *FMR1* gene).

Top-line results for the RECONNECT trial are expected in the first half of 2024. All patients who complete dosing in the RECONNECT trial will be eligible to enroll in our ongoing open-label extension trial.

22q

Phase 2 INSPIRE Trial

In June 2022, we announced top-line results from our Phase 2 INSPIRE clinical trial, a 14-week, open-label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for treatment of behavioral symptoms of 22q. The Phase 2 trial was designed for signal detection by assessing the safety, tolerability and efficacy of Zygel for the treatment of behavioral symptoms of 22q in children and adolescents. Zygel was administered to patients with 22q as an add-on therapy to their standard of care and utilized a variety of efficacy assessments. Patients who completed the initial 14-week treatment period and met certain requirements were eligible to enroll in a 24 week open label extension, for a total treatment period of 38 weeks. In December 2022, we announced additional data from patients who completed 38 weeks of treatment in the INSPIRE trial. Key findings from the trial include:

- The total score and all five subscales of the Anxiety, Depression and Mood Scale (ADAMS) showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline;
- All five subscales of the Aberrant Behavior Checklist - Community, or ABC-C, showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline;
- The Pediatric Anxiety Rating Scale (PARS - R) showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline; and
- The majority of patients showed clinically meaningful improvements at week 14 as demonstrated by the CGI-I. Seventy-five percent of patients were rated by the clinicians as "improved," "much improved" or "very much improved" with nearly two-thirds (62.5%) of the patients being "much improved" or "very much improved."

Zygel was shown to be generally well tolerated over 38 weeks, and the safety profile was consistent with previously released data from other Zygel clinical trials. Three patients reported treatment related adverse events which were all mild application site adverse events. One patient discontinued treatment due to adverse events not related to Zygel.

Based on the positive Phase 2 data, we held an initial meeting with the FDA in the fourth quarter of 2022 to obtain feedback on the data and the regulatory path forward for Zygel in the treatment of children and adolescents with 22q. We expect that we will continue a productive dialogue with the FDA on this topic in 2023 and arrive at an acceptable trial design by the end of 2023. The Company does not expect to commence another trial in 22q until after the RECONNECT top line results are available in the first half of 2024.

Impact of COVID-19, Respiratory Syncytial Virus (RSV) and Influenza

We continue to closely monitor the status of COVID-19, including its potential impact on our clinical development plans, patient recruitment and overall clinical trial timelines going forward. In response to the impact of COVID-19, for our current clinical development programs, we implemented multiple measures consistent with the FDA's guidance on the conduct of clinical trials of medical products during COVID-19, including remote site monitoring and patient visits using telemedicine where needed and appropriate, direct-to-patient drug shipments and local study-related clinical laboratory collection.

There is a possibility that our current or future clinical trial sites may be affected by COVID-19 due to prioritization of hospital resources toward COVID-19, as well as the inability to access sites for initiation, patient enrollment and monitoring. As a result, patient screening, new patient enrollment, monitoring and data collection may be affected or delayed.

In the fall of 2022, there was a significantly higher prevalence of influenza and RSV, in addition to the ongoing presence of COVID-19, leading to a "tripledemic". The impact of the tripledemic was greatest in children, who are the primary population for our clinical trials.

We are aware that several clinical sites involved in our clinical trials have in the past temporarily stopped or delayed enrolling new patients, with exemptions if appropriate, and it is possible that these or other clinical sites may be similarly affected in the future. These developments may delay or extend our projected clinical trial timelines. Some of our third-party manufacturers, which we use for the supply of materials for product candidates or other materials necessary to manufacture products to conduct preclinical tests and clinical trials, and contract research organizations may be impacted by COVID-19. Should they experience disruptions, such as temporary closures or suspension of services, we would likely experience delays in advancing our current or planned clinical trials. As of the date of these financial statements, we are not aware of any specific event or circumstance that would require us to update our estimates, assumptions and judgments or revise the carrying value of its assets or liabilities. Actual results could differ from these estimates, and any such differences may be material to our consolidated financial statements.

Cannabidiol Science Overview

The endocannabinoid system includes the endocannabinoids, primarily 2-arachidonoylglycerol, or 2-AG, and anandamide, or AEA, and the cannabinoid receptors CB_1 and CB_2. The disruption of the endocannabinoid system may play a core role in the underlying pathophysiology of FXS leading to an imbalance of excitatory and inhibitory signaling and resulting behavioral symptoms.

Cannabidiol modulates the endocannabinoid system by inhibiting the metabolism (breakdown) of 2-AG and AEA. This inhibition is thought to result in increased 2-AG and AEA availability, greater CB_1 and CB_2 activation, reduced excitatory signaling and increased synaptic plasticity. Cannabidiol may restore homeostatic mechanisms in patients with endocannabinoid system dysfunction, restoring the balance of excitatory and inhibitory neuronal signaling. The effect of cannabidiol on the endocannabinoid system is the scientific basis for the use of cannabidiol in the treatment of FXS and 22q. Cannabidiol may also treat the neuropsychiatric symptoms of these conditions due to its activity as an agonist at $5\text{-}HT_{1A}$ and an antagonist at GPR55 receptors. Cannabidiol also reduces seizure frequency by blocking of the pro-excitatory actions of an endogenous membrane phospholipid, lysophosphatidylinositol (LPI), at GPR55 receptors. Cannabidiol acts as a GPR55 antagonist, blocking the effects of the LPI, resulting in dampening of neuronal hyperexcitability.

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

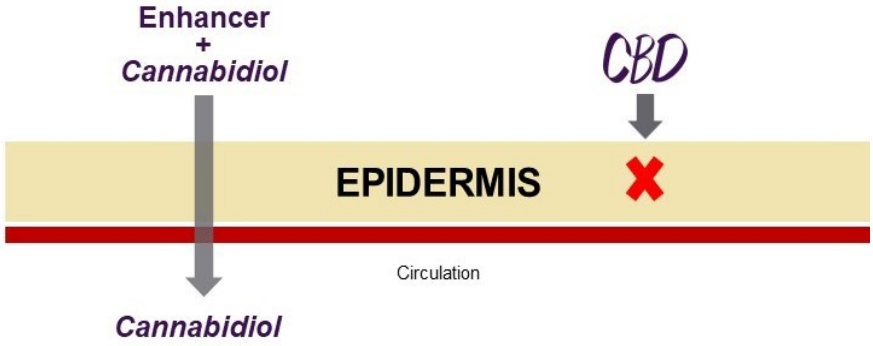
2020. The cannabinoid therapeutics market is expected to grow significantly due to the potential benefits these products may provide over existing therapies.

Product Candidates

Zygel - Cannabidiol Transdermal Gel

Zygel is the first and only pharmaceutically-produced cannabidiol formulated as a permeation-enhanced gel for transdermal delivery (see Figure 1) and manufactured without the presence of THC, and the formulation is patent protected through 2030.

Figure 1 — Permeation-enhanced transdermal gel delivery of cannabidiol.



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

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

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

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

FXS Overview

FXS is a rare genetic condition that causes intellectual disability, anxiety disorders, behavioral and learning challenges and various physical characteristics. The impairment can range from learning disabilities to more severe cognitive or intellectual disabilities. FXS is the leading known cause of both inherited intellectual disability and ASD. 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 U.S. Census data, various literature and third-party references FXS prevalence is estimated at approximately 78,000 patients in the United States or approximately 1 in 3,600 to 4,000 males and 1 in 4,000 to 6,000

females of all races and ethnic groups. We believe that approximately 60% of all patients with FXS have a completely methylated *FMR1* gene.

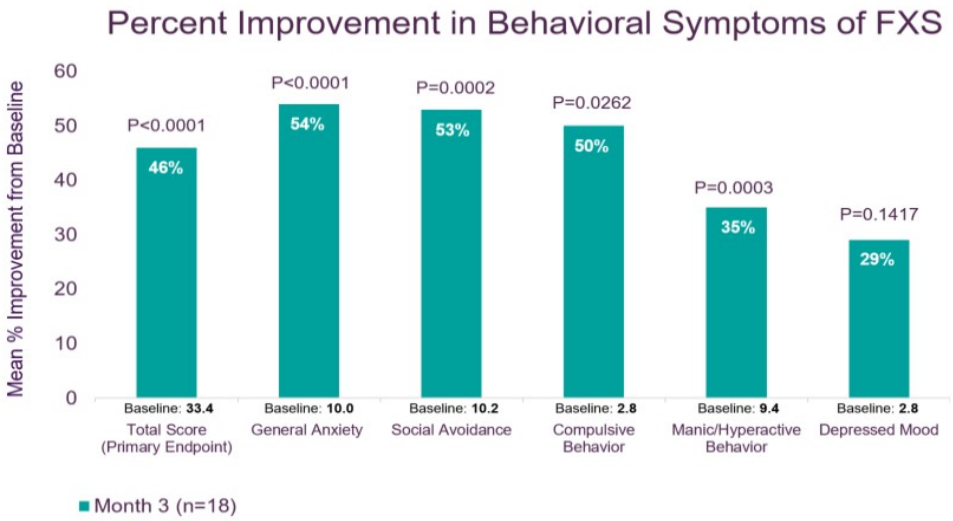
We believe Zygel may provide an effective treatment for patients with FXS that have a completely methylated *FMR1* gene based on its capacity to interact with the endocannabinoid system, which is compromised in patients with FXS. The endocannabinoid system facilitates synaptic homeostasis and plasticity resulting in feedback inhibition of neuronal signaling. Endocannabinoid system-mediated feedback inhibition and synaptic plasticity are thought to be disrupted in FXS due to absence of FMRP when the *FRM1* gene is completely methylated. Cannabidiol may help restore synaptic homeostasis in FXS. This modulation is the scientific basis for the use of cannabidiol in the treatment of FXS. We anticipate Zygel may be used as first line therapy to treat patients suffering from behavioral symptoms of FXS.

FAB-C

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

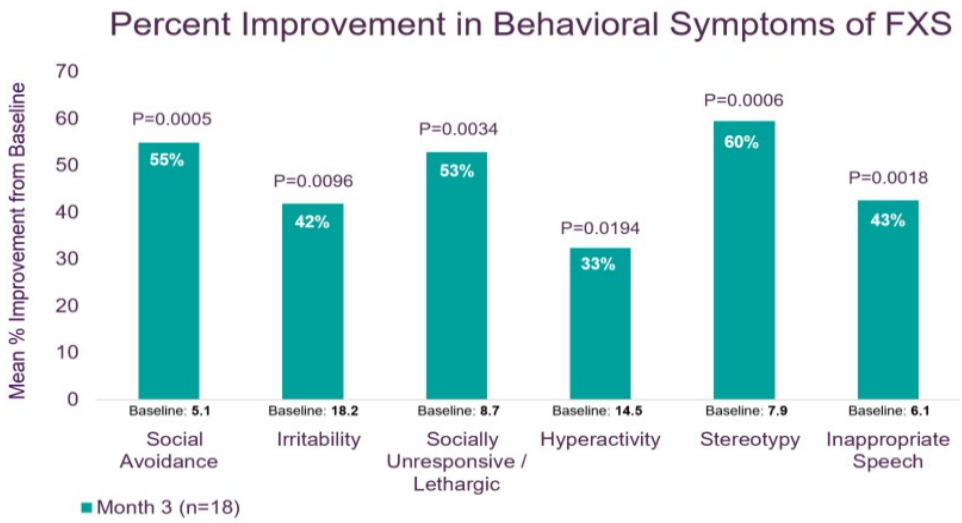
The FAB-C trial successfully met its primary endpoint, achieving a 46% improvement ($p<0.0001$) in the total score of ADAMS at week 12 compared to baseline.

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:

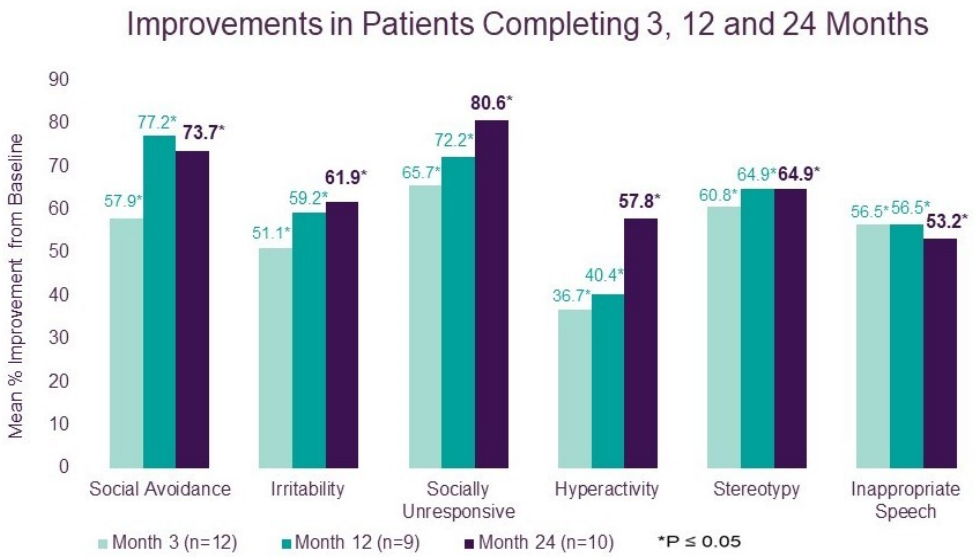


We evaluated multiple other secondary endpoints including CGI-I, the Pediatric Anxiety Rating Scale, or PARS-R, Visual Analog Scales for Anxiety, Hyperactivity and Tantrum/Mood Lability, the Vineland Adaptive Behavior III, a Quality of Sleep measurement and the Pediatric Quality of Life, or PedsQL™.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

Zygel was shown to be generally 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 gastrointestinal, or GI, events during the 12-week treatment period, and no THC was detected in the plasma. Of the 18 patients who completed the study, 13 enrolled in the open-label extension and seven patients are still being treated with Zygel as of January 23, 2023. These patients have now been on Zygel between 71 and 74 months.

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

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



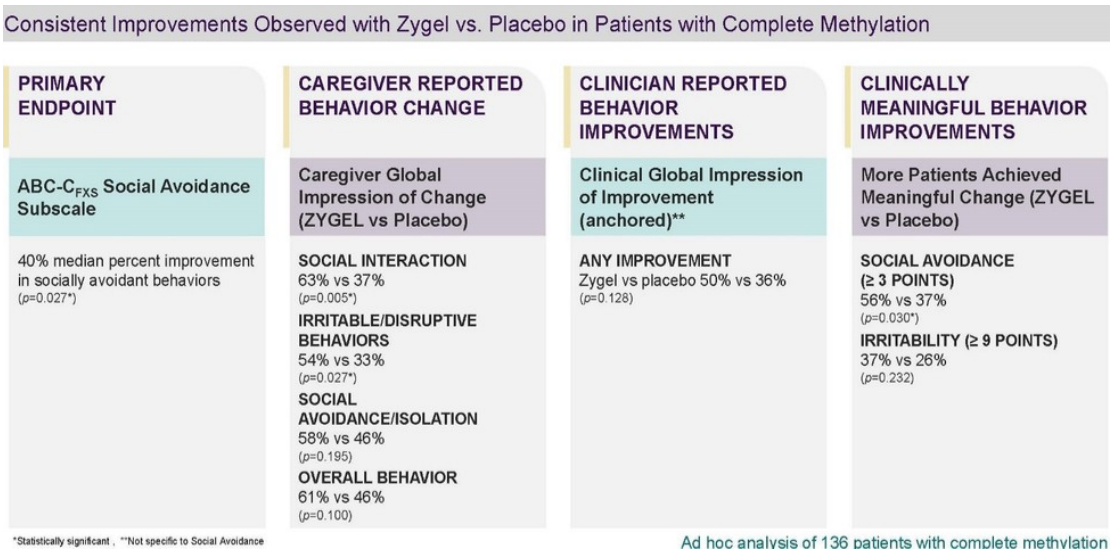
CONNECT-FX

In July 2018, we initiated our CONNECT-FX (**C**linical study **o**f Ca**nn**abidiol (CBD) in Childr**e**n and Adoles**c**en**t**s with **F**ragile **X**) clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study designed to assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the *FMR1* gene. In June 2020, we announced that Zygel did not achieve statistical significance versus placebo in the primary endpoint of improvement in the Social Avoidance subscale of the ABC-C_{FXS}. Zygel also did not demonstrate statistical significance versus placebo in the three key secondary endpoints, which were the change from baseline to the end of the treatment period in the Irritability subscale score of the ABC-C_{FXS}, the Socially Unresponsive/Lethargic subscale score of the ABC-C_{FXS} and CGI-I. The results of the CONNECT-FX trial, including the ad hoc analyses discussed below, were published in the peer reviewed *Journal of Neurodevelopmental Disorders* in November 2022.

