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

FORM 10-K

(Mark One)
[X] ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015
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	**Name of each exchange on which registered**
Common Stock, par value $0.001 per share	**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 and posted on its corporate Web site, if any, every Interactive Data File requirement to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).
☒ Yes ☐ No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

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

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

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

As of June 30, 2015, the last business day of the registrant's most recently completed second fiscal quarter, the registrant's common stock was not publicly traded. The registrant's common stock began trading on the NASDAQ Global Market on August 5, 2015. As of March 10, 2016, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $58.0 million, based upon the closing price on the NASDAQ Global Market reported for such date.

There were 9,199,919 shares of the registrant's common stock, par value $0.001 per share, outstanding as of March 10, 2016.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates certain information by reference from the registrant's proxy statement for the 2016 annual meeting of stockholders to be filed no later than 120 days after the end of the registrant's fiscal year ended December 31, 2015.

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FORWARD-LOOKING STATEMENTS

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

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

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

- our estimates regarding expenses, future revenue, capital requirements and timing and availability of and the need for additional financing;
- the success and timing of our preclinical studies and clinical trials;
- the potential results of preclinical studies and clinical trials for ZYN002 and ZYN001;
- our dependence on third parties in the conduct of our preclinical studies and clinical trials;
- the difficulties and expenses associated with obtaining and maintaining regulatory approval of ZYN002 and ZYN001;
- our plans and ability to develop and commercialize ZYN002 and ZYN001;
- the successful development of our commercialization capabilities, including sales and marketing capabilities;
- the size and growth of the potential markets for ZYN002 and ZYN001, market acceptance of ZYN002 and ZYN001 and our ability to serve those markets;
- the rate and degree of market acceptance of ZYN002 and ZYN001;
- legal and regulatory developments in the United States and foreign countries;
- our ability to limit our exposure under product liability lawsuits;
- the success of competing therapies and products that are or become available;
- our exposure to additional scrutiny as a public company;
- our ability to obtain additional funding on acceptable terms, or at all;
- obtaining and maintaining intellectual property protection for ZYN002 and ZYN001;
- recently enacted and future legislation regarding the healthcare system;
- the performance of third parties upon which we depend, including third-party contract research organizations ("CROs") and third-party manufacturers; and
- our ability to recruit or retain key scientific or management personnel or to retain our executive officers.

In light of these risks and uncertainties, expected results or other anticipated events or circumstances discussed in this Report (including the exhibits hereto) might not occur. We undertake no obligation, and specifically decline any obligation, to publicly update or revise any forward-looking statements, even if experience or future developments make it clear that projected results expressed or implied in such statements will not be realized, except as may be required by law.

See Item 1A, “Risk Factors,” in this Report for a more complete discussion of these risks and uncertainties and for other risks and uncertainties. Those factors and the other risk factors described therein are not necessarily all of the important factors that could cause actual results or developments to differ materially from those expressed in any of our forward-looking statements. Other unknown or unpredictable factors also could harm our results. Consequently, there can be no assurance that actual results or developments anticipated by us will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, us. Given these uncertainties, you are cautioned not to place undue reliance on such forward-looking statements.

PART I

Item 1. Business

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

Company Overview

We are a specialty pharmaceutical company focused on developing and commercializing proprietary next-generation synthetic cannabinoid therapeutics formulated for transdermal delivery. We are evaluating two patent-protected product candidates, ZYN002 and ZYN001, in five indications. We intend to study ZYN002 in patients with refractory epilepsy, osteoarthritis, or OA, and Fragile X syndrome, or FXS. We intend to study ZYN001 in patients with fibromyalgia and peripheral neuropathic pain. We believe these product candidates will provide new treatment options for patients, as well as additional treatment options for patients not currently receiving adequate relief from current treatment regimens. We initiated Phase 1 clinical trials for ZYN002 in October 2015 and expect to initiate Phase 2 clinical trials for ZYN002 in the second half of 2016. We expect to initiate Phase 1 clinical trials for ZYN001 in the second half of 2016.

Cannabinoids are a class of compounds derived from *Cannabis* plants. The two primary cannabinoids contained in *Cannabis* are cannabidiol, or CBD, and Δ9-tetrahydrocannabinol, or THC. Clinical and preclinical data suggest that CBD has positive effects on treating refractory epilepsy, arthritis and FXS, and THC has positive effects on treating pain. In addition to ZYN002 and ZYN001 potentially offering first-line therapies to patients suffering from OA, FXS, fibromyalgia and peripheral neuropathic pain, we believe ZYN002 may provide a complementary treatment for patients suffering from epilepsy who are refractory to their current treatment regimens.

We believe that we offer an attractive alternative to existing cannabinoid therapies by synthetically manufacturing and transdermally delivering our product candidates. Most cannabinoid therapies have drawbacks and limitations due to their botanical (plant-derived) nature, as well as the fact that they are administered orally. Botanical cannabinoids create significant challenges for drug manufacturers because of the natural resources and security measures required to grow *Cannabis*, as well as the strict batch controls required by regulatory agencies in pharmaceutical manufacturing. In addition, we believe all currently approved and development-stage cannabinoid therapeutics, except ZYN002 and ZYN001, are designed to be administered orally which can lead to limitations in safety and efficacy including low bioavailability, inconsistent plasma levels, degradation by stomach acids, and significant first-pass liver metabolism. First-pass liver metabolism refers to the process by which the liver breaks down therapeutics ingested directly or indirectly through the gastrointestinal system, such as through oral or oral mucosal delivery methods, allowing only a small amount of drug to be absorbed into the circulatory system. In contrast, transdermal therapeutics are absorbed through the skin directly into the systemic circulation, avoiding first-pass liver metabolism and degradation by stomach acids, and potentially enabling lower dosage levels of active pharmaceutical ingredients and rapid and reliable absorption with high bioavailability, fewer negative psychoactive effects and fewer drug-drug interactions.

ZYN002 is the first and only synthetic CBD formulated as a permeation-enhanced gel for transdermal delivery, and is patent-protected through 2030. CBD is the primary non-psychoactive component of *Cannabis*. In preclinical animal studies, ZYN002's permeation enhancer increased delivery of CBD through the layers of the skin and into the circulatory system. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism. In addition, an *in vitro* study performed by us demonstrated that CBD is degraded to THC in an acidic environment such as the stomach. We believe such degradation may lead to increased psychoactive effects and may be avoided or minimized with the transdermal delivery of ZYN002, which maintains CBD in a neutral pH. ZYN002, which is being developed as a clear gel with once- or twice-daily dosing, is targeting treatment of refractory epilepsy, OA and FXS, which collectively affect millions of patients using treatments that currently comprise a multi-billion dollar market. We have been granted orphan drug designation from the U.S. Food and Drug Administration, or FDA, for ZYN002 for the treatment of FXS.

ZYN001 is a pro-drug of THC that enables effective transdermal delivery via a patch and is patent-protected through 2031. A pro-drug is a drug administered in an inactive or less active form and designed to enable more effective delivery, which is then converted into an active form through a normal metabolic process. In addition, we expect that ZYN001 will be classified by the FDA as a new chemical entity, or NCE. In our preclinical animal studies, ZYN001 demonstrated effective skin permeation with sustained delivery and rapid conversion of ZYN001 to THC. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism. In addition, preclinical testing conducted has shown no genotoxicity findings and

safety pharmacology findings consistent with those seen with THC. ZYN001 is targeting two pain indications, fibromyalgia and peripheral neuropathic pain.

In October 2015, we initiated a Phase 1 single rising dose clinical trial for ZYN002 in healthy human subjects (and in patients with refractory epilepsy) to evaluate the tolerability and pharmacokinetic, or PK, profile of ZYN002. Initial results from this trial indicate the ZYN002 was safe and well-tolerated at all tested dose levels. In January 2016, we initiated a Phase 1 multiple rising dose clinical trial for ZYN002 in healthy volunteers (and patients with epilepsy) to examine the tolerability, PK and pharmacodynamics, or PD, of multiple doses of ZYN002.

We plan to evaluate the tolerability and PK profile of ZYN001 in Phase 1 single rising dose clinical trials in healthy human subjects in the second half of 2016. Subsequent to the single rising dose clinical trials, we intend to conduct Phase 1 multiple rising dose clinical trials to examine the tolerability, PK and PD of multiple doses of ZYN001 in healthy human subjects and in patients with fibromyalgia. To complete the Phase 1 program for both product candidates, we will conduct bioequivalence clinical trials assessing the PK when applied to various parts of the body (e.g., arm, thigh and back).

Following the Phase 1 clinical trials, we intend to initiate a Phase 2a randomized, double-blind, placebo-controlled clinical trial comparing the efficacy and safety of multiple doses of ZYN002 to placebo in refractory epilepsy and OA. We intend to initiate an open label Phase 2a clinical trial in FXS to evaluate efficacy and safety. We also intend to initiate a Phase 2a randomized, double-blind, placebo-controlled clinical trial comparing the efficacy and safety of multiple doses of ZYN001 to placebo in fibromyalgia and peripheral neuropathic pain.

Our key development programs and expected timelines for the development of ZYN002 and ZYN001 are shown in the table below:

Product Candidate	Target Indication	Delivery Method	Current Development Status	Expected Next Steps
ZYN002	Refractory Epilepsy Osteoarthritis Fragile X Syndrome	Permeation-enhanced Gel	Phase 1	2H16: Initiate Phase 2a
ZYN001	Fibromyalgia Peripheral Neuropathic Pain	Transdermal Patch	Preclinical	2H16: Initiate Phase 1 1H17: Initiate Phase 2a

Cannabinoid Science Overview

Cannabinoids refer to a unique class of compounds derived from the *Cannabis* plant. Of the over 70 cannabinoid compounds currently identified, THC and CBD are the primary cannabinoids used for pharmaceutical purposes. THC was identified as the major psychoactive cannabinoid and subsequently found to be a partial agonist of the CB_1 and CB_2 receptors, activation of which stimulates the endogenous noradrenergic pathway, inducing antinociception and suggesting a role for THC in pain management.

CBD, the main non-psychoactive component of *Cannabis*, has little affinity for the CB_1 and CB_2 receptors. It does, however, produce multiple effects, including blocking the equilibrative nucleoside transporter, the orphan G-protein-coupled receptor GRP55, and the transient receptor potential of melastatin type 8 channel; enhancing activity of $5\text{-}HT_{1a}$ and glycine receptors and the transient receptor potential of ankyrin type 1 channel; and regulating the intracellular effects of calcium. The influence of CBD on these targets — each of which we believe plays a key role in neuronal excitability — is the scientific basis for its antiepileptic potential.

CBD inhibits the metabolism (breakdown) of two endocannabinoids (anandamide and 2-arachidonoylglycerol, or 2-AG). Inhibition of the metabolism of these endocannabinoids is thought to result in increased anandamide and 2-AG availability and greater CB_1 and CB_2 activation. Therefore, CBD acts as a facilitator of the endogenous endocannabinoid system, which modifies release of other neurotransmitters from presynaptic terminals. This modulation of neurotransmitter release from presynaptic neurons of various classes is the scientific basis for the use of CBD in the treatment of FXS.

CBD exerts a range of anti-inflammatory effects, including attenuation of the endothelial cell activation, chemotaxis of inflammatory cells, suppression of T-cell macrophage reactivity, and induction of apoptosis of T cells, which suggests a possible therapeutic role in the treatment of OA. CBD's agonist effect on TRPV1 receptors leads to antihyperalgesia, which further suggests a possible role in the treatment of OA. Third-party studies suggest that psychotropic effects of *Cannabis* are caused by THC, not CBD.

Clinical and preclinical data suggest that THC has positive effects on treating pain and CBD has positive effects on treating epilepsy, arthritis and FXS. Clinical data suggest that THC and CBD have 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. Dronabinol and nabilone, oral formulations of THC, have been approved by the FDA. In third-party studies, adverse events from oral THC including dronabinol and nabilone were primarily psychotropic and related to peak plasma levels. Many patients have received CBD-enriched *Cannabis* and Epidiolex®, a liquid formulation of highly concentrated CBD which is currently in development. The cannabinoid therapeutics market is expected to grow significantly due to the potential benefits these products may provide over existing therapies. For example, opioids are often the standard of care for treating various pain diseases but patients frequently experience adverse side effects, including addiction and opioid-induced constipation.

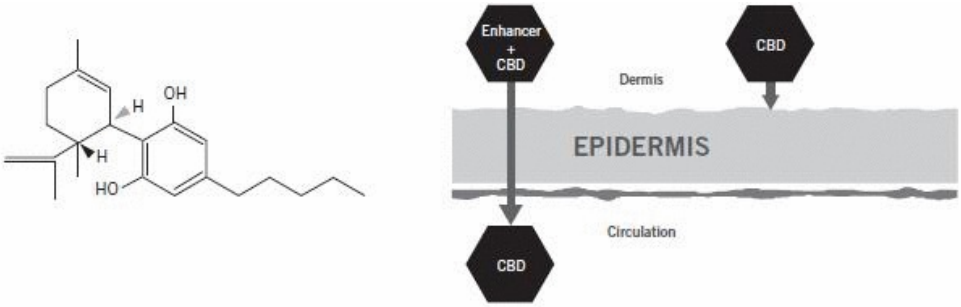
Our Product Candidates

ZYN002

Overview

ZYN002 is the first and only synthetic CBD formulated as a patent-protected permeation-enhanced gel for transdermal delivery (see Figure 1).

Figure 1 — Chemical structure and delivery of CBD.



ZYN002 is being developed as a clear gel that is designed to provide consistent, controlled drug delivery with convenient once- or twice-daily dosing. Because CBD is virtually insoluble in water, we use 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 ZYN002 increases the delivery of CBD through the layers of the skin and into the circulatory system.

Transdermal delivery allows the CBD in ZYN002 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 directly into the systemic circulation, enabling the potential to have rapid and reliable absorption with high bioavailability.

Market Overview and Rationale

We intend to study ZYN002 in the treatment of refractory epilepsy, OA and FXS.