We performed a pre-planned ad hoc analysis of the most severely impacted patients in the trial as defined by patients having at least 90% methylation, which we refer to as highly methylated, of the impacted *FMR1* gene, which accounted for 80% of the patients enrolled in the CONNECT-FX trial. This analysis demonstrated those patients receiving Zygel achieved statistical significance in the primary endpoint of improvement compared to placebo (p=0.020) in the Social Avoidance subscale of the ABC-C_{FXS} at 12 weeks of treatment, and the results of the Caregiver Global Impression - Change survey for these patients also showed a broad shift toward global improvement from baseline to week 12 with three of the four behavioral domains (social avoidance and isolation, irritable and disruptive behaviors, and social interactions) showing a statistically significant change in favor of patients on Zygel and the fourth domain (overall behavior) trending toward significance.

Following completion of the CONNECT-FX trial, we performed a subsequent analysis of the CONNECT-FX population within those patients having 100% methylation, which we refer to as completely methylated, of the impacted *FMR1* gene to evaluate the effect of Zygel versus placebo within this patient population. The completely methylated patients participating in CONNECT-FX consisted of 137 of 212 (65%) in the intent to treat population, with one patient excluded from the efficacy analysis due to lack of a post-baseline efficacy measure. The analysis demonstrated that these completely methylated patients receiving Zygel similarly achieved statistical significance in the primary endpoint of improvement compared to placebo (p=0.027) in the Social Avoidance subscale of the ABC-C_{FXS} at 12 weeks of treatment.

The data collected from the CONNECT-FX trial in patients with a completely methylated *FMR1* gene across the primary and key secondary endpoints used in the CONNECT-FX trial can be summarized in the following chart:



Based on what we learned from the CONNECT-FX trial and discussions with the FDA, we have modified certain aspects of the CONNECT-FX trial design into the trial design for our confirmatory Phase 3 clinical trial in FXS, which we refer to as our RECONNECT (A Randomized, Double-Blind, Placebo-Controlled, Multiple-Center, Efficacy and Safety Study of ZYN002 Administered as a Transdermal Gel to Children, Adolescents, and Young Adults with Fragile X Syndrome) clinical trial. These modifications include assessing the primary efficacy outcomes for patients with complete methylation of the *FMR1* gene, extending the length of the trial from 14 to 18 weeks, adding a third weight-based dose for the heaviest patients in the trial and making the trial more patient-friendly through virtual visits, fewer assessments being administered and reduced frequency of lab and ECG tests.

RECONNECT

In September 2021, we initiated our RECONNECT trial, a pivotal, multi-national, confirmatory Phase 3 trial of Zygel in patients with FXS. The trial is designed to confirm the positive results observed in the pre-planned, *ad hoc* analysis of the highly methylated patients and the subsequent analysis of completely methylated patients who participated in our CONNECT-FX trial.

RECONNECT is an 18-week trial that is expected to enroll approximately 200 patients, aged three through 22 years, at approximately 29 clinical sites in the United States, Australia, the UK and Ireland. Approximately 160 of the patients enrolled will have complete (100%) methylation of their *FMR1* gene and approximately 40 patients will have partial methylation of their *FMR1* gene. Patients will be randomized 1:1 to either Zygel or placebo. Randomization will be stratified by gender, methylation status and weight.

The primary endpoint for the trial will be the change from baseline to the end of the treatment period in the ABC-C$_{FXS}$ Social Avoidance subscale in patients who have complete methylation of their *FMR1* gene. Change from baseline in the ABC-C$_{FXS}$ Social Avoidance subscale is the same primary endpoint used in the CONNECT-FX trial.

Key secondary efficacy endpoints include: the change from baseline to the end of the treatment period in the ABC-C$_{FXS}$ Irritability subscale in patients who have complete methylation of their *FMR1* gene; the percent of patients with any

improvement on the CaGI-C at the end of the treatment period for Social Interactions among patients with complete methylation of the *FMR1* gene; the percent of patients rated as improved on the CGI-I scale among patients with complete methylation (100%) of the *FMR1* gene; and the change from baseline to the end of the treatment period in the ABC-C_{FXS} Social Avoidance subscale among all randomized patients (complete and partial methylation of the *FMR1* gene).

Top-line results for the RECONNECT trial are expected in the first half of 2024. All patients who complete dosing in the RECONNECT trial will be eligible to enroll in our ongoing open-label extension trial, which also includes patients who participated in our FAB-C and CONNECT-FX trials.

We received written scientific advice from the EMA providing clarity and guidance on the clinical and regulatory requirements for the submission of a Marketing Authorisation Application, or MAA, in the European Union, or EU, for Zygel for the treatment of behavioral symptoms associated with FXS. Based on the EMA' s scientific advice, we believe that the successful completion of the current development program for Zygel in FXS will satisfy the requirements of an MAA in the EU.

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

22q Overview

22q is the second most common genetic disorder behind Down Syndrome. It is a rare disorder, affecting approximately 83,000 patients in the U.S, which results from a microdeletion occurring on the long arm of chromosome 22 at a location designated q11.2. There are no drugs with an approved indication for the treatment of 22q.

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

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

Phase 2 Clinical Trial

In May 2019, we initiated our open-label Phase 2 INSPIRE (Assessing the Impact of Zygel [Transdermal Cannabidiol Gel] on Pediatric Behavioral and Emotional Symptoms of 22q11.2 Deletion Syndrome) clinical trial, a 14-week, open label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for treatment of behavioral symptoms of 22q. Recruitment into the INSPIRE trial had been delayed initially due to the impact of COVID-19 and resulting significant travel restrictions in Australia and, in the fourth quarter of 2021, we added an additional U.S. clinical trial site to the INSPIRE trial to assist in the completion of enrollment.

In June 2022, we announced top-line results from our open-label Phase 2 INSPIRE clinical trial, a 14-week, open-label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for treatment of behavioral symptoms of 22q. The Phase 2 trial was designed for signal detection by assessing the safety, tolerability and efficacy of Zygel for the treatment of behavioral symptoms of 22q in children and adolescents. Zygel was administered to patients with 22q as an add-on therapy to their standard of care and utilized a variety of efficacy assessments. In December 2022, we announced

additional data from patients who completed 38 weeks of treatment in the INSPIRE trial. Key findings from the trial include:

- The total score and all five subscales of the Anxiety, Depression and Mood Scale (ADAMS) showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline;

- All five subscales of the Aberrant Behavior Checklist - Community (ABC-C) showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline;

- The Pediatric Anxiety Rating Scale (PARS - R) showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline; and

- The majority of patients showed clinically meaningful improvements at week 14 as demonstrated by the CGI-I. Seventy-five percent of patients were rated by the clinicians as "improved," "much improved" or "very much improved" with nearly two-thirds (62.5%) of the patients being "much improved" or "very much improved."

Zygel was shown to be generally well tolerated over 38 weeks, and the safety profile was consistent with previously released data from other Zygel clinical trials. Three patients reported treatment related adverse events which were all mild application site adverse events. One patient discontinued treatment due to adverse events not related to Zygel.

Based on the positive Phase 2 data, we held an initial meeting with the FDA in the fourth quarter of 2022 to obtain feedback on the data and the regulatory path forward for Zygel in the treatment of children and adolescents with 22q. We expect that we will continue a productive dialogue with the FDA on this topic and arrive at an acceptable trial design by the end of 2023. The Company does not expect to commence another trial in 22q until after the RECONNECT top line results are available in the first half of 2024.

Other Recent Zygel Development Program

We previously evaluated Zygel for the treatment of pediatric and adolescent patients with Autism Spectrum Disorder (ASD). This clinical program consisted of our 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. Patients treated with Zygel demonstrated statistically significant improvement at week 14 compared to baseline for each ABC-C subscale (Irritability, Inappropriate Speech, Stereotypy, Social Withdrawal, and Hyperactivity). Patients receiving Zygel achieved statistically significant caregiver-reported improvements compared to baseline across all subscales of the AIM: Atypical behavior ($p<0.001$), Communication ($p<0.001$), Peer Interaction ($p<0.001$), Repetitive Behavior ($p<0.001$), and Social Reciprocity ($p=0.0053$). In addition, statistically significant improvements compared to baseline were observed at week 14 of treatment with Zygel in the Autism Parenting Stress Index ($p<0.0001$). Despite the positive results seen in the BRIGHT trial, in June 2022 we announced that given the difficult financing market, we decided to defer the start of the Phase 3 development program in ASD in favor of focusing our resources on FXS and 22q.

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 1, 2023, we own a total of 18 issued U.S. patents and 14 pending U.S. applications. The U.S. patents will expire between 2026 and 2040. 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 200 corresponding foreign issued patents and 142 corresponding foreign patent applications.

Our Zygel patent portfolio currently consists of nine issued patents in the United States, and ten pending United States patent applications. There are 48 issued patents in Japan, Canada, Mexico, Hong Kong, the United Kingdom and multiple countries in the European Union, and one pending Patent Cooperation Treaty, or PCT, application. The issued patents claim the permeation enhanced formulation of Zygel and methods of use relating to Zygel, including methods of treating FXS, 22q and ASD. Pending applications include claims directed to methods of treating FXS, 22q and ASD. The issued patents will expire between 2026 and 2040. We anticipate that any patents issued from our pending U.S. applications or pending PCT applications will expire between 2038 and 2041.

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

Trade Secrets and Proprietary Information

We seek to protect our proprietary information, including our trade secrets and proprietary know-how, by generally 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 APIs used in our product candidates are synthesized by contract manufacturers. Zygel is manufactured and filled into unit of use sachets by contract manufacturers.

We selected our contract manufacturers for their specific competencies in manufacturing, product design and materials. FDA regulations require that certain product candidates and commercial products be produced under applicable 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, if our product candidates are approved for marketing.

Commercial Operations

Our Vice President of Commercial and Business Development is responsible for pre-commercialization activities, including global market analysis, strategic optimization and value development associated with our product candidates, as well as business development activities as we evaluate partnering options. However, we do not currently have a fully integrated organization for the sales, marketing and distribution of pharmaceutical products. We currently plan to commercialize Zygel, if approved, in the United States and to enter into collaborations or licensing and co-promotion

agreements with third parties for the commercialization of our products in other territories. As we plan 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 and technologies that may become available in the future.

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

FXS

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

22q

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

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. In addition, labelers of drug products (the entity owning the National Drug Code listed for a product) participating in Medicaid and Medicare are required to comply with mandatory price reporting, discount, rebate, and other requirements. 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 EC, but country-specific regulation remains essential in many respects. The process of obtaining regulatory marketing approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and may not be successful.

U.S. Government Regulation

The FDA is the primary body that regulates pharmaceuticals in the United States, and its regulatory authority is based in the FDC Act. Pharmaceutical products are also subject to other federal, state and local statutes and regulations. In particular, while the U.S. Drug Enforcement Agency, or the DEA, has advised that it will not regulate Zygel as a controlled substance due to no detectable amounts of THC in its formulation, in some jurisdictions, cannabidiol may be classified as a controlled substance and is therefore subject to additional regulations by the appropriate regulatory authority. 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, as applicable, the FDA's good laboratory practices, or GLP, regulations and the Animal Welfare Act;
- submission to the FDA of an investigational new drug application, or 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 new drug application, or 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 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.

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 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 we plan to submit an IND with the FDA for Zygel in 22q in 2024.

We plan to submit NDAs for our product candidates to the FDA upon completion of all requisite clinical trials. The clinical investigation of a 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 in healthy volunteers. These studies are designed to evaluate the safety, metabolism, pharmacokinetics, or 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. If the FDA issues a clinical hold halting a clinical trial, the agency must notify the IND sponsor of the grounds for the hold. Any identified deficiencies must be resolved before the FDA will lift the hold and allow the clinical trial to begin or resume. 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), nonclinical 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.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product candidate as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, manufacturers must develop methods for testing the identity, strength, quality, potency and purity of the final product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

There are also various laws and regulations regarding laboratory practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances in connection with our research. In each of these areas, the FDA and other regulatory authorities have broad regulatory and enforcement powers, including the ability to levy fines and civil penalties, suspend or delay issuance of approvals, seize or recall products, and withdraw approvals.

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

New Drug Applications (NDA)

In order to obtain approval to market a drug in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the product candidate for the proposed indication. The application includes all relevant data available from pertinent nonclinical 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, where applicable. A description of any studies or data 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 $3,242,026 for fiscal year 2023. The applicant under an approved new drug application is also subject to an annual program fee, currently $393,933 per product for fiscal year 2023. These fees are typically increased annually. There may be some instances in which the user fee is waived, including in the case of an orphan drug designation, such as with Zygel for FXS and 22q. The FDA will initially review the NDA for completeness before it accepts the NDA for filing. The FDA has up to 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. If the application is not sufficiently complete, the FDA may refuse to accept the NDA for filing and request additional information. A refusal to file, which requires resubmission of the NDA with the requested additional information, delays review of the application. If the NDA submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Most NDAs for standard review product candidates are reviewed within 12 months of submission. The FDA can extend this review to consider certain late-submitted information or information intended to clarify information already provided in the submission. Most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. The FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP. The FDA may refer applications for novel product candidates that present challenging questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA may inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or, if the FDA concludes that an NDA does not meet the regulatory standards for approval, a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. Data from clinical trials are not always conclusive, and the FDA's interpretation of data may differ from that of the sponsor. 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 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, as well as exclusion from participation in federal healthcare programs, suspension and debarment from government contracts, and refusal of orders under existing government contracts as other potential penalties. 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. Manufacturers and other parties involved in the drug supply chain for prescription drug products must also comply with product tracking and tracing requirements and for notifying the FDA of counterfeit, diverted, stolen and intentionally adulterated products or products that are otherwise unfit for

distribution in the United States. 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 the change 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/or 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 and/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

In 2021, we received guidance from the DEA that any pharmaceutically manufactured cannabidiols which do not contain any quantity of THC (or any other controlled substance) would not be classified as a controlled substance. As part of the specifications for Zygel, we require receipt of a Certificate of Analysis from our manufacturers confirming that THC is not detected in the API used in our manufacturing process. This results in Zygel no longer being subject to regulation under the CSA.

While the DEA has advised that Zygel will not be subject to regulation under the CSA, states and foreign regulators could still regulate it as a controlled substance. Individual states in the U.S. may also maintain separate controlled substance laws and regulations, including licensing, recordkeeping, security, distribution and dispensing requirements, apart from the requirements under the CSA. State authorities, including Boards of Pharmacy, may choose to regulate use of controlled substances in each state. Failure to maintain compliance with applicable requirements (if any), 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.

We currently use contract manufacturers in the United States and Canada to manufacture the API for Zygel and contract manufacturers in the United Kingdom and Australia to manufacture the drug product. We have previously conducted clinical trials for Zygel in the United States, Australia and New Zealand, and plan to continue conducting clinical trials in these jurisdictions, along with the United Kingdom and Ireland. We may decide to develop, manufacture or commercialize our product candidates in additional countries. As a result, depending on the classification of pharmaceutically manufactured cannabidiols like Zygel in those jurisdictions, we may be subject to controlled substance laws and regulations from the TGA in Australia, Health Canada's Office of Controlled Substances in Canada, Medsafe 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 or other 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 term 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 MAA. In the European Union, marketing authorization for a medicinal product can be obtained through a centralized procedure, decentralized procedure, mutual recognition procedure, or the national procedure of an individual EU Member State. In accordance with the centralized procedure, the applicant can submit a single application for marketing authorization to the EMA to be assessed by the Committee of Medicinal Products for Human Use, or CHMP. The agency will provide a positive opinion regarding the application if it meets certain quality, safety and efficacy requirements. Following the opinion of the EMA, the European Commission makes a final decision to grant a centralized marketing authorization that permits the marketing of a product in all 27 EU Member States and three of the four European Free Trade Association, or EFTA, States, Iceland, Liechtenstein and Norway. The centralized procedure is mandatory for certain medicinal products, including orphan medicinal products, medicinal products derived from certain biotechnological processes, advanced therapy medicinal products and certain other medicinal products containing a new active substance for the treatment of certain diseases. This route is optional for certain other products, including medicinal products that are a significant therapeutic, scientific or technical innovation, or whose authorization would be in the interest of public or animal health.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application process is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

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

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

Data Exclusivity

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

Orphan Drug Designation (United States and EU)

United States - Under the Orphan Drug Act, the FDA may grant orphan drug designation to an investigational new 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 drug 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.

EU - 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. Product candidates that qualify for orphan drug 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 product candidates may be smaller, simply because of the smaller patient population. Nonetheless, the same approval standards apply to orphan-designated product candidates as for other drug candidates. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

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

The FDA has programs to expedite submission and consideration of certain drug product candidates 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 investigational 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. Product candidates with fast track designation also may be eligible for more frequent meetings and correspondence with the FDA about the product candidates' development. In May 2019, we received Fast Track designation from the FDA for Zygel 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 candidate qualifies for fast track designation or breakthrough therapy designation, the FDA may later decide that the product candidate 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 United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system. The United States government, state legislatures and foreign governments also have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

In recent years, Congress has considered reductions in Medicare reimbursement levels for drugs administered by physicians. CMS, the agency that administers the Medicare and Medicaid programs, also has authority to revise reimbursement rates and to implement coverage restrictions for some drugs. Cost reduction initiatives and changes in coverage implemented through legislation or regulation could decrease utilization of and reimbursement for any approved products. While Medicare regulations apply only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from federal legislation or regulation may result in a similar reduction in payments from private payers.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the Affordable Care Act, substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacted the pharmaceutical industry. The Affordable Care Act was 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 healthcare and health insurance industries,

impose new taxes and fees on pharmaceutical and medical device manufacturers, and impose additional health policy reforms. Among other things, the Affordable Care Act expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum Medicaid rebate for both branded and generic drugs, expanded the 340B program, and revised the definition of Average Manufacturer Price, or AMP, which could increase the amount of Medicaid drug rebates manufacturers are required to pay to states. The legislation also extended Medicaid drug rebates, previously due only on fee-for-service Medicaid utilization, to include the utilization of Medicaid managed care organizations as well and created an alternative rebate formula for certain new formulations of certain existing products that is intended to increase the amount of rebates due on those drugs. On February 1, 2016, CMS issued final regulations to implement the changes to the Medicaid Drug Rebate program under the Affordable Care Act, which became effective in 2016. Since that time, there have been significant ongoing efforts to modify or eliminate the Affordable Care Act.

The Affordable Care Act has been subject to challenges in the courts. In 2021, in an appeal from the lower courts regarding the constitutionality of the ACA, the Supreme Court ruled that the plaintiffs lacked standing to challenge the law as they had not alleged personal injury traceable to the allegedly unlawful conduct. As a result, the Supreme Court did not rule on the constitutionality of the ACA or any of its provisions.

Other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011 and subsequent legislation has resulted in automatic reductions to several government programs, including aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year. These reductions are in place to 2030. The Bipartisan Budget Act of 2018 increased labeler responsibility for prescription costs in the Medicare Part D coverage gap. The American Taxpayer Relief Act, passed in 2013, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. The Inflation Reduction Act of 2022 (IRA), includes several provisions that may impact our business to varying degrees, including provisions that reduce the out-of-pocket cap for Medicare Part D beneficiaries to $2,000 starting in 2025; impose new manufacturer financial liability on certain drugs under Medicare Part D; allow the U.S. government to negotiate Medicare Part B and Part D price caps for certain high-cost drugs and biologics without generic or biosimilar competition; require companies to pay rebates to Medicare for certain drug prices that increase faster than inflation; and delay the rebate rule that would limit the fees that pharmacy benefit managers can charge. Further, under the IRA, orphan drugs are exempted from the Medicare drug price negotiation program, but only if they have one rare disease designation and for which the only approved indication is for that disease or condition. If a product receives multiple rare disease designations or has multiple approved indications, it will not qualify for the orphan drug exemption. The effects of the IRA on our business and the healthcare industry in general is not yet known.

Further legislative and regulatory changes under the Affordable Care Act remain possible, although it is unknown what form any such changes or any law would take, and how or whether it may affect our business in the future. We expect that changes or additions to the Affordable Care Act, the Medicare and Medicaid programs, including the recent changes in the IRA allowing the federal government to directly negotiate certain drug prices, as well as changes stemming from other healthcare reform measures, especially with regard to healthcare access, financing or other legislation in individual states, could have a material adverse effect on the healthcare industry.

The Affordable Care Act requires pharmaceutical manufacturers of branded prescription drugs to pay a branded prescription drug fee to the federal government. Each individual pharmaceutical manufacturer pays a prorated share of the branded prescription drug fee, based on the dollar value of its branded prescription drug sales to certain federal programs identified in the law. Furthermore, the law, as subsequently amended by the Bipartisan Budget Act of 2018, requires manufacturers to provide a 70 percent point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D in order to reduce the coverage gap in Medicare drug plans. Provisions of IRA will serve to eliminate this coverage gap by reducing Medicare beneficiaries' out-of-pocket maximum from $7,050 to $2,000, starting January 1, 2025. Also starting January 1, 2025, the IRA will require a standard 10% or 20% discount on drugs dispensed to Medicare Part D beneficiaries based on whether they have met their out-of-pocket maximum.

The Affordable Care Act also expanded the Public Health Service's 340B drug pricing program. As noted above, the 340B drug pricing program requires participating manufacturers to agree to charge statutorily-defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. The Affordable Care Act

expanded the 340B program to include additional types of covered entities: certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, each as defined by the Affordable Care Act. Because the 340B ceiling price is determined based on AMP and Medicaid drug rebate data, revisions to the Medicaid rebate formula and AMP definition could cause the required 340B discounts to increase.

Payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives as well. For example, CMS may develop new payment and delivery models, such as bundled payment models. Recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. Such scrutiny has resulted in several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for pharmaceutical products.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing. These measures have included price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and other transparency measures. In some cases, the measures appeared designed to encourage importation from other countries and bulk purchasing arrangements.

We expect that additional federal, state and foreign healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, once approved, or additional pricing pressures.

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.

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

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

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

In addition, pursuant to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, a voluntary network of national authorities or bodies responsible for HTA in the individual EU Member States was established. The purpose of the network is to facilitate and support the exchange of scientific information concerning HTAs. This may lead to harmonization of the criteria taken into account in the conduct of HTAs between EU Member States and in pricing and reimbursement decisions and may negatively affect price in at least some EU Member States.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on pharmaceutical pricing, as will the recently enacted IRA. 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. Although an arrangement's failure to satisfy an exception or safe harbor does not necessarily mean that the arrangement is illegal, 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, some states 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. Further, laws similar to the California Consumer Privacy Act, or CCPA, which create individual privacy rights for consumers and increase the privacy and security obligations of entities handling certain personal data, have been proposed at the federal level and in other states.

As we conduct clinical trials in Australia, New Zealand, the United Kingdom and Ireland and may in the future 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, for our clinical trials in the United Kingdom and Ireland, there are strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting imposed by the General Data Protection Regulation, or GDPR, for jurisdictions in the European Union, and by the Data Protection Act of 2018 for trials conducted in the United Kingdom. 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 DSCSA, regulates the distribution and tracing of prescription drugs. The DSCSA imposes requirements to ensure accountability in prescription drug distribution, for example, it requires manufacturers to affix a product identifier to each package, bundle pack, case and pallet of a prescription drug product intended for sale. A product identifier is an electronically-readable graphic that contains information including the product' s unique serial number identifier, lot number, and expiration date. The DSCSA 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.

Clinical 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 clinical 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
Ran Barzilay, MD, PhD	Assistant Professor of Psychiatry, University of Pennsylvania Perelman School of Medicine
Elizabeth Berry-Kravis, MD, PhD	Professor of Pediatrics, Neurological Sciences, Biochemistry Rush University Medical Center
Carrie Buchanan, MD, FAAP	Developmental-Behavioral Pediatrician, Center for Translational Research, Greenwood Genetic Center
Geraldine Dawson, PhD	William Cleland Distinguished Professor of Psychiatry and Behavioral Sciences, Director, Duke Center for Autism and Brain Development, Duke University School of Medicine
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
Helen (Honey) Heussler, MBBS	Associate Professor, University of Queensland, Centre for Clinical Trials in Rare Neurodevelopmental Disorders, Children's Health Queensland, Centre for Child Health Research, University of Queensland, Children's Health Queensland Hospital and Health Service
John Messenheimer, MD	Consultant, Neurologist/Epileptologist, John Messenheimer PLLC
Steven J. Siegel, MD, PhD	Chair, Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California
Christopher J. Smith, PhD	Chief Science Officer, Southwest Autism Research & Resource Center; Assistant Professor of Medicine, Mount Sinai School of Medicine
Nicole Tartaglia, MD	Associate Professor, Pediatrics-Developmental Pediatrics, University of Colorado Denver School of Medicine/Children's Hospital of Colorado
Tony J. Simon PhD	Professor Emeritus of Psychiatry and Behavioral Sciences at the University of California, Davis School of Medicine
Kathy Angkustsiri, MD, MAS	Associate Professor of Clinical Pediatrics; Medical Director, 22q Healthy Minds Clinic, UC Davis MIND Institute

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 and Human Capital Resources

The pharmaceutical industry is highly competitive. Attracting, developing and retaining talented people experienced in medical, clinical development, regulatory, manufacturing, finance and other positions is crucial to executing our strategy and our ability to compete effectively. Currently, one third of our employees hold advanced degrees in areas of expertise that are critical to our mission and our success, including medicine, pharmacy, biology, business and law. Our ability to recruit and retain such talent depends on a number of factors, including compensation and benefits, career opportunities

and work environment. To that end, we offer compensation and incentives that include market-competitive pay, equity grants and performance bonuses, healthcare benefits, a retirement savings plan, paid time off and flexible work schedules. We embrace our Company culture and strive to foster a collaborative, inclusive and productive work environment. Digital transformation and the COVID-19 pandemic have fundamentally changed how people work, and we are leaning into digital-first workflows, tools and resources to enable us to be productive, wherever we are. We also believe in the value of people being together to help foster trust, relationships, collaboration and innovation. To fully leverage the contributions of our employees, our workplace model continues to evolve and provide opportunities for both in-office interactions and flexible work from home arrangements.

As of March 22, 2023, we had 27 employees, comprised of 25 full-time employees and 2 part-time employees. All of our employees are located in the U.S., with the exception of one employee located in Australia. In addition to our employees, we rely on third parties in the United States and in various parts of the world to conduct our preclinical studies and clinical trials, to provide services, including data management, statistical analysis and electronic compilation related to our development of Zygel, and to supply API and drug product for our clinical trials. We have no collective bargaining agreements with our employees and none are represented by labor unions.

Available information

Our internet website address is http://www.zynerba.com. Our Annual Reports 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 Securities Exchange Act of 1934, as amended, or 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 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, 2022, 2021 and 2020 were approximately $35.0 million, $37.3 million and $51.3 million, respectively. As of December 31, 2022, we had an accumulated deficit of $274.5 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 and obtain reasonable price increases over time 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 for our product candidates if our clinical trials are successful, to seek reimbursement for any approved product candidates and to launch and commercialize any product candidates for which we receive regulatory approval. As of December 31, 2022, we had approximately $50.6 million in cash and cash equivalents. We believe that cash and cash equivalents as of December 31, 2022 are sufficient to fund operations and capital requirements to mid-year 2024. The progress of Zygel for each target indication is uncertain because it is difficult to predict our spending for our product candidates prior to obtaining FDA approval due to numerous factors, including, without limitation, the rate of progress of clinical trials, the results of preclinical studies and clinical trials for such indication, the costs and timing of seeking and obtaining FDA and other regulatory approvals for clinical trials and FDA guidance regarding clinical trials for such indication. Moreover, changing circumstances may cause us to expend cash significantly faster than we currently anticipate, and we may need to spend more cash than currently expected because of circumstances beyond our control. For these reasons, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of preclinical studies and clinical trials for our product candidates;
- any change in the clinical development plans or target indications for these product candidates;
- the number and characteristics of product candidates that we develop or may in-license;
- the terms of any collaboration agreements we may choose to execute;
- the outcome, timing and cost of meeting regulatory requirements established by the 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 potential legal proceedings;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us;
- the effect of competing product and market developments;
- the extent to which health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic, could disrupt our operations or materially and adversely affect our business and financial conditions;
- the costs and timing of the implementation of commercial scale manufacturing activities; and
- the cost of establishing, or outsourcing, sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own.

We cannot be certain that additional funding will be available on acceptable terms, or at all. Our ability to raise additional funds when needed and on acceptable terms or at all will depend on financial, economic and market conditions and other factors, over which we may have no or limited control. For example, the continued challenging capital markets environment, lower prices for many securities and concerns about potential recessionary factors may affect our ability to raise additional funding through sales of our securities or issuance of indebtedness. 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. For example, despite the positive results seen in the BRIGHT trial, in June 2022 we announced that given the difficult financing market, we decided to defer the start of the Phase 3 development program in ASD in favor of focusing our resources on FXS and 22q. We could also be required to seek funds through arrangements with collaborators or others at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to our candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

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

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

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

Our subsidiary, Zynerba Pharmaceuticals Pty Ltd., is incorporated in Australia where we are currently engaged in research and development activities for Zygel. Our subsidiary is eligible to participate in the Australian Federal Government's Research and Development Tax Incentive program, under which the government provides a cash refund for a portion of eligible research and development expenditures (45% for fiscal years beginning prior to July 1, 2016 and 43.5% for fiscal years beginning on or after July 1, 2016) by small Australian entities, which are defined as Australian entities with less than $20 million (Australian) 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, or the ATO, for a percentage of the research and development costs expended by our subsidiary in Australia. Since the fiscal year ended December 31, 2015, we have been receiving Research and Development Tax Incentive refunds related to research and development expenditures we make.

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 to our anticipated refunds or change to the Research and Development Tax Incentive program would have a negative effect on our future cash flows.

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

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

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

As of December 31, 2022, we had U.S. net operating loss, or NOL, carryforwards of approximately $170.1 million for U.S. federal income tax and approximately $170.2 for state income 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 (the "Code"). Our NOL carryforwards generated in taxable years beginning before January 1, 2018 are permitted to be carried forward for 20 taxable years under applicable U.S. federal income tax law and begin to expire in 2028 if not utilized. NOL carryforwards generated in taxable years beginning after December 31, 2017 may be carried forward indefinitely, but the deductibility of such NOL carryforwards generally will be limited in taxable years beginning after December 31, 2020 to 80% of current year taxable income. NOLs arising in tax years beginning after December 31, 2020 may not be carried back. A full valuation allowance has been provided against our NOLs as of December 31, 2022. We cannot guarantee what the ultimate outcome or amount of the benefit we may receive from the NOLs, if any, will be.