Epilepsy — Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures (transient symptoms due to abnormal neuronal activity in the brain) and by the neurobiological, cognitive, psychological, and social consequences of the condition. Partial seizures usually start in a small area of the temporal lobe or frontal lobe of the brain and quickly involve other areas of the brain that affect alertness and awareness. Partial seizures are the most common type of seizure, representing 35% of all epilepsies.

According to Decision Resources, in 2012 there were approximately 2.2 million epilepsy patients in the United States, and treatments for these patients represented a total U.S. market size of approximately $1.7 billion.

We believe that ZYN002 may provide an effective treatment for refractory epilepsy based on the anticonvulsant effects of CBD due to its ability to reduce neuronal hyperexcitability shown in multiple *in vivo* models of epilepsy conducted by third parties. Epilepsy specialists and patient organizations have shown considerable interest in the potential therapeutic role of CBD in adults with epilepsy and, especially, children with intractable epilepsy. Two companies have active CBD development programs for the treatment of patients with Dravet's syndrome, or DS, or Lennox Gastaut syndrome, or LGS, both of which are rare and severe forms of pediatric epilepsy. Unlike these cannabinoid-based epilepsy development programs, we are conducting development programs for ZYN002 in a much broader subset of the epilepsy population.

No large-scale, placebo-controlled clinical trials of CBD for the treatment of patients with epilepsy (either pediatric or adult) have been published. However, in a small (fifteen patients), third-party Phase 2 clinical trial, patients with a documented history of epilepsy were treated with crystalline CBD or placebo for up to 4.5 months. A total of 88% of the CBD-treated group had a response to treatment, with 50% of patients experiencing considerable improvement and 38% reporting at least partial improvement. In a compassionate access study conducted by a third party, 162 patients with treatment resistant epilepsy were treated for at least 12 weeks with an oral CBD solution. In this open label study, 50% of patients with DS had a 50% reduction in seizures compared to baseline while 69% of patients with LGS had a 50% reduction in seizures compared to baseline. Our expected type of therapy is adjunctive, second-line therapy in patients with partial seizures with secondary generalization on a stable dose of an anticonvulsant with a history of failure.

Osteoarthritis — OA is a degenerative joint disease that leads to wear and tear of the joints and affects the cartilage, joint lining, ligaments and bone. It is the most common form of joint disease and tends to occur most often in the hand joints, spine, hip, knees and great toes. It is characterized by the breakdown of the joint cartilage, bony changes in the joints and deterioration of the tendons and ligaments leading to pain and inflammation of the joint lining.

According to Decision Resources, which defines OA as radiographically confirmed OA of any joint, in 2008 it was predicted that the total number of prevalent cases of OA would be approximately 129.5 million by 2012. Treatment for patients suffering from OA represented a total U.S. market size of approximately $670.0 million in 2012.

We believe that ZYN002 may provide an effective treatment for OA based on research we have conducted. We examined the efficacy of transdermal ZYN002 for reduction of inflammation and pain *in vivo*, assessing adverse effects in a rat with complete Freund's adjuvant-induced monoarthritic knee. ZYN002 gel (0.6, 3.1, 6.2, or 62.3 mg/day) was applied for four consecutive days after arthritis induction. The level of inflammation was assessed by knee joint circumference and immune cell invasion in histological sections.

Measurement of CBD plasma concentration revealed linearity with daily doses of 0.6 to 6.2 mg of ZYN002. Compared with baseline, rats treated with ZYN002 gel had significant, dose-dependent reductions in knee joint and synovial membrane swelling, immune cell infiltration, and spontaneous pain rating scores ($P \leq 0.05$). Paw withdrawal latency, or PWL, recovered to near-baseline levels. Immunohistochemical analysis of spinal cord and dorsal root ganglia revealed dose-dependent reductions of pro-inflammatory biomarkers (CD11b/c, CGRP, TNF). The data suggests that topical ZYN002 has the potential to provide effective relief of pain and inflammation caused by OA. Our expected type of therapy is monotherapy, first-line therapy in patients with OA.

FXS — FXS is a 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. According to the National Fragile X Foundation, FXS affects 1 in 3,600 to 4,000 males and 1 in 4,000 to 6,000 females of all races and ethnic groups. Approximately 1 in 151 women carry the Fragile X gene and could pass it to their children. Approximately 1 in 468 men carry the Fragile X gene and their daughters will also be carriers. FXS is an autism spectrum disorder, and patients with FXS exhibit autism-like symptoms including cognitive impairment, anxiety and mood swings, attention deficit and heightened stimuli. Approximately 7% of women and 18% of men with FXS have seizures. People with FXS are affected throughout their lives. Currently, there are no known cures or approved therapies for the treatment of FXS. Special education and symptomatic treatments for anxiety and irritability are employed to lessen the burden of illness.

FXS is the most common inherited intellectual disability. Based on the 2012 U.S. Census and FXS prevalence rates according to the National Fragile X Foundation, in 2012 there were approximately 71,000 patients with FXS in the United States.

We believe ZYN002 may provide an effective treatment for FXS based on its capacity to interact with the endocannabinoid system, which is compromised in patients with FXS. Specifically, CBD indirectly increases the concentration of the cannabinoids 2-AG and

anandamide, which are endogenous ligands at the CB_1 and CB_2 receptors. Furthermore, the Fragile X mental retardation protein 1 that is diminished in patients with FXS, is required for the production of 2-AG. Therefore, FXS results in the reduction of endogenous stimulation of endocannabinoid receptors while CBD facilitates the availability of endogenous endocannabinoids, potentially attenuating the pathophysiology of the disease. Our expected type of therapy is monotherapy, first-line therapy in patients with FXS.

In vitro and Preclinical Studies

In an *in vitro* study, we evaluated the effects of exposing CBD to acidic conditions. We exposed CBD to simulated gastric fluid. Upon high-performance liquid chromatography analysis of this solution, we found Δ-8 THC and Δ-9 THC compounds formed from the degradation of CBD in this acidic condition. These results suggest that CBD may degrade and form THC if delivered by oral or oral mucosal routes.

The PK of ZYN002 has been studied in three animal species: guinea pigs, Sprague-Dawley, or SD, rats and squirrel monkeys. PK refers to a drug's absorption, distribution, metabolism, and excretion from the body and measures, among other things, the concentration of the drug in the plasma. Based upon preclinical studies, the transdermal route of administration of ZYN002 achieves sustained, consistent CBD plasma levels.

Clinical Trials

We have completed an extensive review of the literature related to preclinical toxicology of CBD and completed a mutagenicity study with ZYN002. This preclinical toxicology analysis was provided to the FDA for a pre- Investigational New Drug, or IND, meeting held in the first quarter of 2015 and, the FDA confirmed that no further preclinical work would be required prior to the initiation of the Phase 1 clinical program. We initiated Phase 1 clinical trials in Australia in October 2015, and we expect to initiate Phase 2 clinical trials in each indication in the second half of 2016. We have initiated a standard toxicology program for ZYN002 concurrently with the clinical program. The toxicology program will consist of standard single-dose toxicology, multiple-dose toxicology, reproductive studies and carcinogenicity studies.

Phase 1 Clinical Trials— In October 2015, we initiated a Phase 1 single rising dose clinical trial of ZYN002. The Phase 1 study was a randomized, double-blind, placebo-controlled, clinical trial to assess the safety and pharmacokinetics of ZYN002 in 32 healthy volunteers and 12 patients with epilepsy. Initial results from the 32 healthy volunteers demonstrated that ZYN002 was safe and well tolerated at all four dose levels. There were no serious adverse events, no drug-related changes in ECGs or clinical laboratory values, and there were no discontinuations due to adverse events. Overall, the incidence of adverse events associated with ZYN002 was similar to placebo. In addition, ZYN002 demonstrated no impairment in the trail making test, a neuropsychological test of visual attention and task switching, which detects several cognitive impairments. Final results, including results from patients with epilepsy, are expected in the first half of 2016.

In January 2016 we initiated a second Phase 1 clinical trial for ZYN002. The randomized, double-blind, placebo controlled trial, titled the "Multiple Rising Dose Study in Healthy Volunteers and Patients with Epilepsy," will evaluate the PK profile and tolerability of ZYN002 in 24 healthy volunteers, followed by 12 patients with epilepsy. Results are expected in the first half of 2016.

To complete the Phase 1 program, we will conduct a bioequivalence clinical trial assessing the PK of ZYN002 when applied to various parts of the body (e.g., arm, thigh and back).

Phase 2a Clinical Trials— We intend to initiate Phase 2a clinical trials for ZYN002 as outlined in the following table:

	Phase 2a Clinical Trials		
Target Indication	**Patient Population**	**Expected Type of Therapy**	**Design**
Refractory Epilepsy	Patients with partial seizures with or without secondary generalization	Adjunctive therapy in patients with partial seizures with secondary generalization on a stable dose of an anticonvulsant with a history of failure	Randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of multiple doses of ZYN002 to placebo
Osteoarthritis	Patients diagnosed with OA	Monotherapy, first-line therapy in patients with OA	Randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of multiple doses of ZYN002 to placebo
Fragile X syndrome	Patients diagnosed with FXS	Monotherapy, first-line therapy in patients with FXS	Open-label trial to evaluate the efficacy and safety of ZYN002

Phase 2b Clinical Trials— Depending on the results of Phase 2a clinical trials, we may need to further define the dosing in Phase 2b trials or we may proceed directly into Phase 3 clinical trials.

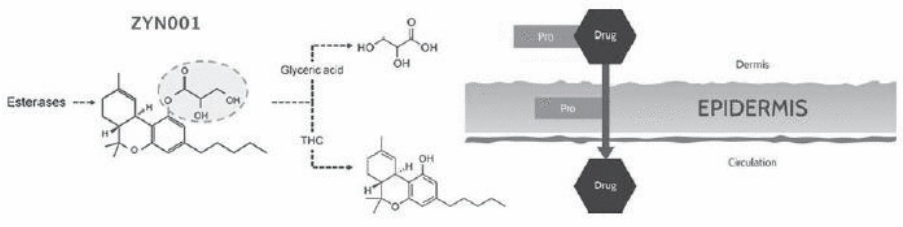
Phase 3 Clinical Trials— We intend to use the data from the Phase 2 clinical trials outlined above to select doses of ZYN002 for our Phase 3 program, which will consist of two randomized, double-blind, placebo-controlled clinical trials for each indication and open-label long-term clinical trials.

ZYN001

Overview

ZYN001 is a pro-drug of THC that enables effective transdermal delivery via a patch and is patent protected through 2031. We expect that ZYN001 will be classified by the FDA as an NCE. The structure of the skin effectively inhibit the transdermal delivery of most therapeutics. Drugs classified as hydrophobic, such as THC, add an additional impediment to their transdermal delivery through the skin. THC is naturally hydrophobic and thus is unable to be effectively delivered through human skin. A pro-drug is a drug administered in an inactive or less active form and designed to enable more effective delivery, and then converted into an active form through a normal metabolic process. Chemically, ZYN001 is the synthetic D-glyceric acid ester of THC. Unlike THC, ZYN001 is able to be efficiently absorbed into the skin through transdermal delivery. After crossing the stratum corneum, ZYN001 is hydrolyzed back to THC and glyceric acid under physiological conditions, mainly due to the action of common enzymes in the skin tissue known as “esterases.” See Figure 2 below.

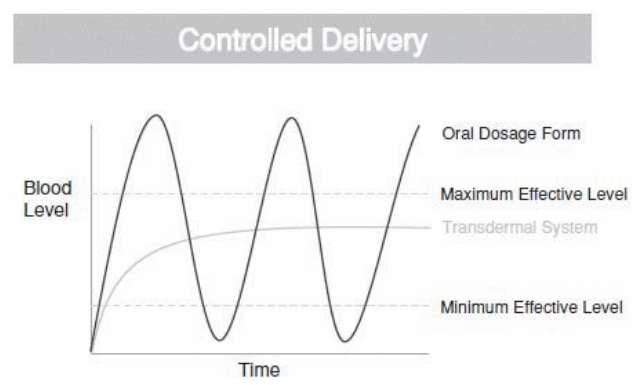
Figure 2. Hydrolysis of ZYN001 into glyceric acid and THC.



The transdermal patch is a non-invasive, non-oral dosage form that has been proven to be an effective method of delivery in other U.S. Food and Drug Administration, or FDA, approved products. The ZYN001 transdermal patch contains a 4% ZYN001 gel formulation. We intend to test the ZYN001 patch for application to the arm, back and thigh. The drug substance is produced synthetically and is not derived or extracted from botanicals. The excipients in the patch have been classified as GRAS, and have been used in transdermal products previously approved by the FDA.

As illustrated below in Figure 3, transdermal delivery often provides more consistent plasma levels without the peaks and valleys often associated with an oral dosage form.

Figure 3. Illustration of transdermal delivery.



Market Overview and Rationale

We intend to study ZYN001 for the treatment of fibromyalgia and peripheral neuropathic pain.

Fibromyalgia — Fibromyalgia is a chronic health problem that causes pain throughout the body and other symptoms such as fatigue and cognitive (memory or thought) problems. According to Decision Resources, in 2012, there were approximately 5.6 million adult fibromyalgia patients in the United States, and pain treatment for these patients represented a total U.S. market size of approximately $1.6 billion.

We believe that ZYN001 may provide an effective treatment for fibromyalgia based on the hypothesis that an endocannabinoid deficiency is the underlying cause of fibromyalgia, which may enable patients to benefit from therapy with an exogenous cannabinoid. Nabilone, a compound which is chemically similar but not identical to THC, has shown significant reduction in fibromyalgia pain in a third-party randomized clinical trial, but it has also been associated with dose limiting psychoactive adverse effects. We believe ZYN001 has the potential to treat fibromyalgia by delivering sustained, consistent plasma levels of THC to provide a therapeutic benefit with minimal psychoactive adverse effects. Our expected type of therapy is monotherapy, first-line therapy in patients with fibromyalgia.