Our NOL carryforwards could expire unused and be unavailable to offset future income tax liabilities because of restrictions under U.S. tax law. Under Section 382 of the Code, 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 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 of the Code and cannot forecast or otherwise determine our ability to derive benefit from our various U.S. 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, 2022, we have been granted approximately $7.9 million in federal and state research grants (all of which was granted prior to 2016). During 2018, we discontinued research and development studies associated with a previous grant and returned $0.7 million to the grantor in early 2019. Although we are not currently conducting research under any grants, we may be subject to audits by government agencies for previous grants. As part of an audit, these agencies may review our performance, cost structures and compliance with applicable laws, regulations, policies and standards and the terms and conditions of the grant. If any of our expenditures are found to be unallowable or allocated improperly or if we have otherwise violated terms of the grant, we may be required to repay funds previously disbursed. Accordingly, an audit could result in a material adjustment to our results of operations and financial condition.

Risks Related to our Business and Industry

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

We currently do not have any marketed products. Our business depends almost entirely on the successful clinical development, regulatory approval and commercialization of our product candidates, and substantial additional clinical development and regulatory approval efforts will be required before we are permitted to commence commercialization, if ever. The clinical trials and manufacturing and marketing of our product candidates will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, Australia, the European Union, the United Kingdom, 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 completed Phase 1, Phase 2 and Phase 3 clinical trials of Zygel may not necessarily be predictive of the results from our ongoing clinical trials for Zygel in patients with FXS or 22q, and any planned or proposed additional clinical trials. For example, the results observed in the pre-planned, ad hoc analysis of highly methylated patients and the subsequent analysis of completely methylated patients who participated in the

CONNECT-FX trial may not be indicative of results we will observe in our confirmatory pivotal RECONNECT trial, and, similarly, the results observed in our INSPIRE trial, including through the 38-week treatment period, may not be indicative of results observed in any future Phase 3 trial of Zygel for the treatment of 22q. In addition, our interpretation of clinical data or our conclusions based on our preclinical in vitro and in vivo models may prove inaccurate or the FDA, EMA or other government regulatory bodies may interpret the clinical data differently. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical trials after achieving positive results in preclinical and early clinical development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical findings while clinical trials were underway or safety or efficacy observations in clinical trials, including adverse events. Moreover, preclinical and clinical data can be susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA approval or a marketing authorization granted by the European Commission. If we fail to produce positive results in our ongoing or planned clinical trials of Zygel for the treatment of symptoms of FXS or 22q, the development timeline and regulatory approval and commercialization prospects for Zygel, and, correspondingly, our business and financial prospects, would be materially adversely affected. Given all of these uncertainties, you should not place undue reliance on early data.

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

We have limited resources to carry out objectives for our current and future pre-clinical studies and clinical trials. Since October 2015, we have conducted numerous clinical trials and plan to conduct clinical trials in the future, which is a time-consuming, expensive and uncertain process. In addition, while we have experienced management and expect to contract out many of the activities related to conducting these programs, we are a small company with only 27 employees and therefore have limited internal resources both to conduct pre-clinical studies and clinical trials and to monitor third-party providers. As our product candidates advance through clinical trials and potential regulatory approval and commercialization, we will need to expand our development, regulatory, commercial and manufacturing operations, either by expanding our internal capabilities or contracting with other organizations to provide these capabilities for us. In the future, we expect to have to manage additional relationships with collaborators or partners, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures.

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

Successful completion of clinical trials is a prerequisite to submitting an NDA to the FDA or an MAA to the EMA. Clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. A product candidate can unexpectedly fail at any stage of clinical development. The historic failure rate for product candidates is high due to scientific feasibility, findings related to safety and efficacy, changing regulatory standards and standards of medical care and other variables. In addition, inconclusive results or results that are not deemed statistically significant may cause delays in clinical development or lead us to reevaluate and redesign our clinical development programs. We do not know whether our clinical trials will begin or be completed on schedule, if at all, as the commencement and completion of clinical trials have in the past and may in the future 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, 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, or concerns from prospective patients relating to public health factors including COVID-19, RSV and influenza;
- 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;
- where applicable, recordkeeping, reporting or security violations at a clinical trial site, leading state authorities or foreign regulatory authorities to suspend or revoke the site's controlled substance registration and causing a delay or termination of planned or ongoing clinical trials;
- delays related to health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic;
- regulatory concerns with cannabinoid products generally and the potential for abuse of those products;
- difficulties retaining patients who have enrolled in a clinical trial who may withdraw due to lack of efficacy, side effects, personal issues or loss of interest and difficulties having subjects return for post-treatment follow-up;
- ambiguous or negative interim results; or
- lack of adequate funding to continue the clinical trial.

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

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

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

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

Because we have limited financial and managerial resources, we are focusing on research programs relating to Zygel for certain indications, which concentrates the risk of product failure in the event Zygel proves to be unsafe or ineffective or inadequate for clinical development or commercialization. In particular, we are studying Zygel in patients with FXS and 22q. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications for Zygel that could later prove to have greater commercial potential. We may also deem it advisable to refocus our clinical development programs based on clinical trial results. Our resource allocation decisions may cause us to fail to capitalize on viable approved commercial products (if any) or profitable market opportunities. For example, despite the positive results seen in the BRIGHT trial, in June 2022 we announced that given the difficult financing market, we decided to defer the start of the Phase 3 development program in ASD in favor of focusing our resources on FXS and 22q. Our spending on proprietary research and development programs relating to Zygel may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for Zygel, we may relinquish valuable rights to Zygel through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to Zygel.

Business interruptions, including any interruptions resulting from public health factors including COVID-19, RSV and influenza 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 candidates 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, health pandemic or other unforeseen disruption, then we or they may be prevented or delayed from effectively operating our or their business, respectively. We continue to closely monitor public health factors including COVID-19, RSV and influenza for potential impact to our clinical development plans, patient recruitment and overall trial timelines going forward. For example, in response to COVID-19, for our clinical development programs that were ongoing and/or completed during 2020, we implemented multiple measures consistent with the FDA' s guidance on the conduct of clinical trials of medical product candidates during the COVID-19 pandemic, including remote site monitoring and patient visits using telemedicine where needed and appropriate, direct to patient drug shipment from investigator sites, and local community study related clinical laboratory collection. We have continued to implement similar measures in our RECONNECT trial, which was initiated in September 2021, and will continue to evaluate them for other planned clinical trials that could be affected by the pandemic or other public health factors in the future.

Moreover, limitations on international travel in the jurisdictions in which we operate may delay key trial activities, including necessary interactions with regulators, ethics committees, and other important agencies and contractors. In addition, we, or our third-party partners, may be faced with limitations in staffing resources that would otherwise be focused on the conduct of clinical trials, the manufacture of clinical supply or performance of other relevant services, and we may face delays in patient recruitment due to sickness or the impact of quarantines or other similar restrictions or guidance on prospective patients.

Although most restrictions have been lifted, the resurgence or emergence of new variants of COVID-19 could in the future negatively impact our manufacturing and supply chain for Zygel, our clinical trial timelines, our financial condition and our results of operation. The extent to which the coronavirus and global efforts to contain its spread will

impact our operations will depend on future developments, which are highly uncertain and cannot be predicted at this time, and include the duration, severity and scope of the outbreak and the actions taken to contain or treat the coronavirus outbreak.

Even if we are able to commercialize Zygel, the product may not receive coverage and adequate reimbursement or appropriate price 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 or Medicare negotiated price may not be adequate to allow us to establish or maintain pricing that would allow us to realize a sufficient return on our investment.

In the United States, the Medicare Modernization Act of 2003 (MMA) 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 Inflation Reduction Act of 2022 (IRA) gives the Secretary of HHS the authority to negotiate prices for certain drugs directly with manufacturers. The MMA's and IRA's provisions, including their focus on cost reduction, the price negotiation program, inflation rebate requirements, and Part D benefit redesign, could limit the coverage and pricing opportunities available for any of our approved products. Furthermore, private payors often follow Medicare in setting their own coverage policies. Therefore, any reduction in coverage or limits on prices that results from these laws or future legislation may result in a similar downward pressures from private payors.

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

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

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

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

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

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

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

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

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

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

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

Political and social pressures and adverse publicity could lead to delays in approval of, and increased expenses for, our product candidates. These pressures could also limit or restrict the introduction and marketing of our product candidates, if approved. 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 and technologies that are either in development or currently marketed. See the section titled "Business — Competition."

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

Our product candidates may compete with other FDA approved cannabinoid drugs, including therapies such as Jazz Pharmaceuticals' 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 may become subject to securities class action litigation, which can be expensive, divert management attention, and, if resolved unfavorably, expose us to significant liabilities.

We have previously been subject to securities litigation and although we reached a final, court-approved settlement on all pending litigation during 2021, there can be no assurance that we will not become subject to additional litigation in the future that could result in substantial costs and a diversion of management's resources and attention. In addition, any adverse determination from future litigation 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, and, as we conduct clinical trials in the United Kingdom and Ireland, we are also subject to the EU's General Data Protection Regulation, or GDPR, and the Data Protection Act of 2018 in the United Kingdom. The legislative and regulatory landscape for data protection continues to evolve, and in recent years there has been an increasing focus on privacy and data security issues. Numerous federal and state laws, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws, govern the collection, use, and disclosure of health-related and other personal information.

In addition, our business processes some personal data, including some data related to health. When conducting clinical trials, we face risks associated with collecting trial participants' data, especially health data, in a manner consistent with applicable laws and regulations. For example, GDPR, which became effective in May 2018, and the U.K. Data Protection Act of 2018 impose several stringent requirements for controllers and processors of personal data of subjects residing in those jurisdictions, including, but not limited to, 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 personal data.

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 the event that we are subject to or affected by HIPAA 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. Any failure, or perceived failure, by us to comply with privacy and data protection laws, rules and regulations, including GDPR, could result in proceedings or actions against us by governmental entities or others. These proceedings or actions may subject us to significant penalties and negative publicity, require us to change our business practices, increase our costs and severely disrupt our business.

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

Risks Related to Government Regulation

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

We are not permitted to market our product candidates in the United States or the European Union until we receive approval of an NDA from the FDA or an MAA from the European Commission, respectively, or in any foreign countries until we receive the requisite approval from such countries. Prior to submitting an NDA to the FDA or an MAA to the EMA for approval of our product candidates, we will need to complete our preclinical studies and clinical trials. Successfully completing our clinical program and obtaining approval of an NDA or MAA is a complex, lengthy, expensive and uncertain process, and the FDA or EMA may delay, limit or deny approval of our product candidates for many reasons, including, among others, because:

- we may not be able to demonstrate that our product candidates are safe and effective in treating patients to the satisfaction of the FDA or EMA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or EMA for marketing approval;

- the FDA or EMA may disagree with the number, design, size, conduct or implementation of our clinical trials;
- the FDA or EMA may require that we conduct additional clinical trials;
- the FDA or EMA or other applicable foreign regulatory authorities may not approve the formulation, labeling or specifications of our product candidates;
- the CROs and other contractors that we may retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA or EMA may find the data from preclinical studies and clinical trials insufficient to demonstrate that Zygel is safe and effective for its 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;
- if the FDA determines that our product candidate has a potential for abuse, it may require us to include a description and analysis of studies or information related to abuse of the drug in the NDA, including, where applicable, a proposal for scheduling under the CSA, and further require us to perform additional studies;
- the FDA, 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 in any jurisdiction where the API used in the manufacturing of Zygel would be deemed a controlled substance, the applicable regulatory agency may impose quotas to limit the quantities of API available to our manufacturers; or
- the FDA, European Commission or other applicable foreign regulatory agencies may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could increase development costs, jeopardize our ability to obtain regulatory approval for and successfully market our product candidates and generate product revenue. Moreover, because our business is almost entirely dependent upon Zygel, any such setback with regard to Zygel in our pursuit of regulatory approval, in any of our planned indications, could have a material adverse effect on our business and prospects.

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

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

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

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

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

If we obtain regulatory approval for Zygel, such approval would be subject to extensive ongoing requirements by the 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 approved product will continue to be closely monitored by the FDA, EMA and other comparable foreign regulatory authorities. If the FDA, EMA 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, in some jurisdictions, 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 any approved 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 any necessary state registrations and registrations with applicable foreign regulatory authorities, and must establish and maintain processes to ensure

compliance with any 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.

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

In 2021, we received guidance from the DEA that any pharmaceutically manufactured cannabidiols which do not contain any quantity of THC (or any other controlled substance) would not be classified as a controlled substance. As part of the specifications for Zygel, we require receipt of a Certificate of Analysis from our manufacturers confirming that THC is not detected in the API used in our manufacturing process. This results in Zygel no longer being subject to regulation under the federal Controlled Substances Act.

While Zygel will not be regulated by the DEA, states and foreign regulators could still regulate it as a controlled substance. Individual states have 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.

We currently use contract manufacturers in the United States and Canada to produce the API for Zygel and contract manufacturers in the United Kingdom and Australia to manufacture the drug product candidates for our clinical trials. For Zygel, we have previously conducted clinical trials in Australia, New Zealand and the United States, and plan to continue conducting trials in those jurisdictions, along with trials in the United Kingdom and Ireland. In addition, we may decide to develop, manufacture or commercialize our product candidates in additional countries. As a result, we will be subject to controlled substance laws and regulations from the TGA in Australia, Health Canada's Office of Controlled Substances in Canada, Medsafe 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.

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 may require import and export licenses. In the United States, the FDA and U.S. Customs and Border Protection; 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; in the United Kingdom, the Drugs & Firearms Unit (Home Office) of the National Drug Control System; and in other countries, similar regulatory authorities, regulate the import and export of pharmaceutical product candidates that contain controlled substances. Specifically, the import and export process may require the issuance of import and export licenses by the relevant controlled substance authority, based on the applicable regulations in these jurisdictions, in both the importing and exporting country. We may not be granted, or if granted, maintain, such licenses from the authorities in certain countries. Even if we obtain the relevant licenses, shipments of API and our product candidates may be held up or lost in transit, which could cause significant delays and may lead to product candidate 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 product candidates in jurisdictions other than the United States and the European Union, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The regulatory approval process outside the United States and the European Union generally includes all of the risks associated with obtaining FDA approval or the approval from the European Commission but can involve additional testing. We may need to partner with third parties in order to obtain approvals outside the United States and the European Union. In addition, in many jurisdictions worldwide, it is required that the product candidate be approved for reimbursement before the product candidate can be approved for sale in such jurisdiction. We may not obtain approvals from regulatory authorities outside the United States and the European Union on a timely basis, if at all. Even if we were to receive approval in the United States or the European Union, approval by the FDA or the European Commission does not ensure approval by regulatory authorities in other countries or jurisdictions. Similarly, approval by one regulatory authority outside the United States and the European Union would not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA or the European Commission. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our product candidates in any market. If we are unable to obtain approval of our product candidates by regulatory authorities in other foreign jurisdictions, the commercial prospects of those product candidates may be significantly diminished and our business prospects could decline.

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

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that may affect our ability to profitably sell our product and product candidates, if approved. The United States government, state legislatures and foreign governments also have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs.

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

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

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

There have been significant ongoing judicial, administrative, executive and legislative efforts to modify or eliminate the Affordable Care Act. For example, the Tax 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 Code, commonly referred to as the individual mandate. The Budget Control Act of 2011 and subsequent legislation,

among other things, resulted in automatic reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013 and remain in place. The American Taxpayer Relief Act, signed into law in 2013, among other things, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

The Affordable Care Act has also been subject to challenges in the courts. Most recently, in 2021, in an appeal from the lower courts regarding the constitutionality of the ACA, the Supreme Court ruled that the plaintiffs lacked standing to challenge the law as they had not alleged personal injury traceable to the allegedly unlawful conduct. As a result, the Supreme Court did not rule on the constitutionality of the ACA or any of its provisions.