Peripheral Neuropathic Pain — Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction of the central or peripheral nervous systems. In patients with peripheral neuropathic pain, the pain is a symptom of another disease that has caused nerve damage — such as a herniated disc (lower back pain), diabetes (diabetic neuropathy), cancer (neuropathic cancer pain), or herpes zoster infection (postherpetic neuralgia) — but it is recognized as a clinical condition on its own. Because the damage does not involve the brain or spinal cord, the resulting neuropathic pain is defined as peripheral.

According to Decision Resources, in 2012 there were approximately 14.0 million peripheral neuropathic pain patients in the United States, and pain treatment for these patients represented a total U.S. market size of approximately $4.0 billion in 2012.

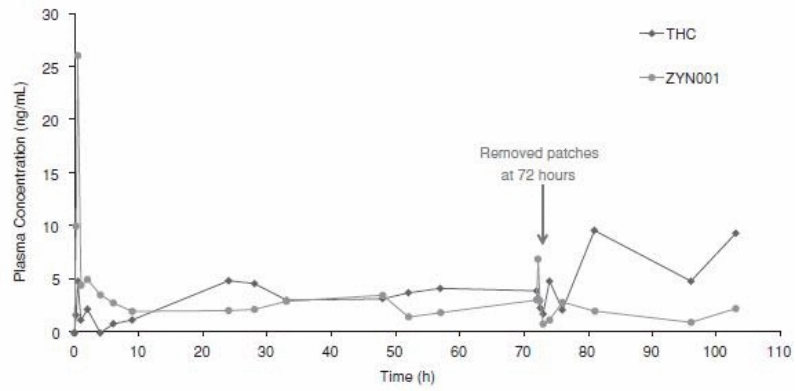
We believe that ZYN001 may provide effective treatment for peripheral neuropathic pain based on third-party studies in animals that have shown that cannabinoid receptors are found in high concentrations in the central nervous system, as well as on peripheral neurons and along the principal nociceptive pathways. The results of a third-party randomized, placebo-controlled clinical trial demonstrated that low-dose vaporized *Cannabis* may reduce neuropathic pain which we believe suggests a role for THC in peripheral neuropathic pain management. Our expected type of therapy is monotherapy, first-line therapy in patients with peripheral neuropathic pain.

Preclinical Studies

In preclinical studies, the transdermal route of administration of ZYN001 achieved consistent THC plasma levels that we believe will deliver therapeutic benefit with minimal psychoactive side effects thereby distinguishing it from oral and oral mucosal delivery systems.

In vivo guinea pig PK — The PK of a 4% ZYN001 patch was examined in a hairless guinea pig model by adhering two patches, with a total of 6.25 cm^2 active area, to the guinea pig. PK refers to a drug's absorption, distribution, metabolism, and excretion from the body and measures, among other things, the concentration of the drug in the plasma. The patches remained on the guinea pig for 72 hours, and blood samples were obtained for 103 hours. Plasma samples were analyzed by liquid chromatography-tandem mass spectrometry, or LC/MSMS. ZYN001, THC, and metabolites of THC (hydroxy-THC, or THC-OH, and 11-nor-delta-9-THC carboxylic acid, or TCH-COOH), were measured. No skin irritation or erythema was shown. Results of this study are reflected in Figure 4 below.

Figure 4. Plasma concentration vs time in guinea pig after ZYN001 patch application.



ZYN001 achieved a steady-state plasma concentration of total THC equivalents of 6.90 ± 1.47 ng/mL. These results demonstrate that ZYN001 was rapidly converted to THC and sustained, consistent plasma levels of THC were achieved.

Clinical Trials

The standard battery of genotoxicology studies required by the FDA for ZYN001 showed no adverse effects. The safety pharmacology studies required by the FDA demonstrated that ZYN001 has a pharmacology profile consistent with THC. The compound is currently being investigated in preclinical toxicology. We discussed our planned preclinical studies and clinical trials for

ZYN001 with the FDA at a Pre-IND meeting in August 2013. We anticipate initiating Phase 1 clinical trials beginning in the second half of 2016. Phase 2 clinical trials investigating ZYN001 in each individual indication are planned to begin in the first half of 2017.

Phase 1 Clinical Trials— We plan to evaluate the tolerability and PK profile of ZYN001 in a Phase 1 single rising dose clinical trial in healthy human subjects. Subsequent to the single rising dose clinical trial, we intend to conduct a Phase 1 multiple rising dose clinical trials to examine the tolerability, PK and PD of multiple doses of ZYN001 in healthy human subjects and in patients with fibromyalgia. To complete the Phase 1 program, we will conduct a bioequivalence clinical trial assessing the PK of ZYN001 when applied to various parts of the body (e.g., arm, thigh and back).

Phase 2a Clinical Trials— We intend to initiate Phase 2a clinical trials for ZYN001 as outlined in the following table:

	Phase 2a Clinical Trials		
Target Indication	**Patient Population**	**Expected Type of Therapy**	**Design**
Fibromyalgia	Patients who meet the American College of Rheumatology criteria for fibromyalgia syndrome	Monotherapy, first-line therapy in patients with fibromyalgia	Randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of multiple doses of ZYN001 to placebo
Peripheral Neuropathic Pain	Patients with peripheral neuropathic pain of at least six months' duration	Monotherapy, first-line therapy in patients with peripheral neuropathic pain	Randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of multiple doses of ZYN001 to placebo

Phase 2b Clinical Trials— Depending on the results of Phase 2a clinical trials, we may need to further define the dosing in Phase 2b clinical trials or we may proceed directly into Phase 3 clinical trials.

Phase 3 Clinical Trials— We intend to use the data from the Phase 2 clinical trials outlined above to select doses of ZYN001 for our Phase 3 program, which will consist of two randomized, double-blind, placebo-controlled clinical trials for each indication and open-label long-term clinical trials.

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 ZYN002 and ZYN001. 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 10, 2016, we owned a total of seven issued U.S. utility patents and two pending U.S. utility patent applications. These U.S. patents and patent applications will expire between 2029 through 2031. We have already obtained additional patent term for

some of the issued patents to compensate us for delays at the U.S. Patent Office, under the patent term adjustment laws. These patents, and any pending applications that ultimately issue as patents, may also be eligible for patent term extension for delay caused by FDA regulatory review, thereby further extending their patent terms.

In addition to our U.S. intellectual property, we own 85 corresponding foreign issued patents and 8 corresponding foreign applications, which will expire between 2026 and 2031.

ZYN002

Our ZYN002 patent portfolio currently consists of two issued patents in the United States, six issued patents in France, Germany, Ireland, Japan, Switzerland, and the United Kingdom and one pending patent application in Canada. The issued patents claim the permeation enhanced formulation of ZYN002 and methods of use relating to ZYN002. The issued patents will expire between 2026 and 2030. Any patents that issue from our currently pending patent applications will expire in 2030.

ZYN001

Our ZYN001 patent portfolio currently consists of two issued patents in the United States, one issued patent in Japan, issued patents in 43 countries in Europe, including France, Germany, Ireland, Italy, Spain and the United Kingdom, and patent applications pending in the United States, Europe, Canada and Japan. The issued patents are composition of matter patents, which cover the chemical structure of the pro-drug ZYN001, the D-glyceric acid ester of THC, and other THC pro-drugs. The issued patents will expire between 2028 and 2031. Any patents that issue from our currently pending patent applications will expire in 2028.

Other

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

Trade Secrets and Proprietary Information

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

Research and Development

We incurred research and development expense of $7.4 million, $2.4 million and $1.1 million for the years ended December 31, 2015, 2014 and 2013, respectively.

Manufacturing

The active pharmaceutical ingredients, or APIs, used in ZYN002 and ZYN001 are synthesized by contract manufacturers. These contract manufacturers have sufficient capabilities to meet our projected product requirements through Phase 3 clinical trials.

The ZYN002 gel is manufactured and filled into single unit tubes by a contract manufacturer. The ZYN001 transdermal patch is manufactured by contract manufacturers and sub-component fabricators. The patch is manufactured by a contract manufacturer. The drug product formulation is manufactured and filled into the patch by another contract manufacturer.

We selected our contract manufacturers and sub-component fabricators for their specific competencies in manufacturing, product design, and materials. FDA regulations require that products be produced under current Good Manufacturing Practices, or cGMPs. Our key suppliers currently meet cGMPs and have sufficient capacities to meet our projected product requirements through Phase 3 clinical trials.

Commercial Operations

We do not currently have an organization for the sales, marketing and distribution of pharmaceutical products. We may rely on licensing and co-promotion agreements with strategic collaborators for the commercialization of our products in the United States and other territories. If we choose to build a commercial infrastructure to support marketing in the United States, such commercial infrastructure could be expected to include a sales force supported by sales management, internal sales support, an internal marketing group and distribution support. To develop the appropriate commercial infrastructure internally, we would have to invest financial and management resources, some of which would have to be deployed prior to any confirmation that ZYN002 or ZYN001 will be approved.

Competition

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

ZYN002

We are studying ZYN002, our proprietary synthetic CBD product candidate, as an adjunctive, second-line therapy in refractory epilepsy patients who are not well controlled by their current anti-epileptic drug, or AED. We also intend to study ZYN002 in a clinical development program as monotherapy first-line treatment in patients with OA and FXS.

Cannabinoid Competition

Cannabinoids, such as GW Pharmaceuticals, PLC, or GW's Epidiolex® and CBD more generally, have shown promise clinically and anecdotally as a treatment for epilepsy. No CBD products or combination THC/CBD products have been approved in the United States. GW is currently investigating Epidiolex, a liquid formulation of highly concentrated CBD, in the United States for the treatment of DS, (severe, infantile-onset, genetic drug-resistant epilepsy with no FDA approved treatments) and LGS (a rare disorder with onset typically between three and five years of age featuring multiple seizure types with slow spike wave complexes on EEG) and childhood epilepsy syndromes. Insys Therapeutics Inc., or Insys, is also developing a synthetic CBD compound for the treatment of DS, LGS, childhood epilepsy syndromes and glioblastoma.

In the combination THC/CBD space, GW's Sativex®, a plant extract combination of THC/CBD for treatment of spasticity associated with multiple sclerosis, is approved in 27 countries outside the United States as an alternative to baclofen and tizanidine.

Additional activity in this space includes companies supplying synthetic cannabinoids, *Cannabis* extracts, and herbal *Cannabis* to researchers for preclinical and clinical investigation.

General Competition and Standard of Care

Within epilepsy, we intend to treat refractory patients who have not responded to previous treatment with AEDs such as depakote, pregabalin, gabapentin, topiramate, and lacosamide. Second and third generation AEDs continue to improve upon first generation therapies, but experts contend that a better understanding of the disorder accompanied by fundamentally innovative treatments will be required to effectively improve treatment outcomes for the high percentage of patients undertreated by AEDs. The majority of AEDs have frequent safety concerns including serious CNS adverse events and drug-drug interactions.

In OA, our expected type of therapy is monotherapy, first-line therapy in patients with OA. Patients try a multitude of prescription and over-the-counter medications to relieve pain including traditional NSAIDs, Cox-2 inhibitors, centrally acting analgesics, topical analgesics, intra-articular corticosteroids, and hyaluronic acid preparations. Though these products offer varying degrees of pain relief, many also have been shown to cause significant adverse effects including potential addiction.

In FXS, our expected type of therapy is monotherapy, first-line therapy in patients with FXS. There are no drugs approved for the treatment of FXS, although various classes of medications are used off-label for the treatment of behavioral and mental health conditions associated with FXS. Some patients with FXS benefit from medications that treat attention deficit disorders and other

patients who experience general anxiety, social anxiety and other chronic conditions may benefit from different types of anti-anxiety medications. We are aware that Neuren Pharmaceuticals and Marinus Pharmaceuticals are developing compounds for the treatment of FXS.

ZYN001

We intend to study ZYN001in a clinical development program as monotherapy, first-line treatment in patients with fibromyalgia and peripheral neuropathic pain.

Cannabinoid Competition

We believe cannabinoids offer a superior treatment paradigm for patients suffering from pain, providing more controlled delivery and therefore treatment effect along with a much more tolerable safety profile. The *Cannabis* therapeutic area currently includes formulated extracts of the *Cannabis* sativa plant and synthetic products, all of which use THC, CBD, or a combination of THC/CBD as the active ingredient. In the United States, two oral capsules — Insys' dronabinol (a synthetic THC) and Meda AB's nabilone (a synthetic derivative of THC) — have been approved and distributed for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have not responded adequately to conventional antiemetic treatments. Dronabinol capsules are also approved for anorexia associated with weight loss in patients with acquired immune deficiency syndrome, or AIDS. Insys is also seeking FDA approval for an orally administered liquid formulation of dronabinol for treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Exploratory research into the effects of THC formulations in other indications is also in progress. GW, is also developing Sativex®, a plant extract combination of THC/CBD for treatment of chronic cancer pain and neuropathic pain in an oral mucosal spray.

General Competition and Standard of Care

In fibromyalgia, our expected type of therapy is monotherapy, first-line therapy in patients with fibromyalgia. There are only three drugs approved by the FDA: pregabalin, duloxetine, and milnacipran. We intend to treat patients whose condition is either newly diagnosed or has not responded to previous treatment with these three currently approved treatments. There is no known cure for the disease and no single therapy is likely to provide significant relief of all symptoms. Low-dose tricyclic antidepressants are prescribed frequently, but are associated with various side-effects. Fibromyalgia is also treated using opioids, but, in addition to debate about their efficacy, these can be addictive for many patients.

In peripheral neuropathic pain, our expected type of therapy is monotherapy, first-line therapy in patients with peripheral neuropathic pain. Peripheral neuropathic pain generally is treated with tricyclic antidepressants, anticonvulsants such as duloxetine, depakote, pregabalin, gabapentin and topiramate, and serotonin/norepinephrine reuptake inhibitors, or SNRIs. Although tricyclic antidepressants, anticonvulsants, and SNRIs often show efficacy in treating neuropathic pain, they also have many drawbacks, including poor tolerability with side effects in most patients.

Government Regulation and Product Approval

As a development stage pharmaceutical company that operates in the United States, we are subject to extensive regulation by the FDA, and other federal, state, and local regulatory agencies. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and its implementing regulations set forth, among other things, requirements for the research, testing, development, manufacture, quality control, safety, effectiveness, approval, labeling, storage, record keeping, reporting, distribution, import, export, advertising and promotion of our products. Although the discussion below focuses on regulation in the United States, we anticipate seeking approval for, and marketing of, our products in other countries. Generally, our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the United States, although there can be important differences. Additionally, some significant aspects of regulation in Europe are addressed in a centralized way through the European Medicines Agency, or EMA, 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 main regulatory body that controls 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. A failure to comply explicitly with any

requirements during the product development, approval, or post-approval periods, may lead to administrative or judicial sanctions. These sanctions could include the imposition by the FDA or an institutional review board, or IRB, 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 before a new drug may be marketed in the United States generally include:

- completion of preclinical studies, animal studies and formulation studies in compliance with the FDA's good laboratory protocols, or GLP, regulations;
- submission to the FDA of an IND to support human clinical testing in the United States;
- approval by an IRB at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled clinical trials in accordance with federal regulations and with current 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 investigational product candidate is produced to assess compliance with cGMP, and to assure that the facilities, methods and controls are adequate; and
- FDA review and approval of the NDA.

Clinical Trials

An IND is a request for authorization from the FDA to administer an investigational product candidate to humans. This authorization is required before interstate shipping and administration of any new drug product to humans in the United States that is not the subject of an approved NDA. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. Clinical trials involve the administration of the investigational product candidate to patients under the supervision of qualified investigators following GCPs, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators and monitors. Clinical trials are conducted under protocols that detail the parameters to be used in monitoring safety, and the efficacy 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. We have begun to conduct our Phase 1, and plan to conduct our Phase 2, clinical trials for ZYN002 in Australia, subject to applicable regulatory approval, and have not filed an investigational new drug application, or IND, with the FDA prior to the commencement of those Phase 1 clinical trials.

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

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

We must file an IND with the FDA and receive approval from the U.S. Drug Enforcement Administration, or DEA, prior to commencement of any clinical trials in the United States. We plan to submit an IND prior to conducting any clinical trials in the United States. We plan to submit NDAs for ZYN002 and ZYN001 to the FDA upon completion of all requisite clinical trials. The informed written consent of each participating subject is required. The clinical investigation of an investigational product candidate is

generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The three phases of an investigation are as follows:

- *Phase 1.* Phase 1 includes the initial introduction of an investigation product candidate into humans. Phase 1 clinical trials may be conducted in patients with the target disease or condition or healthy volunteers. These studies are designed to evaluate the safety, metabolism, PKs and pharmacologic actions of the investigational 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 investigational product candidate's PKs 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 includes the controlled clinical trials conducted to evaluate the effectiveness of the investigational product candidate for a particular indication(s) in patients with the disease or condition under study, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks associated with the product candidate. Phase 2 clinical trials are typically well-controlled, closely monitored, and conducted in a limited subject 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 relationship of the product candidate, and to provide an adequate basis for drug approval. Phase 3 clinical trials usually involve several hundred to several thousand participants. In most cases, the FDA requires two adequate and well controlled Phase 3 clinical trials to demonstrate the efficacy of the 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 order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. In some cases, clinical trials are overseen by an independent group of qualified experts organized by the trial sponsor, or the clinical monitoring board. This group provides authorization for whether or not a trial may move forward at designated check points. These decisions are based on the limited 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 be able to request a special protocol assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim. A sponsor meeting the regulatory criteria may make a specific request for an SPA and provide information regarding the design and size of the proposed clinical trial. An SPA request must be made before the proposed trial begins, and all open issues must be resolved before the trial begins. If a written agreement is reached, it will be documented and made part of the record. The agreement will be binding on the FDA and may not be changed by the sponsor or the FDA after the trial begins except with the written agreement of the sponsor and the FDA or if the FDA determines that a substantial scientific issue essential to determining the safety or efficacy of the product candidate was identified after the testing began. An SPA is not binding if new circumstances arise, and there is no guarantee that a study will ultimately be adequate to support an approval even if the study is subject to an SPA. We expect to test ZYN002 AND ZYN001 in several advanced stage clinical trials, including Phase 3 clinical trial for which we may request an SPA. Having an SPA does not guarantee that a product will receive FDA approval.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational product candidate information is submitted to the FDA in the form of an NDA to request regulatory approval for the product in specified indications.

New Drug Applications

In order to obtain approval to market a drug in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the product candidate for the proposed indication. The application includes all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results as well as positive

findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed 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 investigational product candidate to the satisfaction of the FDA.

In most cases, the NDA must be accompanied by a substantial user fee; there may be some instances in which the user fee is waived. The FDA will initially review the NDA for completeness before it accepts the NDA for filing. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. After 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 such applications for standard review product candidates are reviewed within ten to twelve months. The FDA can extend this review by three months to consider certain late-submitted information or information intended to clarify information already provided in the submission. 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 which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with Good Clinical Practices, or GCP. After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or 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.

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 changes in indications, labeling, or manufacturing processes or facilities, 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 uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of certain FDA-regulated products, including prescription drugs, are required to register and disclose certain clinical trial information on a public website maintained by the U.S. National Institutes of Health, or NIH. Information related to the product, patient population, phase of investigation, study sites and investigator, and other aspects of the clinical trial is made public as part of the registration. Sponsors are also obligated to disclose the results of these trials after completion. 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 regulatory agencies closely regulate the marketing and promotion of drugs through, among other things, standards and regulations for direct-to-consumer advertising, 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 regulations impose stringent restrictions on 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 DOJ, or the Office of the Inspector General of HHS, as well as state authorities. This 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.

Post Approval Regulations

After regulatory approval of a drug is obtained, a company 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. In addition, as a holder of an approved NDA, a company would be required to report adverse reactions and production problems to the FDA, to provide updated safety and efficacy information, and to comply with requirements concerning advertising and promotional labeling for any of its products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval to assure and preserve the long term stability of the drug or biological product. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes extensive procedural and substantive record keeping requirements. In addition, changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon a company and any third-party manufacturers that a company 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.

Controlled Substances

The federal Controlled Substances Act of 1970, or CSA, and its implementing regulations establish a "closed system" of regulations for controlled substances. The CSA imposes registration, security, recordkeeping and reporting, storage, manufacturing, distribution, importation and other requirements under the oversight of the DEA. The DEA is the federal agency responsible for regulating controlled substances, and requires those individuals or entities that manufacture, import, export, distribute, research, or dispense controlled substances to comply with the regulatory requirements in order to prevent the diversion of controlled substances to illicit channels of commerce.

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

The DEA categorizes controlled substances into one of five schedules — Schedule I, II, III, IV, or V — with varying qualifications for listing in each schedule. Schedule I substances by definition have a high potential for abuse, have no currently "accepted medical use" in treatment in the United States and lack accepted safety for use under medical supervision. They may be used only in federally-approved research programs and may not be marketed or sold for dispensing to patients in the United States. Pharmaceutical products having a currently accepted medical use that are otherwise approved for marketing may be listed as Schedule II, III, IV or V substances, with Schedule II substances presenting the highest potential for abuse and physical or psychological dependence, and Schedule V substances presenting the lowest relative potential for abuse and dependence. The regulatory requirements are more restrictive for Schedule II substances than Schedule III substances. For example, all Schedule II drug prescriptions must be signed by a physician, physically presented to a pharmacist in most situations, and cannot be refilled. While *Cannabis* is a Schedule I controlled substance, products approved for medical use in the United States that contain *Cannabis* or *Cannabis* extracts must be placed in Schedules II-V, since approval by the FDA satisfies the "acceptable medical use" requirement.

The DEA inspects all manufacturing facilities to review security, record keeping, reporting and handling prior to issuing a controlled substance registration. The specific security requirements vary by the type of business activity and the schedule and quantity of

controlled substances handled. The most stringent requirements apply to manufacturers of Schedule I and Schedule II substances. Required security measures commonly include background checks on employees and physical control of controlled substances through storage in approved vaults, safes and cages, and through use of alarm systems and surveillance cameras. An application for a manufacturing registration as a bulk manufacturer (not a dosage form manufacturer or a repacker/relabeler) for a Schedule I or II substance must be published in the Federal Register, and is open for 30 days to permit interested persons to submit comments, objections, or requests for a hearing. A copy of the notice of the Federal Register publication is forwarded by the DEA to all those registered, or applicants for registration, as bulk manufacturers of that substance. Once registered, manufacturing facilities must maintain records documenting the manufacture, receipt and distribution of all controlled substances. Manufacturers must submit periodic reports to the DEA of the distribution of Schedule I and II controlled substances, Schedule III narcotic substances, and other designated substances. Registrants must also report any controlled substance thefts or significant losses, and must obtain authorization to destroy or dispose of controlled substances. As with applications for registration as a bulk manufacturer, an application for an importer registration for a Schedule I or II substance must also be published in the Federal Register, which remains open for 30 days for comments. Imports of Schedule I and II controlled substances for commercial purposes are generally restricted to substances not already available from a domestic supplier or where there is not adequate competition among domestic suppliers. In addition to an importer or exporter registration, importers and exporters must obtain a permit for every import or export of a Schedule I and II substance or Schedule III, IV and V narcotic, and submit import or export declarations for Schedule III, IV and V non-narcotics. In some cases, Schedule III non-narcotic substances may be subject to the import/export permit requirement, if necessary to ensure that the United States complies with its obligations under international drug control treaties.

For drugs manufactured in the United States, the DEA establishes annually an aggregate quota for the amount of substances within Schedules I and II that may be manufactured or produced in the United States based on the DEA's estimate of the quantity needed to meet legitimate medical, scientific, research and industrial needs. This limited aggregate amount of *Cannabis* that the DEA allows to be produced in the United States each year is allocated among individual companies, which, in turn, must annually apply to the DEA for individual manufacturing and procurement quotas. The quotas apply equally to the manufacturing of the active pharmaceutical ingredient and production of dosage forms. The DEA may adjust aggregate production quotas a few times per year, and individual manufacturing or procurement quotas from time to time during the year, although the DEA has substantial discretion in whether or not to make such adjustments for individual companies.

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

We currently manufacture the API for ZYN002 and ZYN001 in the United States and Canada. We are currently conducting Phase I clinical trials for ZYN002 in Australia and may conduct Phase 2 clinical trials in Australia subject to regulatory approval. We may also choose to conduct clinical trials for ZYN001 outside the United States subject to regulatory approval. We may decide to develop, manufacture or commercialize our product candidates in additional countries. As a result, we will also be subject to controlled substance laws and regulations from the Therapeutic Goods Administration in Australia, Health Canada's Office of Controlled Substances in Canada, and from other regulatory agencies in other countries where we develop, manufacture or commercialize ZYN002 or ZYN001 in the future.

The Hatch-Waxman Amendments to the FDC Act

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant's product or a method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA, or 505(b)(2) application. An ANDA provides for marketing of a drug product that has the same active ingredients, same strengths and dosage form, as the listed drug and has been shown through PK testing to be bioequivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are generally not required to conduct, or submit results of, preclinical studies or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug. 505(b)(2) applications provide for marketing of a drug product that may have the

same active ingredients as the listed drug and contains full safety and effectiveness data as an NDA, but at least some of this information comes from studies not conducted by or for the applicant. The ANDA or 505(b)(2) applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) 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 already approved product'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 and patent holders once the ANDA or 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. 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, and a decision in the infringement case that is favorable to the ANDA or 505(b)(2) applicant.

The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired.

Marketing Exclusivity

Upon NDA approval of a new chemical entity, which is a drug that contains no active moiety that has been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity during which the FDA cannot approve any ANDA seeking approval of a generic version of that drug. Certain changes to a drug, such as the addition of a new indication to the package insert, are associated with a three-year period of exclusivity during which the FDA cannot approve an ANDA for a generic drug that includes the change. A Section 505(b)(2) NDA may be eligible for three-year marketing exclusivity, assuming the NDA includes reports of new clinical studies (other than bioequivalence studies) essential to the approval of the NDA.

An ANDA may be submitted one year before marketing exclusivity expires if a Paragraph IV certification is filed. In this case, the 30 months stay, if applicable, runs from the end of the five year marketing exclusivity period. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA may be filed before the expiration of the exclusivity period.

Additionally, six months of marketing exclusivity in the United States is available under Section 505A of the FDCA if, in response to a written request from the FDA, a sponsor submits and the agency accepts requested information 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 non-patent exclusivity period for which the drug product is eligible.

Patent Term Extension

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

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. 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 (CTA) much like the IND prior to the commencement of human clinical trials. In Europe, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed.

To obtain regulatory approval to commercialize a new drug under European Union regulatory systems, we must submit a marketing authorization application, or MAA. The MAA is similar to the NDA, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical 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.

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, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, product detention or refusal to permit the import or export of products, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

Other Special Regulatory Procedures

Orphan Drug Designation

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or, if the disease or condition affects more than 200,000 individuals in the United States, if there is no reasonable expectation that the cost of developing and making the drug would be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union community. 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.

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 indication for which it has orphan drug designation, the product is entitled to seven years of market exclusivity, which means the FDA may not approve any other application for the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan drug designation must be requested before submission of an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Priority Review (United States) and Accelerated Review (European Union)

Based on results of the Phase 3 clinical trial(s) submitted in an NDA, upon the request of an applicant, a priority review designation may be granted to a product by the FDA, which sets the target date for FDA action on the application at six months from the FDA's decision on priority review application, or eight months from the NDA filing. Priority review is given where preliminary estimates indicate that a product, if approved, has the potential to provide a safe and effective therapy where no satisfactory alternative therapy exists, or a significant improvement compared to marketed products is possible. If criteria are not met for priority review, the standard FDA review period is ten months from the FDA's decision on priority review application, or 12 months from the NDA filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

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, which takes into consideration: 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

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act and the associated reconciliation bill, which we refer to collectively as the Affordable Care Act. The Affordable Care Act substantially changes the way healthcare will be financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry. The Affordable Care Act is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Among the Affordable Care Act's provisions of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any covered entity engaged in manufacturing or importing certain branded prescription drugs and biological products, apportioned among such entities in accordance with their respective market share in certain government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23.1% and 13.0% of the average manufacturer price, or AMP, for most branded and generic drugs, respectively;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a new partial prescription drug benefit for Medicare recipients, or Medicare Part D, coverage gap discount program, in which manufacturers must agree to offer 50.0% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133.0% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- new requirements to report annually specified financial arrangements with physicians and teaching hospitals, as defined in the Affordable Care Act and its implementing regulations, including reporting any "payments or transfers of value" made or distributed to prescribers, teaching hospitals, and other healthcare providers and reporting any ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations during the preceding calendar year, with data collection required beginning August 1, 2013 and reporting to the Centers for Medicare and Medicaid Services required beginning March 31, 2014 and by the 90th day of each subsequent calendar year;

- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and

- a mandatory nondeductible payment for employers with 50 or more full-time employees (or equivalents) who fail to provide certain minimum health insurance coverage for such employees and their dependents, beginning in 2015 (pursuant to relief enacted by the Treasury Department).