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

The Inflation Reduction Act of 2022, or IRA, includes several provisions that may impact our business to varying degrees, including provisions that reduce the out-of-pocket cap for Medicare Part D beneficiaries to $2,000 starting in 2025; impose new manufacturer financial liability on certain drugs under Medicare Part D; allow the U.S. government to negotiate Medicare Part B and Part D price caps for certain high-cost drugs and biologics without generic or biosimilar competition; require companies to pay rebates to Medicare for certain drug prices that increase faster than inflation; and delay the rebate rule that would limit the fees that pharmacy benefit managers can charge. Further, under the IRA, orphan drugs are exempted from the Medicare drug price negotiation program, but only if they have one rare disease designation and for which the only approved indication is for that disease or condition. If a product receives multiple rare disease designations or has multiple approved indications, it will not qualify for the orphan drug exemption. The effects of the IRA on our business and the healthcare industry in general is not yet known.

We expect that the Affordable Care Act, as well as other healthcare reform measures like the IRA 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 our product and product candidates, if approved, and could seriously harm our future revenues. Any reduction in reimbursement from Medicare, Medicaid, or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain and maintain profitability of our product and product candidates, if approved.

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

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

We have been granted orphan drug designation by the FDA and EC for the use of cannabidiol for the treatment of FXS and 22q, but, if approved, 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 drug candidates for relatively small patient populations as orphan drugs. The FDA may grant orphan drug designation to drug candidates 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, if approved, the cost of developing and making the drug would be recovered from sales in the United States. In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan designation to promote the development of product candidates 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 product candidates 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, if approved, 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 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 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 or EC 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 other 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 candidate nor gives the drug candidate 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 Zygel has received Fast Track designation, the FDA may not approve it at all or any sooner than other product candidates that do 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 and does not increase the likelihood of approval for a product candidate. 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 if it comes to believe a drug candidate no longer adequately addresses an unmet medical need. Fast Track designation alone does not guarantee qualification for the FDA's priority review procedures. If we seek Fast Track designation for other product candidates, we may not receive such a designation from the FDA.

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

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

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

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

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

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

- the federal Physician Payments Sunshine Act, 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, certain other licensed health care practitioners, and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members;

- civil monetary penalties that may apply to pharmaceutical manufacturers (1) found to have knowingly submitted any false pricing or other information to the government, (2) found to have made a misrepresentation in the reporting of our average sales price, (3) failing to submit the required data on a timely basis, (4) failing to participate in or offer negotiated pricing under the Medicare drug price negotiation program, if selected for participation, under the IRA, (5) failing to offer the negotiated price to Medicare beneficiaries, if subject to price negotiation, under the IRA, and (6) failing to pay inflation rebates as required under the IRA, among other conduct; which could also be grounds for the government to terminate government agreements for the purchase and reimbursement of pharmaceuticals and Medicare and other government healthcare program payment for manufacturer's drugs;

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

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

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

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

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, or those of our third-party service providers, are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any physicians or other healthcare providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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

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

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

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA or EMA regulations or similar regulations of other foreign regulatory authorities or to provide accurate information to the FDA, EMA or other foreign regulatory authorities. In addition, misconduct by employees could include intentional failures to comply with certain manufacturing standards, to comply with U.S. federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, to report financial information or data accurately or to disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have implemented, and will enforce, a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity, such as employee training on enforcement of the Code of Business Conduct and Ethics, may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Risks Related to Our Dependence on Third Parties

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

We rely on contract research organizations, or 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 product candidates produced under cGMP requirements, which mandate, among other things, the methods, facilities and controls used in manufacturing, processing and packaging of a drug product candidate 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 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, including, with respect to Zygel, the production of a synthetic cannabidiol containing no detectable

quantities of THC. Further, manufacturers of controlled substances must obtain and maintain any necessary state registrations and registrations with applicable foreign regulatory authorities, and must establish and maintain processes to ensure compliance with any 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, political instability, and other natural or man-made disasters or business interruptions. If their facilities are unable to operate because of an accident or incident, even for a short period of time, some or all of our research and development programs may be harmed or delayed, and our operations and financial condition could suffer. Our third-party manufacturers also may use hazardous materials, including chemicals and compounds that could be dangerous to human health and safety or the environment, and their operations may also produce hazardous waste products. In the event of contamination or injury, our third-party manufacturers could be held liable for damages or be penalized with fines in an amount exceeding their resources, which could result in our clinical trials or regulatory approvals being delayed or suspended.

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

We are not currently party to any collaborative arrangements for the commercialization of Zygel, if approved, or similar arrangements, although we may pursue such arrangements before any commercialization of Zygel, if approved. If we

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

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

Risks Related to Our Intellectual Property

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

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

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

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

inventions claimed in our owned patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

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

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

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

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

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

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

We 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 2022 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. 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. Such litigation has previously been brought against us and resolved. If new securities class action litigation is brought against us in the future, such litigation could result in substantial costs and a diversion of our management's attention and resources.

We may not be able to regain compliance with the continued listing requirements of The Nasdaq Global Market.

On November 1, 2022, we received written notice from the Listing Qualifications Department of the Nasdaq Stock Market LLC, or Nasdaq, notifying us that we were not in compliance with the minimum bid price requirements set forth in Nasdaq Listing Rule 5450(a)(1) for continued listing on The Nasdaq Global Market. Nasdaq Listing Rule 5450(a)(1) requires listed securities to maintain a minimum bid price of $1.00 per share, and Listing Rule 5810(c)(3)(A) provides that a failure to meet the minimum bid price requirement exists if the deficiency continues for a period of 30 consecutive business days. Based on the closing bid price of our common stock for the 30 consecutive business days prior to the date of the Notification Letter, we no longer meet the minimum bid price requirement.

We have 180 calendar days, or until May 1, 2023, to regain compliance with Nasdaq Listing Rule 5450(a)(1). To regain compliance, our common stock must have a closing bid price of at least $1.00 per share for a minimum of 10 consecutive business days at any time prior to May 1, 2023.

If we do not regain compliance by May 1, 2023, we may be eligible for an additional 180 calendar day compliance period if we elect (and meet the listing standards) to transfer to The Nasdaq Capital Market to take advantage of the additional compliance period offered on that market. To qualify, we would be required, among other things, to meet the continued listing requirement for market value of publicly held shares as well as all other standards for initial listing on The Nasdaq Capital Market, with the exception of the Minimum Bid Price Requirement, and we would need to provide written notice of our intention to cure the bid price deficiency during the second compliance period.

There can be no assurance that we will be able to regain compliance with the minimum bid price requirement. However, if we fail to regain compliance with the minimum bid price listing requirement or fail to maintain compliance with all other applicable continued listing requirements and Nasdaq determines to delist our common stock, the delisting could adversely impact us by, among other things, reducing the liquidity and market price of our common stock; reducing the number of investors willing to hold or acquire our common stock; limiting our ability to issue additional securities in the future, including under our ATM arrangement with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc. and our Equity Purchase Agreement with Lincoln Park Capital Fund, LLC; and limiting our ability to fund our operations.

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 13.1% of our voting stock as of March 22, 2023. This concentration of ownership could harm the market price of our common stock by:

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

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

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

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

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

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

Pursuant to our equity incentive plan, our compensation committee is authorized to grant equity-based incentive awards to our directors, executive officers and other employees and service providers. As of March 22, 2023, there were 615,153 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 sixth amended and restated certificate of incorporation also provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

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

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

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

General Risks Relating to the Ownership of Securities

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

The Sarbanes-Oxley Act of 2002 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, subject to an exemption for so long as we remain a "smaller reporting company," an attestation from our independent registered public accounting firm on the effectiveness of our internal control over financial reporting.

Our compliance with the applicable rules of 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, 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. Now that we no longer qualify as an "emerging growth company," these expenses may continue to increase compared to what we incurred in prior years. 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 the Nasdaq Stock Market LLC. Our management and other personnel devote a substantial amount of time to these compliance initiatives.

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

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our company headquarters are located in Devon, Pennsylvania, where we occupy 10,877 square feet of office space. Our current lease for office space terminates on May 31, 2024.

Item 3. Legal Proceedings

There are no material pending legal proceedings involving the Company. We may become engaged in legal actions arising in the ordinary course of our business (such as, for example, proceedings relating to employment matters or minor commercial disputes) from time to time and, while there can be no assurance, we believe that those types of legal actions will not have a material adverse effect on our business, results of operations, financial condition or cash flows.

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 22, 2023, there were 59 holders of record of our common stock. The actual number of holders of our common stock is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend Policy

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

Issuer Repurchases of Equity Securities

None.

Securities Authorized for Issuance Under Equity Compensation Plans

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

Recent Sales of Unregistered Securities

None.

Item 6. Reserved

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 consolidated 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 orphan 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, and chromosome 22q11.2 deletion syndrome, or 22q.

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

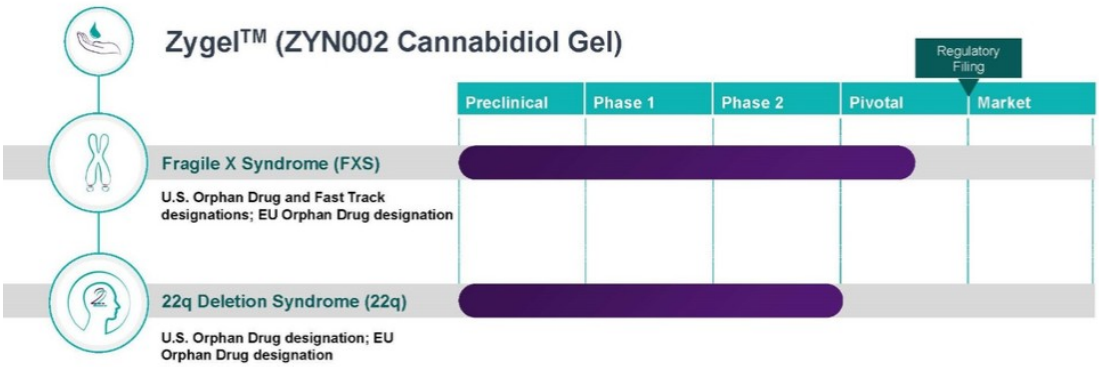
We are currently developing Zygel (also known as ZYN002), the first and only pharmaceutically-produced cannabidiol formulated as a permeation-enhanced gel for transdermal delivery and manufactured without the presence of THC, which is patent protected through 2030. Additional patents expiring between 2026 and in 2040 are directed to methods of use relating to Zygel, including methods of treating FXS or 22q.

In preclinical animal studies, Zygel's permeation enhancer increased delivery of cannabidiol through the layers of the skin and into the circulatory system. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism of cannabidiol when delivered transdermally. In addition, an *in vitro* study published in *Cannabis and Cannabinoid Research* in April 2016 demonstrated that cannabidiol is degraded to THC (the major psychoactive cannabinoid in *Cannabis)* in an acidic environment such as the stomach. As a result, we believe such degradation may lead to increased psychoactive effects if cannabidiol is delivered orally. These effects may be avoided with the transdermal delivery of Zygel, which maintains cannabidiol in a neutral pH.

Zygel is being developed as a clear gel and is targeting treatment of behavioral symptoms of FXS and 22q. We have received orphan drug designations from the United States Food and Drug Administration, or FDA, and the European Commission for cannabidiol, the active ingredient in Zygel, for the treatment of FXS and 22q. In May 2019, we received Fast Track designation from the FDA for treatment of behavioral symptoms associated with FXS. The FDA's Fast Track program is designed to facilitate the development of drugs intended to treat serious conditions and fill unmet medical needs and can lead to expedited review by the FDA in order to get new important drugs to the patient earlier.

Clinical Development Programs

Our clinical programs for Zygel include ongoing and planned clinical trials evaluating Zygel in the treatment of behavioral symptoms of FXS and 22q.



The Zygel safety database across all clinical studies conducted by us includes data from more than 900 volunteers and patients. Across these clinical studies, Zygel has been generally well-tolerated to date, with a safety profile that has been consistent across our Phase 2 and Phase 3 clinical trials.

FXS

CONNECT-FX Trial

In June 2020, we announced results of our CONNECT-FX clinical trial, a multi-national randomized, double-blind, placebo-controlled, 14-week study designed to assess the efficacy and safety of Zygel in children and adolescents ages three through 17 years who have full mutation of the *FMR1* gene. While Zygel did not achieve statistical significance versus placebo in the primary endpoint of improvement in the Social Avoidance subscale of the Aberrant Behavior Checklist - Community FXS, or ABC-C_{FXS}, a pre-planned ad hoc analysis of the most severely impacted patients in the trial, as defined by patients having at least 90% methylation (“highly methylated”) of the impacted *FMR1* gene, demonstrated that those patients receiving Zygel achieved statistical significance in the primary endpoint of improvement at 12 weeks of treatment in the Social Avoidance subscale of the ABC-C_{FXS} compared to placebo. We performed a subsequent analysis of the CONNECT-FX population within those patients having 100% or complete methylation of the impacted *FMR1* gene, which demonstrated that these patients having complete methylation and receiving Zygel similarly achieved statistical significance in the primary endpoint of improvement at 12 weeks of treatment in the Social Avoidance subscale of the ABC-C_{FXS} compared to placebo.

RECONNECT Trial

In September 2021, we initiated our RECONNECT (A Randomized, Double-Blind, Placebo-Controlled, Multiple-Center, Efficacy and Safety Study of ZYN002 Administered as a Transdermal Gel to Children, Adolescents, and Young Adults with Fragile X Syndrome) trial, a pivotal, multi-national, confirmatory Phase 3 trial of Zygel in patients with FXS. The trial is designed to confirm the positive results observed in patients having 100% or complete methylation of the impacted *FMR1* gene in our CONNECT-FX trial.

RECONNECT is an 18-week trial that is expected to enroll approximately 200 patients, aged three through 22 years, at approximately 29 clinical sites in the United States, Australia, the United Kingdom and Ireland. Approximately 160 of the patients enrolled will have complete (100%) methylation of their *FMR1* gene and approximately 40 patients will

have partial methylation of their *FMR1* gene. Patients will be randomized 1:1 to either Zygel or placebo. Randomization will be stratified by gender, methylation status and weight.

The primary endpoint for the trial will be the change from baseline to the end of the treatment period in the ABC-C_{FXS} Social Avoidance subscale in patients who have complete methylation of their *FMR1* gene. The ABC-C_{FXS} Social Avoidance subscale is the same primary endpoint used in the CONNECT-FX trial.

Key secondary efficacy endpoints include: (i) the change from baseline to the end of the treatment period in the ABC-C_{FXS} Irritability subscale in patients who have complete methylation of their *FMR1* gene; (ii) the percent of patients with any improvement on the Caregiver Global Impression of Change, or CaGI-C, at the end of the treatment period for Social Interactions among patients with complete methylation of the *FMR1* gene; (iii) the percent of patients rated as improved on the Clinical Global Impression- Improvement, or CGI-I, scale among patients with complete methylation (100%) of the *FMR1* gene; and (iv) the change from baseline to the end of the treatment period in the ABC-C_{FXS} Social Avoidance subscale among all randomized patients (complete and partial methylation of the *FMR1* gene).

Top-line results for the RECONNECT trial are expected in the first half of 2024. All patients who complete dosing in the RECONNECT trial will be eligible to enroll in our ongoing open-label extension trial.