The Affordable Care Act also established an Independent Payment Advisory Board, or IPAB, to reduce the per capita rate of growth in Medicare spending. Beginning in 2014, the IPAB was mandated to propose changes in Medicare payments if it determines that the rate of growth of Medicare expenditures exceeds target growth rates. The IPAB has broad discretion to propose policies to reduce expenditures, which may have a negative impact on payment rates for pharmaceutical products. A proposal made by the IPAB is required to be implemented by the U.S. federal government's Centers for Medicare & Medicaid Services unless Congress adopts a proposal with savings greater than those proposed by the IPAB. The IPAB has not yet been called upon to act as the annual determinations by the CMS Office of the Actuary have not identified a savings target for implementation years 2015 or 2016.

In addition, other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several categories of healthcare providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our customers and accordingly, our financial operations.

Coverage and Reimbursement

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

The Medicare Modernization Act, or MMA enacted by the U.S. Congress in 2003, changed the way Medicare covers and pays for pharmaceutical products, including creating the Medicare Part D prescription drug benefit, which became effective at the beginning of 2006. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, to obtain payments under this program, we would be required to sell products to Medicare recipients

through prescription drug plans operating pursuant to this legislation. These plans will likely negotiate discounted prices for our products.

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, governments 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 jurisdictions 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 member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. The European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. 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.

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. 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 by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare and Medicaid Services, other divisions of HHS (for example, the Office of Inspector General), the DOJ and individual U.S. Attorney offices within the DOJ, and state and local governments.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some business arrangements from prosecution, the exemptions and safe harbors are drawn narrowly and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from federal Anti-Kickback Statute liability. The reach of the Anti-Kickback Statute was broadened by the Affordable Care Act, which, among other things, amends the intent

requirement of the federal Anti-Kickback Statute. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) 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 claim for payment to the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes "any request or demand" for money or property presented to the U.S. government. Pharmaceutical and other healthcare companies have been prosecuted under these laws for 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. HIPAA created new federal criminal statutes that prohibit knowingly and willfully 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 in connection with the delivery of or payment for healthcare benefits, items or services. 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.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates" — independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

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 order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of pharmaceutical products in a state, 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. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing specified physician prescribing data to pharmaceutical companies for use in sales and marketing, and to prohibit other specified sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

Government Contracts and Grants

To date we have been awarded approximately $7.9 million in state and federal grants which have provided us with funding and resources to continue the development of our product candidates and contributed to research and development efforts outside of our primary therapeutic focus. Approximately $6.0 million of our grant funds have been received from the NIH, and some of these funds support research related to ZYN001.

Scientific Advisors

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

Name	Title
Jacqueline French, MD*	Professor of Neurology, NYU Langone Medical Center
John Messenheimer, MD*	Consultant, Neurologist/Epileptologist, John Messenheimer PLLC
Michael Rogawski, MD, PhD*	Professor of Neurology, UC Davis Center for Neuroscience
Rodney Radtke, MD*	Professor of Neurology, Duke University Medical Center
Randi J. Hagerman, MD†	Medical Director, UC Davis MIND Institute; Distinguished Professor, Endowed Chair in Fragile X Research, Department of Pediatrics, UC Davis School of Medicine
Steven J. Siegel, MD, PhD†	Professor of Psychiatry, University of Pennsylvania, Perelman School of Medicine; Director, Translational Neuroscience Program; Director, Clinical Neuroscience Track
Nicole Tartaglia, MD†	Associate Professor, Pediatrics-Developmental Pediatrics, University of Colorado Denver School of Medicine/Children's Hospital of Colorado
Daniel Clauw, MD◊	Professor of Anesthesiology, Medicine (Rheumatology) and Psychiatry, University of Michigan
Philip Mease, MD◊	Clinical Professor, University of Washington, Seattle; Director of Rheumatology Research, Swedish Medical Center
Lesley Arnold, MD◊	Professor of Psychiatry and Behavioral Neuroscience, University of Cincinnati
Donald Abrams, MD^	Professor of Clinical Medicine, University of California San Francisco School of Medicine; Chief of Hematology/Oncology, San Francisco General Hospital
Miroslav Backonja, MD^	Clinical Professor, University of Wisconsin School of Medicine and Public Health; Medical Director, CRILifetree
Steven P. Cohen, MD^	Professor Anesthesiology & Critical Care Medicine, Johns Hopkins School of Medicine
Mark Wallace, MD^	Professor of Clinical Anesthesia, University of California San Diego

* Epilepsy † FXS ◊ OA and Fibromyalgia ^ Pain

Corporate Information

We were incorporated in Delaware in January 2007.

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

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

Employees

As of March 10, 2016, we had ten full-time employees. Of these, five are engaged in research and development and five participate in finance, legal, human resources and general management. In addition to our full-time employees, we contract with third-parties for the conduct of certain preclinical, manufacturing, accounting and administrative activities. We have no collective bargaining agreements with our employees and none are represented by labor unions.

Implications of Being an Emerging Growth Company

We are an "emerging growth company," as defined in Section 2(a) of the Securities Act of 1933, as amended, or the Securities Act, as modified by the Jumpstart Our Business Startups Act of 2012, or JOBS Act. As such, we are eligible to take advantage of exemptions from various disclosure and reporting requirements that are applicable to other public companies that are not "emerging growth companies" including, but not limited to:

- our exemption from the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act of 2002;
- being permitted to present only two years of audited financial statements and only two years of related Management's Discussion and Analysis of Financial Condition and Results of Operations, in each case, instead of three years for any Securities Act filings;
- being permitted to present the same number of years of selected financial data as the years of audited financial statements presented, instead of five years;
- reduced disclosure obligations regarding executive compensation, including no Compensation Disclosure and Analysis;
- our exemption from any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements; and
- our exemption from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We may rely on these provisions until December 31, 2020. However, if certain events occur prior to the end of such period, including if we become a "large accelerated filer," our annual gross revenue exceeds $1.0 billion or we issue more than $1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company prior to the end of such period.

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

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

Available information

Our Annual Report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act are available free of charge through our website. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the Securities and Exchange Commission, or SEC. The reports filed with the SEC by our executive officers and directors pursuant to Section 16 under the Exchange Act are also made available, free of charge on our website, as soon as reasonably practicable after copies of those filings are provided to us by those persons. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Report.

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 an early stage specialty pharmaceutical company, engaged in developing next-generation transdermal synthetic cannabinoid therapeutics. Since our inception in January 2007, we have devoted substantially all of our resources to the development of our product candidates, ZYN002 and ZYN001. We have generated significant operating losses since our inception. Our net losses for the years ended December 31, 2015, 2014 and 2013 were approximately $12.6 million, $5.7 million and $0.6 million, respectively. As of December 31, 2015, we had an accumulated deficit of $22.6 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 either of our product candidates fails in clinical trials or does not gain regulatory approval, or even if approved, fails 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, ZYN002, ZYN001 or other 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, any product revenue for the foreseeable future, 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 planned clinical trials for our product candidates;
- complete and submit New Drug Applications, or NDAs, to the U.S. Food and Drug Administration, or FDA, and Marketing Authorisation Applications, or MAAs, to the EMA, and obtain regulatory approval for indications for which there is a commercial market;
- complete and submit applications to, and obtain regulatory approval from, other foreign regulatory authorities;
- manufacture any approved products in commercial quantities and on commercially reasonable terms;
- develop a commercial organization, or find suitable partners, to market, sell and distribute approved products in the

markets in which we have retained commercialization rights;

- achieve acceptance among patients, clinicians and advocacy groups for any products we develop;
- obtain coverage and adequate reimbursement from third parties, including government payors; and
- set a commercially viable price for any products for which we may receive approval.

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

We will require additional capital to fund our operations and if we fail to obtain necessary financing, we will not be able to complete the development and commercialization of ZYN002 or ZYN001.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial and increasing amounts to conduct further research and development, preclinical testing and clinical trials of our product candidates, to seek regulatory approvals and reimbursement for our product candidates and to launch and commercialize any product candidates for which we receive regulatory approval. As of December 31, 2015, we had approximately $41.5 million in cash and cash equivalents. We expect that our existing cash and cash equivalents will be sufficient to fund our operations and capital requirements through the end of 2017. We believe that these available funds will be sufficient to complete (i) Phase 1 clinical trials for ZYN002 and three Phase 2a clinical trials for ZYN002, one for each target indication of refractory epilepsy, OA and FXS and (ii) Phase 1 clinical trials for ZYN001 and two Phase 2a clinical trials for ZYN001, one for each target indication of fibromyalgia and peripheral neuropathic pain. The progress of ZYN002 and ZYN001 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 for these product candidates;
- the number and characteristics of product candidates that we develop or may in-license;
- the terms of any collaboration agreements we may choose to execute;
- the outcome, timing and cost of meeting regulatory requirements established by the DEA, the FDA, the EMA or other comparable foreign regulatory authorities;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us;
- the effect of competing product and market developments;
- the costs and timing of the implementation of commercial scale manufacturing activities; and
- the cost of establishing, or outsourcing, sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates or one or more of our other research and development initiatives.

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

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

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, 2015 we have been granted approximately $7.9 million in federal and state research grants (all of which was granted prior to 2015). In connection with these grants, we may be subject to routine audits by government agencies. 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, the expenditures may not be reimbursed and/or we may be required to repay funds already 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, ZYN002 and ZYN001, which are still in preclinical and clinical development, and will require significant capital resources and years of clinical development effort.

We currently have no products on the market, and we initiated clinical trials for our most advanced product candidate, ZYN002, in October 2015. Our business depends almost entirely on the successful clinical development, regulatory approval and commercialization of ZYN002 and ZYN001, and additional preclinical testing and substantial additional clinical development and regulatory approval efforts will be required before we are permitted to commence commercialization, if ever. It will be several years before we can commence and complete a pivotal study for ZYN002 or ZYN001, if ever. The clinical trials and manufacturing and marketing of ZYN002 and ZYN001 will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, Australia, the European Union, Canada, and other jurisdictions where we intend to test and, if approved, market our product candidates. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through preclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication, and potentially in specific patient populations. This process can take many years and may include post-marketing studies and surveillance, which would require the expenditure of substantial resources beyond our existing funds. Of the large number of drugs in development for approval in the United States and the European Union, only a small percentage successfully complete the FDA or EMA regulatory approval processes, 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, ZYN002 and ZYN001 may not have favorable results in our planned clinical trials.

Any positive results from our preclinical testing of ZYN002 and ZYN001 and early clinical trials of ZYN002 may not necessarily be predictive of the results from our planned additional clinical trials in humans. 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 made while clinical trials were underway or safety or efficacy observations made in clinical trials, including adverse events. Moreover, preclinical and clinical data are often 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 or EMA approval. If we fail to produce positive results in our clinical trials of ZYN002 and ZYN001, the development timeline and regulatory approval and commercialization prospects for ZYN002 and ZYN001, and, correspondingly, our business and financial prospects, would be materially adversely affected.

Even if ZYN002 and ZYN001 advance through clinical trials, we may experience difficulties in managing our growth and expanding our operations.

We have limited resources to carry out objectives for our current and future clinical trials. Prior to the commencement of the Phase 1 clinical trials in October 2015, our company had no history of conducting clinical trials, 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 clinical trials, we are a small company with only ten employees and therefore have limited internal resources both to conduct clinical trials and to monitor third-party providers. As our product candidates advance through preclinical studies and clinical trials, we will need to expand our development, regulatory and manufacturing operations, either by expanding our internal capabilities or contracting with other organizations to provide these capabilities for us. In the future, we expect to have to manage additional relationships with collaborators or partners, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures.

Failures or delays in the commencement or completion of our preclinical studies or clinical trials of ZYN002 or ZYN001 could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.

To date, we have only commenced clinical trials for ZYN002; we have not commenced any clinical trials for ZYN001. 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, safety, efficacy, changing standards of medical care and other variables. We do not know whether our clinical trials will begin or be completed on schedule, if at all, as the commencement and completion of clinical trials can be delayed or prevented for a number of reasons, including, among others:

- delays in reaching or failing to reach agreement on acceptable terms with prospective clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different clinical trial sites;
- 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;
- difficulties obtaining institutional review board, or IRB, DEA or comparable foreign regulatory authority, or ethics committee approval to conduct a clinical trial at a prospective site or sites;
- challenges in recruiting and enrolling patients to participate in clinical trials, including the size and nature of the patient population, the proximity of patients to clinical trial sites, eligibility criteria for the clinical trial, the nature of the clinical trial protocol, the availability of approved effective treatments for the relevant indication and competition from other clinical trial programs for similar indications;
- severe or unexpected toxicities or drug-related side effects experienced by patients in our clinical trials or by individuals using drugs similar to our product candidates;
- DEA or comparable foreign regulatory authority-related recordkeeping, reporting or security violations at a clinical trial site, leading the DEA, state authorities or comparable foreign regulatory authorities to suspend or revoke the site's controlled substance license and causing a delay or termination of planned or ongoing clinical trials;
- regulatory concerns with cannabinoid products generally and the potential for abuse of those products;
- difficulties retaining patients who have enrolled in a clinical trial who may withdraw due to lack of efficacy, side effects, personal issues or loss of interest;
- 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, IRBs, ethics committees, data safety monitoring board or other foreign regulatory authorities overseeing the clinical trial at issue or other regulatory authorities due to a number of factors, including, among others:

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

We intend to expend our limited resources to pursue ZYN002 and ZYN001 for certain indications, and may fail to capitalize on other product candidates or other indications for ZYN002 or ZYN001 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 ZYN002 and ZYN001 for certain indications, which concentrates the risk of product failure in the event ZYN002 or ZYN001 proves to be unsafe or ineffective or inadequate for clinical development or commercialization. In particular, we intend to study ZYN002 in patients with refractory epilepsy, OA and FXS and we intend to study ZYN001 in patients with fibromyalgia and peripheral neuropathic pain. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications for ZYN002 or ZYN001 that could later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on proprietary research and development programs relating to ZYN002 and ZYN001 may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for ZYN002 and ZYN001, we may relinquish valuable rights to ZYN002 or ZYN001 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 ZYN002 or ZYN001.