22q

Phase 2 INSPIRE Trial

In June 2022, we announced top-line results from our Phase 2 INSPIRE clinical trial, a 14-week, open-label clinical trial designed to assess the safety, tolerability and efficacy of Zygel for treatment of behavioral symptoms of 22q. The Phase 2 trial was designed for signal detection by assessing the safety, tolerability and efficacy of Zygel for the treatment of behavioral symptoms of 22q in children and adolescents. Zygel was administered to patients with 22q as an add-on therapy to their standard of care and utilized a variety of efficacy assessments. Patients who completed the initial 14-week treatment period and met certain requirements were eligible to enroll in a 24 week open label extension for a total treatment period of 38 weeks. In December 2022, we announced additional data from patients who completed 38 weeks of treatment in the INSPIRE trial. Key findings from the trial include:

- The total score and all five subscales of the Anxiety, Depression and Mood Scale (ADAMS) showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline;
- All five subscales of the Aberrant Behavior Checklist - Community, or ABC-C, showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline;
- The Pediatric Anxiety Rating Scale (PARS - R) showed statistically significant improvements at 14 and 38 weeks of treatment compared to baseline; and
- The majority of patients showed clinically meaningful improvements at week 14 as demonstrated by the CGI-I. Seventy-five percent of patients were rated by the clinicians as "improved," "much improved" or "very much improved" with nearly two-thirds (62.5%) of the patients being "much improved" or "very much improved."

Zygel was shown to be generally well tolerated over 38 weeks, and the safety profile was consistent with previously released data from other Zygel clinical trials. Three patients reported treatment related adverse events which were all mild application site adverse events. One patient discontinued treatment due to adverse events not related to Zygel.

Based on the positive Phase 2 data, we held an initial meeting with the FDA in the fourth quarter of 2002 to obtain feedback on the data and the regulatory path forward for Zygel in the treatment of children and adolescents with 22q. We expect that we will continue a productive dialogue with the FDA on this topic in 2023 and arrive at an acceptable trial design by the end of 2023. The Company does not expect to commence another trial in 22q until after the RECONNECT top line results are available in the first half of 2024.

Impact of COVID-19, Respiratory Syncytial Virus (RSV) and Influenza

We continue to closely monitor the status of COVID-19, including its potential impact on our clinical development plans, patient recruitment and overall clinical trial timelines going forward. In response to the impact of COVID-19, for our current clinical development programs, we implemented multiple measures consistent with the FDA's guidance on the conduct of clinical trials of medical products during COVID-19, including remote site monitoring and patient visits using telemedicine where needed and appropriate, direct-to-patient drug shipments and local study-related clinical laboratory collection.

There is a possibility that our current or future clinical trial sites may be affected by COVID-19 due to prioritization of hospital resources toward COVID-19, as well as the inability to access sites for initiation, patient enrollment and monitoring. As a result, patient screening, new patient enrollment, monitoring and data collection may be affected or delayed.

In the fall of 2022, there was a significantly higher prevalence of influenza and RSV, in addition to the ongoing presence of COVID-19, leading to a "tripledemic". The impact of the tripledemic was greatest in children, who are the primary population for our clinical trials.

We are aware that several clinical sites involved in our clinical trials have in the past temporarily stopped or delayed enrolling new patients, with exemptions if appropriate, and it is possible that these or other clinical sites may be similarly affected in the future. These developments may delay or extend our projected clinical trial timelines. Some of our third-party manufacturers, which we use for the supply of materials for product candidates or other materials necessary to manufacture products to conduct preclinical tests and clinical trials, and contract research organizations may be impacted by COVID-19. Should they experience disruptions, such as temporary closures or suspension of services, we would likely experience delays in advancing our current or planned clinical trials. As of the date of these financial statements, we are not aware of any specific event or circumstance that would require us to update our estimates, assumptions and judgments or revise the carrying value of its assets or liabilities. Actual results could differ from these estimates, and any such differences may be material to our consolidated financial statements.

Operations

We have never been profitable and have incurred net losses since inception. Our net losses were $35.0 million, $37.3 million and $51.3 million for the years ended December 31, 2022, 2021, and 2020 respectively. As of December 31, 2022, our accumulated deficit was $274.5 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, 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, or the ATO, for a percentage of the research and development costs expended by the Subsidiary in Australia. The cash refund is available to eligible companies with an annual aggregate revenue of less than $20.0 million (Australian) during the reimbursable period. We estimate the amount of cash refund we expect to receive related to the Australian research and development tax incentive program and record the incentives when it is probable 1) we will comply with relevant conditions of the program and 2) the incentive will be received. We evaluate the Subsidiary's eligibility under tax incentive programs as of each balance sheet date based on the most current and relevant data available. If the Subsidiary is deemed to be ineligible or unable to receive the Australian research and development tax credit, or the Australian government significantly reduces or eliminates the tax credit, the actual cash refund we receive may materially differ from our estimates.

In December 2018, the Subsidiary submitted an Advance Overseas Finding ("AOF") application to a division of the Australian Government's Department of Industry, Innovation and Science ("AusIndustry"), for a portion of the Company's research and development activities incurred outside of Australia, which was approved by AusIndustry in July 2019. During the year ended December 31, 2019, we recorded $8.3 million as an incentive and tax receivable and recorded a corresponding credit to research and development expense for amounts expected to be received through the AOF for the period January 1, 2018 through December 31, 2019. In June 2020, the ATO informed us that we may not qualify for the AOF program based on their interpretation of certain eligibility requirements and, during the three months ended June 30, 2020, we determined it was no longer probable that the AOF claim would be received and we recorded a full reserve against the AOF receivable.

During the three months ended March 31, 2022, we concluded our conversations with the ATO on these matters and made the decision to no longer pursue the AOF claim, resulting in the write off of both the AOF receivable and the corresponding reserve during the period. During the three months ended March 31, 2022, we received a payment of $8.0 million from the ATO for the non-AOF research and development incentive for the years ended December 31, 2018, 2019 and 2020.

The following table summarizes research and development expenses for the years ended December 31, 2022, 2021, and 2020.

	Year ended December 31,		
	2022	2021	2020
Research and development expenses - before R&D incentive	$ 22,101,576	$ 22,454,878	$ 29,437,551
Research and development incentive (non-AOF)	(1,001,910)	(1,030,389)	(1,890,252)
Research and development expenses (before impact of AOF)	21,099,666	21,424,489	27,547,299
Amounts reserved against AOF refund	—	—	8,107,695
Total research and development expenses	$ 21,099,666	$ 21,424,489	$ 35,654,994

We expect research and development expenses to increase in 2023 as compared to 2022 as we continue to conduct our RECONNECT clinical trial for FXS. These expenditures are subject to numerous uncertainties regarding timing and cost to completion. The impact of inflation could significantly impact the cost of our ongoing operations. Completion of our preclinical development and clinical trials may take several years or more and the length of time generally varies

according to the type, complexity, novelty and intended use of a product candidate. The cost of clinical trials may vary significantly over the life of a project as a result of differences arising during clinical development, including, among others:

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

Due to the early stages of our research and development, we are unable to determine the duration or completion costs of our development of our product candidates. As a result of the difficulties of forecasting research and development costs of our product candidates as well as the other uncertainties discussed above, we are unable to determine when and to what extent we will generate revenue from the commercialization and sale of an approved product candidate.

General and Administrative Expenses — General and administrative expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our executive, finance, legal, human resource, investor relations and commercial functions. Our general and administrative expenses also include facility and related costs not included in research and development expenses, professional fees for legal services, including patent-related expenses, litigation settlement expenses, consulting, tax and accounting services, insurance, market research and general corporate expenses. We expect that our general and administrative expenses will increase for the next several years due to inflation and increased labor costs, and 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 — As of December 31, 2022, we had $170.1 million of federal operating loss carryforwards and $5.7 million of research tax credit carryforwards available to offset future taxable income and income tax, respectively. These operating loss and research tax credit carryforwards will begin to expire in 2028 and 2027, respectively. Operating losses that were generated after December 31, 2017 carryforward indefinitely. At December 31, 2022 and 2021, we concluded that a full valuation allowance is necessary for our deferred tax assets as it is uncertain if the deferred income tax assets associated with our U.S. operations will be realized.

Critical Accounting Estimates

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

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

Research and Development Expenses

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

Results of Operations

Comparison of the Years Ended December 31, 2022 and December 31, 2021

	Year Ended December 31,		Increase (Decrease)	
	2022	2021	$	%
Operating expenses:				
Research and development	$ 21,099,666	$ 21,424,489	$ (324,823)	(2)%
General and administrative	14,151,874	15,345,901	(1,194,027)	(8)
Total operating expenses	35,251,540	36,770,390	(1,518,850)	(4)
Loss from operations	(35,251,540)	(36,770,390)	1,518,850	(4)
Other income (expense)	215,734	(538,634)	754,368	(140)
Net loss	$(35,035,806)	$(37,309,024)	$ 2,273,218	(6)%

Research and Development Expenses

Research and development expenses decreased by $0.3 million, or 2%, to $21.1 million for the year ended December 31, 2022 from $21.4 million for the year ended December 31, 2021. The decrease was primarily related to lower stock-based compensation expenses partially offset by increases in manufacturing costs associated with our Zygel program.

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General and Administrative Expenses

General and administrative expenses decreased by $1.2 million, or 8%, to $14.2 million for the year ended December 31, 2022 from $15.3 million for the year ended December 31, 2021. The decrease was primarily related to lower stock-based compensation expenses and a decrease in proxy solicitation costs related to our annual meeting.

Other Income (Expense)

During the years ended December 31, 2022 and 2021, we recognized $0.8 million and $21,047, respectively, in interest income. The increase in interest income was related to interest income received from the ATO for the payment of the prior year's non-AOF research and development incentives and higher average interest rates earned on our investments. During the years ended December 31, 2022 and 2021, we recognized foreign currency losses of $0.6 million for both periods. Foreign currency gains and losses are due primarily to the remeasurement of the Subsidiary's assets and liabilities, which are denominated in the local currency to the Subsidiary's functional currency, which is the U.S. dollar.

Liquidity and Capital Resources

Since our inception in 2007, we have devoted most of our cash resources to research and development and general and administrative activities. We have financed our operations primarily with the proceeds from the issuance and sale of equity securities (most notably our initial public offering, our follow-on public offerings and sales under our "at-the-market" offerings and through the Equity Purchase Agreement) 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, 2022, our principal sources of liquidity were our cash and cash equivalents of $50.6 million. Our working capital was $45.6 million as of December 31, 2022.

Management believes that cash and cash equivalents as of December 31, 2022 are sufficient to fund operations and capital requirements to mid-year 2024. Substantial additional financings will be needed to fund our operations and to complete clinical development of and to commercially develop our product candidates. There is no assurance that such financing will be available when needed or on acceptable terms. Our ability to access the capital markets or otherwise raise such capital may be adversely impacted by global economic conditions and the recent disruptions to, and volatility in, financial markets in the United States and worldwide resulting from multiple factors such as the ongoing COVID-19 pandemic and conflict in Ukraine.

At The Market Financings

In May 2021, we entered into a Controlled Equity Offering℠ Sales Agreement, or the 2021 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, under a prospectus filed in May 2022, we may sell, from time to time, up to $75.0 million of our common stock. During the year ended December 31, 2022, we sold and issued 4,608,274 shares of common stock under the 2021 Sales Agreement in the open market at a weighted average selling price of $1.35 per share, resulting in gross proceeds of $6.2 million. Net proceeds after deducting commissions and offering expenses were $5.8 million. From January 1, 2023 through March 22, 2023, we sold and issued 1,179,077 shares of our common stock in the open market at a weighted average selling price of $0.56 per share, for gross proceeds of $0.7 million and net proceeds, after deducting commissions and offering expenses, of $0.6 million.

Equity Purchase Agreement

On July 21, 2022, we entered into a purchase agreement, or the Purchase Agreement, with Lincoln Park Capital Fund, LLC, or Lincoln Park, pursuant to which Lincoln Park committed to purchase up to $20.0 million of our common stock. Under the terms and subject to the conditions of the Purchase Agreement, we have the right, but not the obligation, to sell to Lincoln Park, and Lincoln Park is obligated to purchase up to $20.0 million of our common stock. Such sales of common stock will be subject to certain limitations, and may occur from time to time, at our sole discretion, over the 36-month period commencing on July 21, 2022. The number of shares we may sell to Lincoln Park on any single business day in a regular purchase is 150,000, but that amount may be increased up to 300,000 shares, depending upon the market price of our common stock at the time of sale and subject to a maximum limit of $2.0 million per regular purchase. The purchase price per share for each such regular purchase will be based on prevailing market prices of our common stock immediately preceding the time of sale as computed under the Purchase Agreement. In addition to regular purchases, we may also direct Lincoln Park to purchase other amounts as accelerated purchases or as additional accelerated purchases. During the year ended December 31, 2022, we sold and issued 350,000 shares of common stock under the Purchase Agreement at a weighted average selling price of $0.92 per share, resulting in gross of $0.3 million and net proceeds, after deducting offering expenses, of $0.2 million. From January 1, 2023 through March 22, 2023, we sold and issued 1,950,000 shares of common stock under the Purchase Agreement at a weighted average selling price of $0.53 per share, resulting in gross and net proceeds of $1.0 million.

Debt

We had no debt outstanding as of December 31, 2022 or 2021.

Future Capital Requirements

During the year ended December 31, 2022, net cash used in operating activities was $23.0 million, and our accumulated deficit as of December 31, 2022 was $274.5 million. Our expectations regarding future cash requirements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make in the future. To the extent that we enter into any of those types of transactions, we may need to raise substantial additional capital.

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

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

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

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. Other than the Purchase Agreement with Lincoln Park, 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, including through our 2021 Sales Agreement or Purchase Agreement with Lincoln Park, our stockholders will experience dilution.

Cash Flows

The following table summarizes our cash flows from operating, investing and financing activities for the years ended December 31, 2022 and 2021.

	Year Ended December 31,	
	2022	2021
Statement of Cash Flows Data:		
Total net cash (used in) provided by:		
Operating activities	$(23,026,950)	$(33,457,476)
Investing activities	(154,105)	(47,570)
Financing activities	6,014,048	42,155,859
Net (decrease) increase in cash and cash equivalents	$(17,167,007)	$ 8,650,813

Operating Activities

For the year ended December 31, 2022, cash used in operating activities was $23.0 million, compared to $33.5 million for the year ended December 31, 2021. The change from the comparable 2021 period was primarily due to the Company receiving payment of $8.0 million from the ATO for the non-AOF research and development incentive for the years ended December 31, 2018, 2019 and 2020. Our cash flows used in operations may differ substantially from our net loss due to non-cash charges and changes in balance sheet accounts.

We expect cash used in operating activities to increase in 2023 as compared to 2022, as we continue to conduct our RECONNECT clinical trial in FXS.

Investing Activities

For the years ended December 31, 2022 and 2021, cash used in investing activities represented the cost of expenditures made for manufacturing equipment.

Financing Activities

Cash provided by financing activities for the year ended December 31, 2022 consisted of $5.8 million in net proceeds from sales of our shares of common stock under the 2021 Sales Agreement and $0.2 million in net proceeds from sales of our shares under the Purchase Agreement. Cash provided by financing activities for the year ended December 31, 2021 consisted primarily of $42.2 million in net proceeds from sales of our shares of common stock under the 2019 Sales Agreement.

Recently Adopted Accounting Pronouncements

In November 2021, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update No. 2021-10, *Government Assistance (Topic 832): Disclosure by Business Entities about Government Assistance,* or ASU 2021-10, which improves the transparency of government assistance received by most business entities by requiring the disclosure of: (1) the types of government assistance received; (2) the accounting for such assistance; and (3) the effect of the assistance on a business entity's financial statements. This guidance is effective for financial statements issued for

annual periods beginning after 15 December 2021. The adoption of the guidance on January 1, 2022 did not have a material impact on our consolidated financial statements.

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, 2022, we had cash and cash equivalents of $50.6 million consisting primarily of cash and money market account balances. Because of the short-term maturities of our cash and cash equivalents, we do not believe that an immediate 10% increase in interest rates would have any significant impact on the realized value of our investments. Accordingly, we do not believe we are exposed to material market risk with respect to our cash and cash equivalents.