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 EMA, 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 ZYN002's or ZYN001's clinical and other benefits outweigh its safety risks;
- 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 where the standard of care is potentially different from that in the United States;
- if and when our NDAs or MAAs are submitted to the FDA or EMA, as applicable, the regulatory agency 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 Risk Evaluation and Mitigation Strategy, or REMS, which would use risk minimization strategies beyond the professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks, as a condition of approval or post-approval, and the EMA may grant only conditional approval or impose specific obligations as a condition for marketing authorization, or may require us to conduct post-authorization safety studies;
- the FDA, EMA, DEA or other applicable foreign regulatory agencies may not approve the manufacturing processes or facilities of third-party manufacturers with which we contract or DEA or other applicable foreign regulatory agency quotas may limit the quantities of controlled substances available to our manufacturers; or
- the FDA or EMA may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market ZYN002 or ZYN001. Moreover, because our business is almost entirely dependent upon these two product candidates, any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

We are conducting clinical trials for ZYN002 and may choose to conduct clinical trials for ZYN001 outside the United States, and the FDA may not accept data from such trials.

We are conducting clinical trials outside the United States. For ZYN002, we are currently conducting Phase 1 clinical trials, and may conduct Phase 2 clinical trials, in Australia, subject to applicable regulatory approval. We may also choose to conduct clinical trials for ZYN001 outside the United States, subject to applicable regulatory approval. We plan to submit NDAs for ZYN002 and ZYN001 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 applicable to the U.S. 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 ZYN002 or ZYN001 receive regulatory approval, they may still face future development and regulatory difficulties.

If we obtain regulatory approval for ZYN002 or ZYN001, such approval would be subject to extensive ongoing requirements by the DEA, FDA, EMA and other foreign regulatory authorities related to the manufacture, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting of safety and other post-market information. The safety profile of any product will continue to be closely monitored by the FDA, EMA and other comparable foreign regulatory authorities. If the FDA, EMA 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, impose ongoing requirements for potentially costly post-approval studies or post-market surveillance or impose a recall.

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

- issue untitled letters 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;
- suspend any ongoing clinical trials;
- 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.

ZYN002 and ZYN001 will be subject to controlled substance laws and regulations; failure to receive necessary approvals may delay the launch of our products and failure to comply with these laws and regulations may adversely affect the results of our business operations.

ZYN002 and ZYN001 contain controlled substances as defined in the federal Controlled Substances Act of 1970, or CSA. Controlled substances that are pharmaceutical products are subject to a high degree of regulation under the CSA, which establishes, among other things, certain registration, manufacturing quotas, security, recordkeeping, reporting, import, export and other requirements administered by the DEA. The DEA classifies controlled substances into five schedules: Schedule I, II, III, IV or V substances. Schedule I substances by definition have a high potential for abuse, have no currently "accepted medical use" in the United States, lack accepted safety for use under medical supervision, and may not be prescribed, marketed or sold in the United States. Pharmaceutical products approved for use in the United States may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse among such substances. Schedule I and II drugs are subject to the strictest controls under the CSA, including manufacturing and procurement quotas, security requirements and criteria for importation. In addition, dispensing of Schedule II drugs is further restricted. For example, they may not be refilled without a new prescription.

While *Cannabis* is a Schedule I controlled substance, products approved for medical use in the United States that contain *Cannabis* or *Cannabis* extracts must be placed in Schedules II - V, since approval by the FDA satisfies the "accepted medical use" requirement. If and when ZYN002 or ZYN001 receives FDA approval, the DEA will make a scheduling determination and place it in a schedule other than Schedule I in order for it to be prescribed to patients in the United States. If approved by the FDA, we expect the finished dosage forms of ZYN002 and ZYN001 to be listed by the DEA as a Schedule II or III controlled substance. Consequently, their manufacture, importation, exportation, domestic distribution, storage, sale and legitimate use will be subject to a significant degree of regulation by the DEA. The scheduling process may take one or more years beyond FDA approval, thereby significantly delaying the launch of ZYN002 or ZYN001. Furthermore, if the FDA, DEA or any foreign regulatory authority determines that ZYN002 or ZYN001 may have potential for abuse, it may require us to generate more clinical data than that which is currently anticipated, which could increase the cost and/or delay the launch of ZYN002 or ZYN001.

Because ZYN002 and ZYN001 contain active ingredients of *Cannabis*, which are Schedule I substances, to conduct preclinical studies and clinical trials with ZYN002 and ZYN001 in the United States prior to approval, each of our research sites must submit a research protocol to the DEA and obtain and maintain a DEA researcher registration that will allow those sites to handle and dispense ZYN002 and ZYN001 and to obtain the product from our manufacturer. If the DEA delays or denies the grant of a research registration to one or more research sites, the preclinical studies or clinical trials could be significantly delayed, and we could lose and be required to replace clinical trial sites, resulting in additional costs.

We expect that ZYN002 and ZYN001 will be scheduled as Schedule II or III, as a result of which we will also need to identify wholesale distributors with the appropriate DEA registrations and authority to distribute the products to pharmacies and other healthcare providers, and these distributors would need to obtain Schedule II or III distribution registrations. The failure to obtain, or delay in obtaining, or the loss of any of those registrations could result in increased costs to us. If ZYN002 or ZYN001 is a Schedule II drug, pharmacies would have to maintain enhanced security with alarms and monitoring systems and they must adhere to recordkeeping and inventory requirements. This may discourage some pharmacies from carrying the product. Furthermore, state and federal enforcement actions, regulatory requirements, and legislation intended to reduce prescription drug abuse, such as the requirement that physicians consult a state prescription drug monitoring program, may make physicians less willing to prescribe, and pharmacies to dispense, Schedule II products.

We may manufacture the commercial supply of ZYN002 and ZYN001 outside of the United States. If ZYN002 or ZYN001 is approved by the FDA and classified as a Schedule II or III substance, an importer can import for commercial purposes if it obtains from the DEA an importer registration and files an application with the DEA for an import permit for each import. The DEA provides annual assessments/estimates to the International Narcotics Control Board which guides the DEA in the amounts of controlled substances that the DEA authorizes to be imported. The failure to identify an importer or obtain the necessary import authority, including specific quantities, could affect the availability of ZYN002 or ZYN001 and have a material adverse effect on our business, results of operations and financial condition. In addition, an application for a Schedule II importer registration must be published in the Federal Register, and there is a waiting period for third party comments to be submitted.

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

We currently manufacture the API for ZYN002 and ZYN001 in the United States and Canada. We are currently conducting Phase I clinical trials for ZYN002 in Australia. In addition, we may decide to develop, manufacture or commercialize our product candidates in additional countries. As a result, we will also be subject to controlled substance laws and regulations from the Therapeutic Goods Administration in Australia, Health Canada's Office of Controlled Substances in Canada, and from other regulatory agencies in other countries where we develop, manufacture or commercialize ZYN002 or ZYN001 in the future. We plan to submit NDAs for ZYN002 and ZYN001 to the FDA upon completion of all requisite clinical trials and will require additional DEA approvals at such time as well.

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

The shipment, import and export of ZYN002 and ZYN001 and the API used to manufacture ZYN002 and ZYN001 will require import and export licenses. In the United States, the FDA, U.S. Customs and Border Protection, and the DEA; in Canada, where our API is manufactured, the Canada Border Services Agency and Health Canada; in Australia, where we are currently conducting clinical trials, the Australian Customs and Board Protection Service and the Therapeutic Goods Administration; and in other countries, similar regulatory authorities, regulate the import and export of pharmaceutical products that contain controlled substances. Specifically, the import and export process requires the issuance of import and export licenses by the relevant controlled substance authority in both the importing and exporting country. We may not be granted, or if granted, maintain, such licenses from the authorities in certain countries. Even if we obtain the relevant licenses, shipments of API and our product candidates may be held up in transit, which could cause significant delays and may lead to product batches being stored outside required temperature ranges. Inappropriate storage may damage the product shipment resulting in delays in clinical trials or, upon commercialization, a partial or total loss of revenue from one or more shipments of API or ZYN002 or ZYN001. A delay in a clinical trial or, upon commercialization, a partial or total loss of revenue from one or more shipments of API or ZYN002 or ZYN001 could have a material adverse effect on our business, results of operations and financial condition.

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

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

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

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

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or Affordable Care Act, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug products. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on pharmaceutical and medical device manufacturers, and impose additional health policy reforms, any of which could negatively impact our business. A significant number of provisions are not yet, or have only recently become effective, but the Affordable Care Act is likely to continue the downward pressure on pharmaceutical and medical device pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

In addition, other legislative changes have been proposed and adopted since passage of the Affordable Care Act. The Budget Control Act of 2011, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction of an amount greater than $1.2 trillion for the fiscal years 2012 through 2021, triggering the legislation's automatic reduction to several government programs. This included aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, which went into effect in April 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several categories of healthcare providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. If we ever obtain regulatory approval and successfully commercialize ZYN002, ZYN001 or other product candidates that we may develop, these new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our customers and accordingly, our financial operations.

We expect that the Affordable Care Act, as well as other healthcare reform measures that have been and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product, and could seriously harm our future revenue. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may compromise our ability to generate revenue, attain profitability or commercialize our products.

We have been granted orphan drug status by the FDA for ZYN002 for the treatment of FXS, but we may be unable to maintain the benefits associated orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.

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

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

As a result, even though ZYN002 has received orphan drug exclusivity in FXS in the United States, the FDA can still approve other drugs that have a different active ingredient for use in treating the same indication; this is also the case for the EMA if ZYN002 receives orphan drug exclusivity in the European Union. Furthermore, the FDA can waive orphan drug exclusivity if we are unable to manufacture sufficient supply of ZYN002 or the EMA could reduce the term of exclusivity if ZYN002 is sufficiently profitable.

We have received orphan drug designation for ZYN002 in FXS from the FDA and may seek orphan drug designation in the future with the EMA, but exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan designated indication and may be lost if the FDA or EMA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Even if we are able to commercialize ZYN002 or ZYN001, the products may not receive coverage and adequate reimbursement from third-party payors, which could harm our business.

The availability of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of our product candidates, if approved, will depend substantially on the extent to which the costs of these product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize ZYN002 or ZYN001. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or Medicare Modernization Act, established the Medicare Part D program and provided authority for limiting the number of drugs that will be covered in any therapeutic class thereunder. The Medicare Modernization Act, including its cost reduction initiatives, could decrease the coverage and reimbursement rate that we receive for any of our approved products. Furthermore, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments 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 the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or 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 member states of the European Union, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations or the successful completion of health technology assessment procedures with governmental authorities can take considerable time after receipt of marketing approval 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 European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of any product candidate approved for marketing is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, financial condition, results of operations or prospects could be adversely affected.

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

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing approval. As a pharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare,

Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. Restrictions under applicable federal and state healthcare laws and regulations that may affect our ability to operate include the following:

- the U.S. federal healthcare Anti-Kickback Statute impacts our marketing practices, educational programs, pricing policies and relationships with healthcare providers or other entities, by prohibiting, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- federal civil and criminal false claims laws and civil monetary penalty laws impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent (including through impermissible promotion of our 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;
- the U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also created federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services;
- HIPAA, as amended by HITECH, and the rules and regulations promulgated thereunder, establish federal standards for maintaining the privacy and security of certain patient health information known as Protected Health Information, or PHI, and impose notification obligations in the event of a breach of the privacy or security of PHI;
- the U.S. federal physician payment transparency requirements under the Affordable Care Act require 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 healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and certain other healthcare providers and their immediate family members and applicable group purchasing organizations; and
- 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;
- some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may 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 practitioners, and the handling of healthcare 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 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. 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.

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

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

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

We do not currently have any sales, marketing or distribution capabilities. If ZYN002 or ZYN001 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 when product development is successful and regulatory approval has been obtained, our ability to generate significant revenue depends on the acceptance of our products by physicians and patients. The market acceptance of any product depends on a number of factors, including the indication statement and warnings approved by regulatory authorities in the product label, continued demonstration of efficacy and safety in commercial use, physicians' willingness to prescribe the product, reimbursement from third-party payors such as government healthcare systems and insurance companies, the price of the product, the nature of any post-approval risk management plans mandated by regulatory authorities, competition, and marketing and distribution support. 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 ZYN002 and ZYN001 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 plan to market ZYN002 and ZYN001 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 ZYN002 or ZYN001 in those countries. These countries may not be willing or able to amend or otherwise modify their laws and regulations to permit ZYN002 or ZYN001 to be marketed, or achieving such amendments to the laws and regulations may take a prolonged period of time. We would be unable to market ZYN002 or ZYN001 in countries with such obstacles in the near future or perhaps at all without modification to laws and regulations.

ZYN002 and ZYN001 contain controlled substances, the use of which may generate public controversy.

Since our product candidates contain controlled substances, their regulatory approval may generate public controversy. Political and social pressures and adverse publicity could lead to delays in approval of, and increased expenses for, our product candidates. These pressures could also limit or restrict the introduction and marketing of our product candidates. Adverse publicity from *Cannabis* misuse or adverse side effects from *Cannabis* or other cannabinoid products 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, including Armando Anido, our chairman and chief executive officer, Terri B. Sebree, our president, Richard A. Baron, our chief financial officer, and Suzanne M. Hanlon, our general counsel and vice president of human resources. The loss of one or more members of our 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 enter the market. We believe that a significant number of products are currently available, 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 either of our product candidates, ZYN002 or ZYN001, is approved for the indications we are currently pursuing, it will compete with a range of therapeutic treatments that are either in development or currently marketed.

We are aware of multiple companies that are working in the *Cannabis* therapeutic area, including pharmaceutical companies such as GW, which markets Sativex, a botanical cannabinoid oral mucosal for the treatment of spasticity due to multiple sclerosis and which is also in development in neuropathic pain in several foreign countries and is seeking FDA approval in the United States, and is developing Epidiolex, a liquid formulation of highly purified CBD extract, as a treatment for DS, LSG and various childhood epilepsy syndromes; Insys, which is seeking FDA approval for an orally-administered liquid formulation of its synthetic CBD compound as a

treatment for DS, LGS, and other childhood epilepsy syndromes; and Nemus Bioscience, Inc. which is focused on the discovery, development and commercialization of *Cannabis* therapeutics.

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 commercialize ZYN002 or ZYN001 successfully.

Our product candidates may compete with non-synthetic cannabinoid drugs, including therapies such as GW's Sativex. Our product candidates may also compete with medical 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. In markets where recreational and/or medical 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 ZYN002 and ZYN001.

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 third parties 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.

The market opportunity for refractory epilepsy will be limited to those patients who are not currently receiving adequate relief from current treatment regimens, which may reduce our targeted market.

Pre-existing treatments may be adequate to treat certain patients with refractory epilepsy. Whenever the first-line therapy fails or is unsuccessful, then second-line therapy may be administered. For refractory epilepsy, ZYN002 is particularly targeted to provide an additional treatment option for patients not currently receiving adequate relief from current treatment regimens. If a more successful first-line therapy is developed, it may significantly reduce the patient population to which we can supply, which may affect our ability to successfully commercialize ZYN002 for refractory epilepsy.

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

Our use of ZYN002 and ZYN001 in clinical trials and the sale of ZYN002 and ZYN001, 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 ZYN002 or ZYN001. 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 ZYN002 or ZYN001 following marketing approval, if obtained;
- damage to our reputation and exposure to adverse publicity;
- increased FDA or EMA warnings on product labels;
- litigation costs;

- distraction of management's attention from our primary business;
- loss of revenue; and
- the inability to successfully commercialize ZYN002 or ZYN001, if approved.

We will need to obtain product liability insurance coverage for our clinical trials. We may not be able to obtain such coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. 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.

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

Despite the implementation of security measures, our information technology and other internal infrastructure systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. A significant disruption in the availability of our information technology and other internal infrastructure systems could cause delays in our research and development work. 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. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed.

Risks Related to Our Dependence on Third Parties

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

We rely on CROs, clinical data management organizations and consultants to design, conduct, supervise and monitor our preclinical studies and clinical trials. We and our CROs are required to comply with various regulations, including GCP, which are enforced by 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, EMA or other comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with such requirements. In addition, our clinical trials must be conducted with products produced under cGMP requirements, which mandate the methods, facilities and controls used in manufacturing, processing and packaging of a drug product to ensure its safety and identity. Failure to comply with these regulations may require us to repeat preclinical studies and clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and preclinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed. 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 for ZYN002 and ZYN001.

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

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

- an inability to initiate or continue preclinical studies or clinical trials of product candidates under development;
- delay in submitting regulatory applications, or receiving regulatory approvals, for product candidates;
- loss of the cooperation of a collaborator;
- subjecting our product candidates to additional inspections by regulatory authorities; and
- in the event of approval to market and commercialize a product candidate, 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 is 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. 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 ZYN002 or ZYN001, if approved, could be delayed or terminated.

We are not currently party to any collaborative arrangements for the commercialization of ZYN002 or ZYN001, if approved, or similar arrangements, although we may pursue such arrangements before any commercialization of ZYN002 or ZYN001, if approved. If we entered 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 United States Patent and Trademark Office, or U.S. PTO, and various foreign national or international patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and various foreign national or international patent agencies in several stages over the lifetime of the patent. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of patent rights include, but are not limited to, failure to timely file national and regional stage patent applications based on our international patent application, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

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

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

While our preclinical studies and clinical trials are ongoing, we believe that the use of ZYN002 and ZYN001 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 ZYN002 and ZYN001 progress toward commercialization, the possibility of a patent infringement claim against us increases. We attempt to ensure that our product candidates and the methods we employ to manufacture them, as well as the methods for their uses we intend to promote, do not infringe other parties' patents and other proprietary rights. There can be no assurance they do not, however, and competitors or other parties may assert that we infringe their proprietary rights in any event.

We are aware of an allowed U.S. patent owned by a third party with claims that are directed to a method of treating partial seizures by administering a medication containing CBD at doses at or above 400mg. This patent could be construed to cover ZYN002 for our refractory epilepsy development program if the therapeutic dose for CBD contained in ZYN002 is determined to be at or above 400mg. If and when ZYN002 is approved by the FDA for treatment of refractory epilepsy, if it has a label that contains dosing of ZYN002 with CBD at or above 400mg, such third party may then seek to enforce its patent, if issued, by filing a patent infringement lawsuit against us. In such lawsuit, we may incur substantial expenses defending our rights to commercialize ZYN002 for refractory epilepsy, and in connection with such lawsuit and under certain circumstances, it is possible that we could be required to cease or delay the commercialization of ZYN002 for refractory epilepsy and/or be required to pay monetary damages or other amounts, including royalties on the sales of ZYN002 for refractory epilepsy. Moreover, such lawsuit may also consume substantial time and resources of our management team and board of directors. The threat or consequences of such a lawsuit may also result in royalty and other monetary obligations, which may adversely affect our results of operations and financial condition.

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

Competitors may infringe our patents or misappropriate or otherwise violate our intellectual property rights. To counter infringement or unauthorized use, litigation may be necessary in the future to enforce or defend our intellectual property rights, to protect our trade secrets or to determine the validity and scope of our own intellectual property rights or the proprietary rights of others. Also, third parties may initiate legal proceedings against us to challenge the validity or scope of intellectual property rights we own. 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 2014 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:

- trading volatility of low-priced stock;
- 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;
- results of clinical trials of ZYN002, ZYN001 or product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to our preclinical and clinical development programs;
- the results of our efforts to in-license or acquire additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our common stock;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical sector; and
- general economic, industry and market conditions.

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

The stock market in general has, from time to time, experienced extreme price and volume fluctuations, including in recent months. In addition, in the past, following periods of volatility in the overall market and decreases in the market price of a company's securities, securities class action litigation has often been instituted against these companies. This litigation, if instituted against us, could result in substantial costs and a diversion of our management's attention and resources.

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

Our executive officers, directors, and holders of 5.0% or more of our capital stock collectively beneficially own approximately 55% of our voting stock at March 10, 2016. 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.

For as long as we are an "emerging growth company" we intend to take advantage of reduced disclosure and governance requirements applicable to emerging growth companies, which could result in our common stock being less attractive to investors and could make it more difficult for us to raise capital as and when we need it.

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

Investors may find our common stock less attractive because we rely on these exemptions, which could contribute to a less active trading market for our common stock or volatility in our stock price. In addition, we may be less attractive to investors and it may be difficult for us to raise additional capital as and when we need it. Investors may be unable to compare our business with other companies in our industry if they believe that our financial accounting is not as transparent as other companies in our industry. If we are unable to raise additional capital as and when we need it, our financial condition and results of operations may be materially and adversely affected.

We may take advantage of these reporting exemptions until we are no longer an emerging growth company, which in certain circumstances could be for up to five years. See "Item 1. Business — Corporate Information — Implications of Being an Emerging Growth Company" above.

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

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. Commencing with our annual report on Form 10-K for the year ending December 31, 2016, we will be 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 will need to include 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 generally requires an attestation from our independent registered public accounting firm on the effectiveness of our internal control over financial reporting. However, for as long as we remain an emerging growth company as defined in the JOBS Act, we intend to take advantage of the exemption permitting us not to comply with the independent registered public accounting firm attestation requirement.

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

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

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

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

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

As a public company, we have incurred and are continuing to incur significant legal, accounting and other expenses that we did not incur as a private company, and these expenses may increase even more after we are no longer an "emerging growth company." We are subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Protection Act, as well as rules adopted, and to be adopted, by the SEC and NASDAQ Stock Market. Our management and other personnel devote a substantial amount of time to these compliance initiatives.

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

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your 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 10, 2016, there were 216,762 shares of our common stock available for future grant under our 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 662/3% of our outstanding capital stock;
- not provide for cumulative voting rights, thereby allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election; and
- provide that special meetings of our stockholders may be called only by the board of directors or by such person or persons designated by a majority of the board of directors to call such meetings.

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

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

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

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

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

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our company headquarters are located in Devon, Pennsylvania where we occupy approximately 3,800 square feet of office space pursuant to a five-year lease which expires on May 31, 2020. In addition, one of our employees works in Covington, Kentucky where we lease office space and a shared conference room and business facilities pursuant to a lease agreement; that lease agreement is month-to-month.

Item 3. Legal Proceedings

We are not currently a party to any legal proceedings.

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." Prior to such time, there was no public market for our common stock. The following table sets forth the high and low sales price of our common stock, as reported by the NASDAQ Global Market for the period indicated:

Year ended December 31, 2015	High	Low
Fourth Quarter	$ 18.25	$ 9.33
Third Quarter (August 4, 2015 - September 30, 2015)	$ 43.00	$ 12.00

Holders of Common Stock

As of March 10, 2016, there were 101 holders of record of our common stock.

Dividend Policy

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

Issuer Repurchases of Equity Securities

None.

Securities Authorized for Issuance Under Equity Compensation Plans

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

Recent Sales of Unregistered Securities

Except as previously reported in our quarterly reports on Form 10-Qs filed with the SEC on August 27, 2015 and November 12, 2015, there were no unregistered sales of equity securities during the period.

Use of Proceeds

Our IPO was effected through a Registration Statement on Form S-1 (File No. 333-205355) that was declared effective by the SEC on August 4, 2015, which registered an aggregate of 3,450,000 shares of our common stock. On August 10, 2015, 3,450,000 shares of common stock were sold on our behalf at an IPO price of $14.00 per share, including 450,000 shares of common stock upon the exercise by the underwriters of their option to purchase additional shares at the IPO price, for aggregate gross proceeds of $48.3 million. As of the date of filing this report, the offering has terminated, and all of the securities registered pursuant to the offering have been sold prior to termination. Jefferies LLC and Piper Jaffray & Co. acted as joint book-running managers in the IPO, and Canaccord Genuity Inc. and Oppenheimer & Co. Inc. acted as co-managers in the IPO.

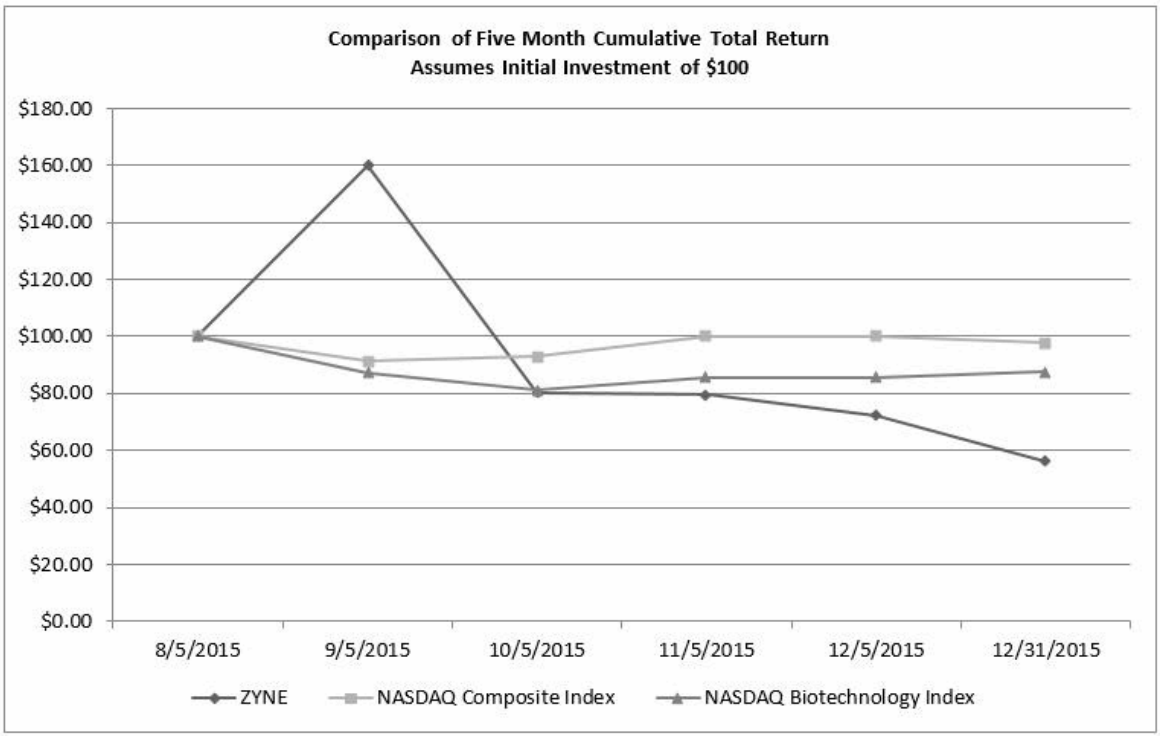
On August 10, 2015 we received proceeds from the IPO of $44.8 million, which was net of underwriting discounts and commissions of approximately $3.5 million. Of this amount, we paid offering expenses of approximately $2.7 million. All of the foregoing expenses were direct or indirect payments to persons other than (i) our directors, officers or any of their associates; (ii) persons owning 10% or more of our common stock; or (iii) our affiliates. As of December 31, 2015, we have used approximately $5.0 million of the net offering proceeds from our IPO to fund the development efforts of ZYN002 (including funding of our recently initiated Phase 1 clinical trials), development efforts of ZYN001, working capital, research and development and general corporate purposes. None of

the net proceeds have been paid directly or indirectly to (i) our directors, officers or any of their associates; (ii) persons owning 10% or more of our common stock; or (iii) our affiliates, other than payments in the ordinary course of business to officers for salaries and to non-employee directors as compensation for board or board committee service.