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

Item 8. Financial Statements and Supplementary Data

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

Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

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

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Zynerba Pharmaceuticals, Inc. and subsidiary (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations, stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2022, 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, 2022 and 2021, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

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

Evaluation of prepaid development expenses and accrued research and development expenses

As discussed in Notes 2, 4 and 6 to the consolidated financial statements, research and development costs are expensed as incurred, which include accrued external research and development expenses incurred under arrangements with third parties, such as contract research organizations (CROs) that conduct clinical trials and contract manufacturing organizations (CMOs). At the end of each reporting period, the Company compares the payments made to each service provider to the estimated progress towards completion of the related project, considering factors such as the number of patients enrolled in studies, milestones achieved and other criteria related to the efforts of its vendors. Depending on the timing of payments to vendors and estimated services provided, the Company will record net prepaid or accrued expenses related to these costs. The prepaid development expenses and accrued research and development expenses were $0.7 million and $4.2 million, respectively, as of December 31, 2022.

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

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

/s/ KPMG LLP

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

Philadelphia, Pennsylvania
March 28, 2023

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 50,640,993	$ 67,808,000
Incentive and tax receivables	1,225,383	9,580,468
Prepaid expenses and other current assets	2,908,731	2,831,392
Total current assets	54,775,107	80,219,860
Property and equipment, net	409,572	385,833
Right-of-use assets	336,215	565,814
Total assets	$ 55,520,894	$ 81,171,507
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,942,830	$ 1,798,813
Accrued expenses	7,014,882	7,896,598
Lease liabilities	214,901	209,068
Total current liabilities	9,172,613	9,904,479
Lease liabilities, long-term	119,524	353,694
Total liabilities	9,292,137	10,258,173
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; 47,895,687 shares issued and outstanding at December 31, 2022 and 41,217,537 shares issued and outstanding at December 31, 2021	47,896	41,218
Additional paid-in capital	320,698,146	310,353,595
Accumulated deficit	(274,517,285)	(239,481,479)
Total stockholders' equity	46,228,757	70,913,334
Total liabilities and stockholders' equity	$ 55,520,894	$ 81,171,507

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS

	Year ended December 31,		
	2022	2021	2020
Operating expenses:			
Research and development	$ 21,099,666	$ 21,424,489	$ 35,654,994
General and administrative	14,151,874	15,345,901	16,407,548
Total operating expenses	35,251,540	36,770,390	52,062,542
Loss from operations	(35,251,540)	(36,770,390)	(52,062,542)
Other income (expense):			
Interest income	846,860	21,047	243,992
Foreign exchange (loss) gain	(631,126)	(559,681)	481,719
Total other income (expense)	215,734	(538,634)	725,711
Net loss	$(35,035,806)	$(37,309,024)	$(51,336,831)
Net loss per share basic and diluted	$ (0.82)	$ (0.95)	$ (1.90)
Basic and diluted weighted average shares outstanding	42,662,770	39,259,495	27,022,931

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
YEARS ENDED DECEMBER 31, 2020, 2021 and 2022

	Common stock		Additional	Accumulated	Total stockholders'
	Shares	Amount	paid-in capital	deficit	equity
Balance at December 31, 2019	**23,211,391**	**$23,211**	**$226,409,156**	**$(150,835,624)**	**$75,596,743**
Issuance of common stock, net of issuance costs	6,596,873	6,597	30,699,492	—	30,706,089
Issuance of restricted stock	167,000	167	(167)	—	—
Stock-based compensation expense	—	—	5,177,527	—	5,177,527
Net loss	—	—	—	(51,336,831)	(51,336,831)
Balance at December 31, 2020	**29,975,264**	**29,975**	**262,286,008**	**(202,172,455)**	**60,143,528**
Issuance of common stock, net of issuance costs	10,244,326	10,245	42,210,099	—	42,220,344
Issuance of restricted stock	984,822	985	(985)	—	—
Exercise of stock options	13,125	13	47,893	—	47,906
Stock-based compensation expense	—	—	5,810,580	—	5,810,580
Net loss	—	—	—	(37,309,024)	(37,309,024)
Balance at December 31, 2021	**41,217,537**	**41,218**	**310,353,595**	**(239,481,479)**	**70,913,334**
Issuance of common stock, net of issuance costs	4,958,274	4,958	6,014,544	—	6,019,502
Commitment shares issued under an equity purchase agreement	347,222	347	(347)	—	—
Issuance of restricted stock	1,372,654	1,373	(1,373)	—	—
Stock-based compensation expense	—	—	4,331,727	—	4,331,727
Net loss	—	—	—	(35,035,806)	(35,035,806)
Balance at December 31, 2022	**47,895,687**	**$47,896**	**$320,698,146**	**$(274,517,285)**	**$46,228,757**

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year ended December 31,		
	2022	2021	2020
Cash flows from operating activities:			
Net loss	$(35,035,806)	$(37,309,024)	$(51,336,831)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	219,283	247,140	207,035
Stock-based compensation	4,331,727	5,810,580	5,177,527
Changes in operating assets and liabilities:			
Incentive and tax receivables	8,355,084	(537,882)	5,571,383
Prepaid expenses and other assets	(58,998)	2,472,624	(2,981,094)
Right-of-use assets and liabilities	1,263	(7,542)	(3,027)
Accounts payable	70,568	(723,903)	(2,145,165)
Accrued expenses	(910,071)	(3,409,469)	4,196,132
Net cash used in operating activities	(23,026,950)	(33,457,476)	(41,314,040)
Cash flows from investing activities:			
Purchases of property and equipment	(154,105)	(47,570)	(445,314)
Net cash used in investing activities	(154,105)	(47,570)	(445,314)
Cash flows from financing activities:			
Proceeds from the issuance of common stock	6,557,290	43,193,660	31,707,228
Payment of financing fees and expenses	(543,242)	(1,085,707)	(853,929)
Proceeds from the exercise of stock options	—	47,906	—
Net cash provided by financing activities	6,014,048	42,155,859	30,853,299
Net (decrease) increase in cash and cash equivalents	(17,167,007)	8,650,813	(10,906,055)
Cash and cash equivalents at beginning of year	67,808,000	59,157,187	70,063,242
Cash and cash equivalents at end of year	$ 50,640,993	$ 67,808,000	$ 59,157,187
Supplemental disclosures of cash flow information:			
Financing costs included in accounts payable and accrued expenses at end of year	$ 55,387	$ 42,500	$ 17,275
Property and equipment acquired but unpaid at end of year	$ 88,917	$ —	$ —

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 (collectively, "Zynerba," the "Company," or "we"), is a clinical stage specialty pharmaceutical company focused on the development of pharmaceutically-produced transdermal cannabinoid therapies for orphan neuropsychiatric disorders, including Fragile X syndrome ("FXS") and chromosome 22q11.2 deletion syndrome ("22q"). We have been granted orphan drug designations from the United States Food and Drug Administration ("FDA") and the European Commission for the use of cannabidiol for the treatment of FXS and 22q. In addition, we have received Fast Track designation from the FDA for treatment of behavioral symptoms associated with FXS. The Company has decided to prioritize its resources on FXS and 22q, both of which have no approved products. While we believe the data from the Company's autism spectrum disorder ("ASD") clinical development program to date are compelling, given the difficult financial market, the Company has decided to defer the start of the Phase 3 development program in ASD.

The Company has incurred losses and negative cash flows from operations since inception and has an accumulated deficit of $274.5 million as of December 31, 2022. 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.

Management believes that the Company's cash and cash equivalents as of December 31, 2022 are sufficient to fund operations and capital requirements to mid-year 2024. Substantial additional financings will be needed by the Company to fund its operations, and to complete clinical development of and to commercially develop its product candidates. The Company's ability to raise sufficient additional financing depends on many factors beyond its control, including the current and ongoing volatility in the capital markets as a result of the COVID-19 pandemic. There is no assurance that such financing will be available when needed or on acceptable terms.

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

(2) Summary of Significant Accounting Policies

a. Basis of Presentation

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

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 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.

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

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, 2022 and 2021, the Company invested a portion of its cash balances in money market funds that seek to maintain a stable net asset value. These investments have been included as cash equivalents on the consolidated balance sheets.

e. Incentive and Tax Receivables

The Company's subsidiary, Zynerba Pharmaceuticals Pty Ltd (the "Subsidiary"), is incorporated in Australia. The Subsidiary is eligible to participate in an Australian research and development tax incentive program. As part of this program, the Subsidiary is eligible to receive a cash refund from the Australian Taxation Office ("ATO"), for a percentage of the research and development costs expended by the Subsidiary in Australia. The cash refund is available to eligible companies with an annual aggregate revenue of less than $20.0 million (Australian) during the reimbursable period. The Company estimates the amount of cash refund it expects to receive related to the Australian research and development tax incentive program and records the incentives when it is probable 1) the Company will comply with relevant conditions of the program and 2) the incentive will be received. The Company evaluates its eligibility under tax incentive programs as of each balance sheet date based on the most current and relevant data available. If the Company is deemed to be ineligible or unable to receive the Australian research and development tax credit, or the Australian government significantly reduces or eliminates the tax credit, the actual cash refund the Company receives may materially differ from its estimates.

In December 2018, the Company submitted an Advance Overseas Finding ("AOF") application to a division of the Australian Government's Department of Industry, Innovation and Science ("AusIndustry"), for a portion of the Company's research and development activities incurred outside of Australia, which was approved by AusIndustry in July 2019. 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. In June 2020, the ATO informed the Company that it may not qualify for the AOF program based on their interpretation of certain eligibility requirements and, during the three months ended June 30, 2020, the Company determined it was no longer probable that the AOF claim would be received and the Company recorded a full reserve against the AOF receivable.

During the three months ended March 31, 2022, the Company concluded its conversations with the ATO on these matters and made the decision to no longer pursue the AOF claim, resulting in the write off of both the AOF receivable and the corresponding reserve during the period. During the three months ended March 31, 2022, the Company received a payment of $8.0 million from the ATO for the non-AOF research and development incentive for the years ended December 31, 2018, 2019 and 2020.

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, 2022, incentive and tax receivables included $0.2 million for refundable GST on expenses incurred with Australian vendors during the three months ended December 31, 2022.

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

Current incentive and tax receivables consisted of the following as of December 31, 2022 and 2021:

	December 31, 2022	December 3 2021
Research and development incentive (non-AOF) for the period 1/1/18 - 12/31/18	$ —	$ 3,144,15
Research and development incentive (non-AOF) for the period 1/1/19 - 12/31/19	—	2,914,93
Research and development incentive (non-AOF) for the period 1/1/20 - 12/31/20	—	1,993,03
Research and development incentive (non-AOF) for the period 1/1/21 - 12/31/21	—	1,226,68
Research and development incentive (non-AOF) for the period 1/1/22 - 12/31/22	977,714	-
Research and development incentive (AOF) for the period 1/1/18 - 12/31/19	—	8,566,84
Goods and services tax	247,669	301,65
Total incentive and tax receivables before reserve for AOF	1,225,383	18,147,31
Reserve for research and development incentive (AOF) for the period 1/1/18 - 12/31/19	—	(8,566,84
Total incentive and tax receivables - current assets	$ 1,225,383	$ 9,580,46

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, 2022, 2021 and 2020, 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.

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

The following table summarizes research and development expenses for the years ended December 31, 2022, 2021, and 2020:

	Year ended December 31,		
	2022	2021	2020
Research and development expenses - before R&D incentive	$ 22,101,576	$ 22,454,878	$ 29,437,551
Research and development incentive (non-AOF)	(1,001,910)	(1,030,389)	(1,890,252)
Research and development expenses (before impact of AOF)	21,099,666	21,424,489	27,547,299
Amounts reserved against AOF refund	—	—	8,107,695
Total research and development expenses	$ 21,099,666	$ 21,424,489	$ 35,654,994

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 compensation expense for 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, which were established by the Company's board of directors.

For grants of 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 has historically used comparable public companies, in addition to the Company's historical volatility, as a basis for its expected volatility to calculate the fair value of option grants. For option grants issued beginning in 2022, the Company used its own stock price volatility, over the expected term of the award, as the basis for its expected volatility. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected term of the option.

j. 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, 2022 and 2021, 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, 2022 and does not expect a significant change in the balance of unrecognized tax benefits within the next 12 months.

k. 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

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

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, 2022, 2021 and 2020 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,		
	2022	2021	2020
Stock options	6,276,016	5,224,913	4,546,484
Unvested restricted stock	2,114,512	989,822	173,800
	8,390,528	6,214,735	4,720,284

l. 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.

m. 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.

n. Recent Accounting Pronouncements

In November 2021, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update No. 2021-10, *Government Assistance (Topic 832): Disclosure by Business Entities about Government Assistance* ("ASU 2021-10"), which improves the transparency of government assistance received by most business entities by requiring the disclosure of: (1) the types of government assistance received; (2) the accounting for such assistance; and (3) the effect of the assistance on a business entity' s financial statements. This guidance is effective for financial statements issued for annual periods beginning after 15 December 2021. The Company adopted ASU 2021-10 effective January 1, 2022, and the adoption did not have a material impact on its consolidated financial statements.

(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.

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

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, 2022 and 2021:

	Carrying amount as of December 31, 2022	Fair Value Measurement as of December 31, 2022		
		Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 44,663,395	$44,663,395	$ —	$ —
	$ 44,663,395	$44,663,395	$ —	$ —

	Carrying amount as of December 31, 2021	Fair Value Measurement as of December 31, 2021		
		Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 67,709,279	$67,709,279	$ —	$ —
	$ 67,709,279	$67,709,279	$ —	$ —

(4) Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following as of December 31, 2022 and 2021:

	December 31, 2022	December 31, 2021
Prepaid development expenses	$ 668,096	$ 543,897
Prepaid insurance	1,546,784	1,952,867
Deferred financing costs	155,956	137,615
Other current assets	537,895	197,013
Total prepaid expenses and other current assets	$ 2,908,731	$ 2,831,392

(5) Property and Equipment

Property and equipment consisted of the following as of December 31, 2022 and 2021:

	Estimated useful life (in years)	December 31, 2022	December 31, 2021
Equipment	2–5	$ 828,666	$ 740,543
Computer equipment	3–5	30,319	30,319
Furniture and fixtures	3–5	311,356	311,356
Leasehold improvements	various	68,881	68,881
Construction in process		234,241	79,342
Total cost		1,473,463	1,230,441
Less accumulated depreciation		(1,063,891)	(844,608)
Property and equipment, net		$ 409,572	$ 385,833

Depreciation expense was $219,283, $247,140 and $207,035 for the years ended December 31, 2022, 2021 and 2020, respectively.

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

(6) Accrued Expenses

Accrued expenses consisted of the following as of December 31, 2022 and 2021:

	December 31, 2022	December 31, 2021
Accrued compensation	$ 2,016,402	$ 2,412,291
Accrued research and development	4,239,719	5,125,010
Other	758,761	359,297
Total accrued expenses	$ 7,014,882	$ 7,896,598

(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, 2022, no shares of preferred stock were issued.

Common Stock

a. At The Market Financing

In May 2021, the Company entered into a Controlled Equity Offering℠ Sales Agreement (the "2021 Sales Agreement") with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., as sales agents (collectively, the "2021 Sales Agents"), pursuant to which, under a prospectus filed by the Company in May 2022, the Company may sell, from time to time, up to $75.0 million of its common stock. During the year ended December 31, 2022, the Company sold and issued 4,608,274 shares of common stock under the 2021 Sales Agreement in the open market at a weighted average selling price of $1.35 per share, resulting in gross proceeds of $6.2 million. Net proceeds after deducting commissions and offering expenses were $5.8 million. From January 1, 2023 through March 22, 2023, the Company sold and issued 1,179,077 shares of its common stock in the open market at a weighted average selling price of $0.56 per share, for gross proceeds of $0.7 million and net proceeds, after deducting commissions and offering expenses, of $0.6 million.

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

b. Equity Purchase Agreement

On July 21, 2022 (the "Effective Date"), the Company entered into a Purchase Agreement (the "Purchase Agreement") with Lincoln Park Capital Fund, LLC ("Lincoln Park") pursuant to which Lincoln Park committed to purchase up to $20.0 million of the Company's common stock. Under the terms and subject to the conditions of the Purchase Agreement, the Company has the right, but not the obligation, to sell to Lincoln Park, and Lincoln Park is obligated to purchase up to $20.0 million of the Company's common stock. Such sales of common stock will be subject to certain limitations, and may occur from time to time, at the Company's sole discretion, over the 36-month period commencing on the Effective Date. The number of shares the Company may sell to Lincoln Park on any single business day in a regular purchase is

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

150,000, but that amount may be increased up to 300,000 shares, depending upon the market price of the Company's common stock at the time of sale and subject to a maximum limit of $2.0 million per regular purchase. The purchase price per share for each such regular purchase will be based on prevailing market prices of the Company's common stock immediately preceding the time of sale as computed under the Purchase Agreement. In addition to regular purchases, the Company may also direct Lincoln Park to purchase other amounts as accelerated purchases or as additional accelerated purchases.

Pursuant to the terms of the Purchase Agreement, the Company issued 347,222 shares of its common stock to Lincoln Park as consideration for its commitment to purchase shares of the Company's common stock under the Purchase Agreement.

During the year ended December 31, 2022, the Company sold and issued 350,000 shares of common stock under the Purchase Agreement at a weighted average selling price of $0.92 per share, resulting in gross of $0.3 million and net proceeds, after deducting offering expenses, of $0.2 million. From January 1, 2023 through March 22, 2023, the Company sold and issued 1,950,000 shares of common stock under the Purchase Agreement at a weighted average selling price of $0.53 per share, resulting in gross and net proceeds of $1.0 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, 2023, the number of shares of common stock that may be issued under the 2014 Plan was automatically increased by 1.5 million shares, increasing the total number of shares of common stock available for issuance under the 2014 Plan to 12,304,869 shares. As of December 31, 2022, 1,442,876 shares were available for future issuance under the 2014 Plan.

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

Stock-based compensation expense for 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, which were established by the Company's board of directors. The Company's board of directors determines if the performance conditions have been met.

During 2021, the Company granted 551,911 time-based restricted stock awards to employees and non-employee directors of which 474,911 restricted stock awards remained outstanding as of December 31, 2022. In addition, during 2021, the Company granted 506,911 performance-based restricted stock awards to employees of which 187,964 restricted stock awards have fully vested and 281,947 restricted stock awards remained outstanding as of December 31, 2022. The performance-based conditions for these performance-based grants were deemed probable of achievement during 2021 and, as of December 31, 2022, the Company has recorded $1.7 million in stock-based compensation expense related to these grants. As of December 31, 2022, there was $13,565 of unrecognized stock-based compensation

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

expense related to these performance-based awards, which will be expensed over the estimated service period related to each performance condition.

During 2022, the Company granted 841,654 time-based restricted stock awards to employees, non-employee directors and consultants of which 804,654 restricted stock awards remained outstanding as of December 31, 2022. In addition, during 2022, the Company granted 556,500 performance-based restricted stock awards to employees of which 548,000 restricted stock awards remained outstanding as of December 31, 2022. As of December 31, 2022, satisfaction of the related performance conditions has not been deemed probable of being achieved and there was $1.1 million of unrecognized stock-based compensation expense related to these performance-based awards, which will be expensed over the estimated service period related to each performance condition once the performance conditions have been deemed probable.

During the years ended December 31, 2022, 2021 and 2020, the Company recorded $4,331,727, $5,810,580, and $5,177,527, respectively, in stock-based compensation expense related to its stock option grants and restricted stock awards, as follows:

	Stock Option Grants			Restricted stock awards		
	2022	2021	2020	2022	2021	2020
Research and development	$1,032,267	$1,479,681	$2,053,675	$ 940,627	$1,348,290	$141,213
General and administrative	1,243,842	1,696,490	2,922,620	1,114,991	1,286,119	60,019
	$2,276,109	$3,176,171	$4,976,295	$2,055,618	$2,634,409	$201,232

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, 2020	4,546,484	$ 9.76		
Granted	869,867	3.71		
Exercised	(13,125)	3.65		
Forfeited	(178,313)	10.69		
Outstanding as of December 31, 2021	5,224,913	8.74		
Granted	1,136,728	2.17		
Forfeited	(85,625)	10.97		
Outstanding as of December 31, 2022	6,276,016	7.52	5.92	$ —
Exercisable as of December 31, 2022	4,441,441	9.41	4.82	$ —
Vested and expected to vest as of December 31, 2022	6,276,016	$ 7.52		

The weighted-average grant date fair value of options granted during the years ended December 31, 2022, 2021, and 2020 was $1.74, $2.86, and $3.58, 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,		
	2022	2021	2020
Weighted-average risk-free interest rate	2.02%	0.40%	1.27%
Expected term of options (in years)	6.11	6.21	6.18
Expected stock price volatility	100.23%	95.94%	82.00%
Expected dividend yield	0%	0%	0%

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

As of December 31, 2022, there was $3.3 million of unrecognized stock-based compensation expense related to stock options, which is expected to be recognized over a weighted-average period of 2.26 years. During the year ended December 31, 2021, the Company received $47,906 in cash from the exercise of employee stock options.

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

	Shares	Weighted Average Grant Date Fair Value	Aggregate Intrinsic Value
Unvested as of December 31, 2020	173,800	$ 3.64	
Granted	1,058,822	3.61	
Forfeited	(74,000)	3.58	
Vested	(168,800)	3.60	
Unvested as of December 31, 2021	989,822	3.62	
Granted	1,398,154	2.17	
Forfeited	(25,500)	2.41	
Vested	(247,964)	3.61	
Unvested as of December 31, 2022	2,114,512	$ 2.86	$1,120,691
Expected to vest as of December 31, 2022	1,561,512	$ 2.85	$ 827,601

As of December 31, 2022, there was $1.1 million of unrecognized stock-based compensation expense related to unvested restricted stock awards, which is expected to be recognized over a weighted-average period of 0.56 years.

(9) Operating Lease Obligations

The Company adopted Accounting Standards Update (“ASU”) No. 2016-02, *Leases (Topic 842), Accounting Standards Codification 842* (“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 March 1, 2021, the Company extended its lease for three additional years until May 31, 2024. 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 March 1, 2021, 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 $755,085 and right-of-use assets to $752,391, which was recorded net of a deferred rent liability of $2,694. As of December 31, 2022, the Company’ s right-of-use asset, net of amortization, was $336,215.

Other operating lease information as of December 31, 2022:

Weighted-average remaining lease term - operating leases	1.4 years
Weighted-average discount rate - operating leases	2.76 %

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

The following is a maturity analysis of the annual undiscounted cash flows of the operating lease liabilities as of December 31, 2022:

Year ending:	December 31, 2022
December 31, 2023	$ 240,420
December 31, 2024	100,175
Total minimum lease payments	340,595
Less: imputed lease interest	(6,170)
Total lease liabilities	$ 334,425

Lease expense for the years ended December 31, 2022, 2021, and 2020 was comprised of the following:

	Year ended December 31,		
	2022	2021	2020
Operating lease expense	$ 241,683	$ 244,209	$ 256,837
Variable lease expense	61,625	60,864	58,697
Total lease expense	$ 303,308	$ 305,073	$ 315,534

Total cash payments related to leases for the years ended December 31, 2022, 2021, and 2020 were $302,045, $310,448 and $318,561, respectively.

(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. The Company provides an employer match on the first 6% of employee contributions and employer matching contributions vest immediately. For the years ended December 31, 2022, 2021 and 2020, the Company provided an employer match of 67%, 33% and 33%, respectively. For the years ended December 31, 2022, 2021, and 2020, the Company's contributions to the plan were $240,833, $111,258 and $111,846, respectively.

(11) Income Taxes

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

	Year ended December 31,		
	2022	2021	2020
United States	$(33,308,897)	$(34,729,615)	$(40,407,933)
Foreign	(1,726,909)	(2,579,409)	(10,928,898)
Total	$(35,035,806)	$(37,309,024)	$(51,336,831)

The Company had $170.1 million and $160.6 million of federal net operating loss carryforwards and $5.7 million and $4.7 million of U.S. research tax credit carryforwards as of December 31, 2022 and 2021, respectively. The U.S. federal net operating loss carryforwards and research tax credit carryforwards begin to expire in 2028 and 2027, respectively. Federal net operating losses that were generated after December 31, 2017 carryforward indefinitely. The Company has $170.2 million and $160.6 million of state net operating loss carryforwards as of December 31, 2022 and 2021, respectively. The state net operating loss carryforwards begin to expire in 2028. As of December 31, 2022 and 2021, the Company had $2.8 million and $3.0 million, respectively, of Australian net operating loss carryforwards, which have an indefinite life.

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

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

The components of the net deferred income tax asset as of December 31, 2022 and 2021 are as follows:

	December 31, 2022	December 31, 2021
Deferred tax assets:		
Net operating loss carry forwards	$ 49,832,469	$ 46,999,701
Research and development credit carry forwards	5,687,207	4,761,598
Research and development expenditure capitalization	5,436,581	—
Stock-based compensation	9,277,449	8,656,457
Property and equipment	39,703	16,839
Other	786,861	703,134
Gross deferred tax assets	71,060,270	61,137,729
Less valuation allowance	(71,060,270)	(61,137,729)
Net deferred tax asset	$ —	$ —

The Tax Cuts and Jobs Act passed in 2017 included a provision which requires taxpayers to capitalize and amortize U.S.-based research or experimental expenditures ("R&E") over a period of five years and non-U.S. R&E over 15 years effective for tax years beginning after December 31, 2021, pursuant to Internal Revenue Code Section 174.

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, 2022 and 2021, 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 $9.9 million and $6.6 million during the years ended December 31, 2022 and 2021, respectively, due primarily to the generation of net operating loss carryforwards during those years and the capitalization of R&E in 2022.

The Company does not have unrecognized tax benefits as of December 31, 2022 and 2021, respectively. The Company recognizes interest and penalties accrued on any unrecognized tax benefits as a component of income tax expense.

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

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,		
	2022	2021	2020
Federal income tax benefit at statutory rate	21.0%	21.0%	21.0%
State income tax, net of federal benefit	7.1	7.1	6.4
Nondeductible research and development expenses	(0.7)	(1.1)	(4.6)
Other permanent differences	(1.6)	(0.8)	0.2
Research and development credit benefit	2.8	2.6	2.2
Adjustment of prior years' income taxes	(0.3)	(11.0)	(0.1)
Change in valuation allowance	(28.3)	(17.8)	(25.1)
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 U.S. tax returns for the tax years 2011 to 2022 remain open and subject to examination.

(12) Commitments and Contingencies

a. Leases

The Company is a party to a noncancelable operating lease for office space, under a long-term lease arrangement. As of December 31, 2022, future minimum lease commitment for the Company's noncancelable lease was $423,750.

b. Employment Agreements

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

c. Litigation

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

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, 2022. 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, 2022, 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, 2022. 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, 2022, 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, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

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 on Schedule 14A for the 2023 annual meeting of stockholders to be filed no later than 120 days after the end of our fiscal year ended December 31, 2022 (the "2023 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 2023 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, 2022.

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	6,126,016	$ 7.45	1,442,876
Equity compensation plans not approved by security holders	150,000 (1)	10.23	— (2)
Total	6,276,016	$ 7.52	1,442,876

(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 2023 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 2023 Proxy Statement.

Item 14. Principal Accounting Fees and Services

Our independent registered public accounting firm is KPMG LLP, Philadelphia, PA, Auditor Firm ID: 185

The information required by this item is incorporated herein by reference to the material under the captions "Independent Auditors and Related Fees" in our 2023 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., as amended. Incorporated herein by reference to Exhibit 3.1 to the registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2021 (File No. 001-37526) filed on August 9, 2021.
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. Incorporated herein by reference to Exhibit 4.2 to the registrant's Annual Report on Form 10-K (File No. 001-37526) filed on March 10, 2021.
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 February 14, 2022, by and between the registrant and Albert P. Parker. Incorporated herein by reference to Exhibit 10.3(A) to the registrant's Annual Report on Form 10-K for the year ended December 31, 2021 (File No. 001-37526) filed on March 1, 2022.
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(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.
10.6(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.

10.6(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.
10.6(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.
10.6(E)+	Form of Restricted Stock Grant Agreement under Amended and Restated 2014 Omnibus Incentive Compensation Plan. Incorporated herein by reference to Exhibit 10.2 to the registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2021 (File No. 001-37526) filed on August 9, 2021.
10.7+	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.
10.8+	Zynerba Pharmaceuticals, Inc. Non-Employee Director Compensation Policy. Incorporated herein by reference to Exhibit 10.8 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2021 (File No. 001-37526) filed on March 1, 2022.
10.9+	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.
10.10	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.
10.11	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.
10.12	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.
10.13	Lease amendment No. 3 dated November 19, 2019, by and between Provco Devon, L.L.C. and the registrant. Incorporated herein by reference to Exhibit 10.20 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2020 (File No. 001-37526) filed on March 10, 2021.
10.14	Lease amendment No. 4 dated March 1, 2021, by and between Provco Devon, L.L.C. and the registrant. Incorporated herein by reference to Exhibit 10.21 to the registrant's Annual Report on Form 10-K for the year ended December 31, 2020 (File No. 001-37526) filed on March 10, 2021.
10.15	Controlled Equity Offering℠ Sales Agreement, dated May 11, 2021, 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 Quarterly Report on Form 10-Q for the quarter ended March 31, 2021 (File No. 001-37526) filed on May 12, 2021.
10.16	Purchase Agreement, dated as of July 21, 2022, by and between Zynerba Pharmaceuticals, Inc. and Lincoln Park Capital Fund, LLC. Incorporated herein by reference to Exhibit 10.1 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on July 22, 2022.
10.17	Registration Rights Agreement, dated as of July 21, 2022, by and between Zynerba Pharmaceuticals, Inc. and Lincoln Park Capital Fund, LLC. Incorporated herein by reference to Exhibit 10.2 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on July 22, 2022.
21.1	List of subsidiaries of the registrant (filed herewith).
23.1	Consent of independent registered public accounting firm (filed herewith).
31.1	Certifying Statement of the Chief Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (filed herewith).
31.2	Certifying Statement of the Chief Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (filed herewith).
32.1	Certifying Statement of the Chief Executive Officer pursuant to Section 1350 of Title 18 of the United States Code (furnished herewith).

32.2	Certifying Statement of the Chief Financial Officer pursuant to Section 1350 of Title 18 of the United States Code (furnished herewith).
101 INS	Inline XBRL Instance Document (filed herewith).
101 SCH	Inline XBRL Taxonomy Extension Schema Document (filed herewith).
101 CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document (filed herewith).
101 DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document (filed herewith).
101 LAB	Inline XBRL Taxonomy Extension Label Linkbase Document (filed herewith).
101 PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document (filed herewith).
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 28, 2023

ZYNERBA PHARMACEUTICALS, INC.

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

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Armando Anido Armando Anido	Chairman and Chief Executive Officer (Principal Executive Officer)	March 28, 2023
/s/ James E. Fickenscher James E. Fickenscher	Chief Financial Officer (Principal Financial and Accounting Officer)	March 28, 2023
/s/ John P. Butler John P. Butler	Director	March 28, 2023
/s/ Warren D. Cooper, MB, BS, BSc, MFPM Warren D. Cooper, MB, BS, BSc, MFPM	Director	March 28, 2023
/s/ William J. Federici William J. Federici	Director	March 28, 2023
/s/ Daniel L. Kisner, MD Daniel L. Kisner, MD	Director	March 28, 2023
/s/ Kenneth I. Moch Kenneth I. Moch	Director	March 28, 2023
/s/ Pamela Stephenson Pamela Stephenson	Director	March 28, 2023