Performance Graph

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

The following graph illustrates a comparison of the total cumulative stockholder return for our common stock since August 5, 2015, which is the first trading day for our stock, to two indices: the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The graph assumes an initial investment of $100 on August 5, 2015, in our common stock, the stocks comprising the NASDAQ Composite Index, and the stocks comprising the NASDAQ Biotechnology Index. Historical stockholder return is not necessarily indicative of the performance to be expected for any future periods.



Item 6. Selected Financial Data

This section should be read together with our consolidated financial statements and accompanying notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations" appearing elsewhere in this Report. We derived the consolidated statements of operations data for the years ended December 31, 2015, 2014 and 2013 and the selected consolidated balance sheet data as of December 31, 2015 and 2014 from our audited consolidated financial statements and accompanying notes appearing elsewhere in this Report. The selected consolidated financial data in this section are not intended to replace our consolidated financial statements and the related notes. Our historical consolidated results are not necessarily indicative of the results that may be expected in the future.

Statements of Operation Data:

	Year Ended December 31,		
	2015	2014	2013
Revenue	$ 278,900	$ 810,012	$ 943,904
Operating expenses:			
Research and development	7,445,669	2,401,406	1,134,041
General and administrative	5,364,390	4,076,339	444,302
Total operating expenses	12,810,059	6,477,745	1,578,343
Loss from operations	(12,531,159)	(5,667,733)	(634,439)
Other income (expense):			
Interest (expense) income, net	7,352	(1,844)	(2,351)
Loss before income taxes	(12,523,807)	(5,669,577)	(636,790)
Income tax expense	(27,543)	—	—
Net loss	(12,551,350)	(5,669,577)	(636,790)
Accretion of redeemable convertible preferred stock	—	(87,954)	(161,834)
Net loss applicable to common stockholders	$ (12,551,350)	$ (5,757,531)	$ (798,624)
Per share information:			
Net loss per share basic and diluted	$ (2.82)	$ (6.44)	$ (1.63)
Basic and diluted weighted average shares outstanding	4,457,719	894,575	490,760

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

	As of December 31,	
	2015	2014
BALANCE SHEET DATA:		
Cash and cash equivalents	$ 41,513,060	$ 9,330,681
Total assets	43,643,541	11,616,671
Total liabilities	3,937,617	3,145,535
Convertible preferred stock	—	16,522,811
Total stockholders' equity (deficit)	39,705,924	(8,051,675)

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

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

Overview

Company Overview

We are a specialty pharmaceutical company focused on developing and commercializing proprietary next-generation synthetic cannabinoid therapeutics formulated for transdermal delivery. We are evaluating two patent-protected product candidates, ZYN002 and ZYN001, in five indications. We intend to study ZYN002 in patients with refractory epilepsy, OA, and FXS. We intend to study ZYN001 in patients with fibromyalgia and peripheral neuropathic pain. We believe these product candidates will provide new treatment options for patients, as well as additional treatment options for patients not currently receiving adequate relief from current treatment regimens. We initiated Phase 1 clinical trials for ZYN002 in October 2015 and expect to initiate Phase 2 clinical trials for ZYN002 in the second half of 2016. We expect to initiate Phase 1 clinical trials for ZYN001 in the second half of 2016.

Cannabinoids are a class of compounds derived from *Cannabis* plants. The two primary cannabinoids contained in *Cannabis* are CBD and THC. Clinical and preclinical data suggest that CBD has positive effects on treating refractory epilepsy, arthritis and FXS, and THC has positive effects on treating pain. In addition to ZYN002 and ZYN001 potentially offering first-line therapies to patients suffering from OA, FXS, fibromyalgia and peripheral neuropathic pain, we believe ZYN002 may provide a complementary treatment for patients suffering from epilepsy who are refractory to their current treatment regimens.

ZYN002 is the first and only synthetic CBD formulated as a permeation-enhanced gel for transdermal delivery, and is patent-protected through 2030. CBD is the primary non-psychoactive component of *Cannabis*. In preclinical animal studies, ZYN002's permeation enhancer increased delivery of CBD through the layers of the skin and into the circulatory system. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism. In addition, an *in vitro* study performed by us demonstrated that CBD is degraded to THC in an acidic environment such as the stomach. We believe such degradation may lead to increased psychoactive effects and may be avoided or minimized with the transdermal delivery of ZYN002, which maintains CBD in a neutral pH. ZYN002, which is being developed as a clear gel with once- or twice-daily dosing, is targeting treatment of refractory epilepsy, OA and FXS, which collectively affect millions of patients using treatments that currently comprise a multi-billion dollar market. We have been granted orphan drug designation from the FDA for ZYN002 for the treatment of FXS.

ZYN001 is a pro-drug of THC that enables effective transdermal delivery via a patch and is patent-protected through 2031. A pro-drug is a drug administered in an inactive or less active form and designed to enable more effective delivery, which is then converted into an active form through a normal metabolic process. In addition, we expect that ZYN001 will be classified by the FDA as a NCE. In our preclinical animal studies, ZYN001 demonstrated effective skin permeation with sustained delivery and rapid conversion of ZYN001 to THC. These preclinical studies suggest increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism. In addition, preclinical testing conducted has shown no genotoxicity findings and safety pharmacology findings consistent with those seen with THC. ZYN001 is targeting two pain indications, fibromyalgia and peripheral neuropathic pain.

In October 2015, we initiated a Phase 1 single rising dose clinical trial for ZYN002 in healthy human subjects (and in patients with refractory epilepsy) to evaluate the tolerability and PK profile of ZYN002. Initial results from this trial indicate the ZYN002 was safe and well-tolerated at all tested dose levels. In January 2016, we initiated a Phase 1 multiple rising dose clinical trial for ZYN002 in healthy volunteers and patients with epilepsy to examine the tolerability, PK and PD of multiple doses of ZYN002.

Our key development programs and expected timelines for the development of ZYN002 and ZYN001 are shown in the table below:

Product Candidate	Target Indication	Delivery Method	Current Development Status	Expected Next Steps
ZYN002	Refractory Epilepsy Osteoarthritis Fragile X Syndrome	Permeation-enhanced Gel	Phase 1	2H16: Initiate Phase 2a
ZYN001	Fibromyalgia Peripheral Neuropathic Pain	Transdermal Patch	Preclinical	2H16: Initiate Phase 1 1H17: Initiate Phase 2a

We have never been profitable and have incurred net losses since inception. Our net losses were $12.6 million, $5.7 million and $0.6 million for the years ended December 31, 2015, 2014 and 2013, respectively. 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 statements of operations as well as factors that impact those items.

Revenue — Our revenue consists of state and federal research grants and fees received from research services for third-party product development. Revenue is recognized when persuasive evidence of an arrangement exists, delivery has occurred or services have been rendered, the price is fixed or determinable and collectability is reasonably assured.

Research and Development Expenses — Our research and development expenses relating to our product candidates consist 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, contractor laboratories and independent contractors; and
- depreciation, maintenance and other facility-related expenses.

We expense all research and development costs as incurred. Preclinical development expenses for our product candidates are a significant component of our current research and development expenses. 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, 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.

We incurred research and development expenses of $7.4 million, $2.4 million and $1.1 million for the years ended December 31, 2015, 2014 and 2013, respectively.

Our research and development expenses in 2015 were higher than in past years as a result of preclinical studies and our Phase 1 clinical trials of ZYN002 as well as preclinical development of ZYN001 in advance of our expected initiation of our Phase 1 clinical trials for ZYN001 in the second half of 2016; we expect research and development expenses in future years to continue to increase as we continue our clinical trials and begin new phases for each of our product candidates. Our research and development expenses in

2015 were net of a $0.4 million Australian tax incentive, which we expect will result in a refund of $0.4 million of certain research and development costs incurred in Australia.

Our research and development expenditures are subject to numerous uncertainties regarding timing and cost to completion. Completion of our preclinical development and clinical trials may take several years or more and the length of time generally varies according to the type, complexity, novelty and intended use of a product candidate. The cost of clinical trials may vary significantly over the life of a project as a result of differences arising during clinical development, including, among others:

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

Due to the early stages of our research and development, we are unable to determine the duration or completion costs of our development of ZYN002 and ZYN001. As a result of the difficulties of forecasting research and development costs of ZYN002 and ZYN001 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, accounting, legal and human resource functions. Our general and administrative expenses also include facility and related costs not included in research and development expenses, professional fees for legal services, including patent-related expenses, consulting, tax and accounting services, insurance and general corporate expenses. We expect that our general and administrative expenses will increase with the continued development and potential commercialization of our product candidates.

We expect that our general and administrative expenses in 2016 and for the next several years will be higher than in past years as we increase our headcount. We also anticipate increased expenses relating to our operations as a public company, including increased costs for the hiring of additional personnel, and for payment to outside consultants, including lawyers and accountants, to comply with additional regulations, corporate governance, internal control and similar requirements applicable to public companies, as well as increased costs for insurance.

Interest Income (Expense), net — Interest income consists primarily of interest earned on our money market bank account. Interest expense consists of interest expense on our note payable that was paid off during 2014.

Income Taxes — As of December 31, 2015, we had $17.7 million of federal operating loss carryforwards and $0.4 million of research tax credit carryforwards available to offset future taxable income. These operating loss and research tax credit carryforwards will begin to expire in 2028 and 2027, respectively. At December 31, 2015 and 2014, we concluded that a full valuation allowance is necessary for our deferred tax assets. For the year ended December 31, 2015, there was less than $0.1 million of income tax expense associated with our Australian subsidiary.

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

Critical Accounting Policies and Use of Estimates

We have based our management's discussion and analysis of financial condition and results of operations on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements as well as the reported revenue and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments, including those related to preclinical development expenses and stock-based compensation. We base our estimates on historical experience and on various other factors that we believe to be appropriate under the circumstances. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully discussed in note 2 to our audited consolidated financial statements appearing elsewhere in this Report, we believe that the following accounting policies are critical to the process of making significant judgments and estimates in the preparation of our financial statements.

Research and Development Expenses

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

Fair Value of Common Stock and Stock-Based Compensation

We account for grants of stock options and restricted stock to employees based on their grant date fair value and recognize compensation expense over the vesting periods. We estimate the fair value of stock options as of the date of grant using the Black-Scholes option pricing model, which requires management to apply judgment and make estimates including the volatility of our common stock, the expected term of our stock options, the expected dividend yield and the fair value of our common stock on the date of grant. We estimate the fair value of restricted stock based on the closing price of our common stock on the date of grant. We account for stock options and restricted stock awards to non-employees, if any, using the fair value approach. Stock options and restricted stock awards to non-employees are subject to periodic revaluation over their vesting terms.

Prior to our IPO in August 2015, in the absence of a public trading market for our common stock, on each grant date, we developed an estimate of the fair value of our common stock for the option and restricted stock grants based in part on input from an independent third-party valuation firm. We determined the fair value of our common stock using methodologies, approaches and assumptions consistent with the AICPA Practice Guide, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*. In addition, our board of directors considered various objective and subjective factors, along with input from management and an independent third-party valuation firm, to estimate the fair value of our common stock, including external market conditions affecting the pharmaceutical industry, trends within the pharmaceutical industry, the prices at which we sold shares of our different series of preferred stock, the superior rights and preferences of each series of preferred stock relative to our common stock at the time of each grant, our results of operations and financial position, the status of our research and development efforts and progress of our preclinical programs, our stage of development and business strategy, the lack of an active public market for our common and our preferred stock, and the likelihood of achieving a liquidity event.

Results of Operations

Comparison of the Years Ended December 31, 2015 and December 31, 2014

Revenue

Revenue in 2015 was entirely related to work performed in connection with grants received prior to 2015; grants received were recorded as deferred revenue and is recognized as revenue as the designated preclinical study progresses and amounts are earned. Revenue decreased $0.5 million, or 65.6%, to $0.3 million for the year ended December 31, 2015 from $0.8 million for the year ended December 31, 2014. The decrease primarily related to a $0.4 million decrease in grant revenue as a result of the termination of work on two grants and a temporary slowdown in research activities associated with our remaining grant. Also in 2014, we recorded $0.1 million of research services revenue. There was no research services revenue in 2015.

Research and Development Expenses

Research and development expenses increased by $5.0 million, or 210.1%, to $7.4 million for the year ended December 31, 2015 from $2.4 million for the year ended December 31, 2014. The increase was primarily the result of increased consulting costs of $4.0 million related to increased product development activities and increased compensation expense of $1.4 million related to increased headcount and the recognition of $0.5 million of stock-based compensation expense in the 2015 period, partially offset by an $0.4 million Australian tax incentive related to research and development costs incurred in Australia.

Our expenditures associated with ZYN002, ZYN001 and other research and development projects for the year ended December 31, 2015 were $4.0 million, $1.9 million and $1.5 million, respectively. Our expenditures associated with ZYN002, ZYN001 and our other projects in the year ended December 31, 2014 were $0.6 million, $0.6 million and $1.2 million, respectively.

General and Administrative Expenses

General and administrative expenses increased by $1.3 million, or 31.6%, to $5.4 million for the year ended December 31, 2015 from $4.1 million for the year ended December 31, 2014. Contributing to the increase were increases of $2.6 million in personnel costs, including $1.1 million of stock-based compensation expense recognized in the 2015 period (vesting of stock based compensation awards was contingent upon the completion of our IPO), approximately $0.6 million in professional service costs, including a $0.5 million payment during 2015 to broker-dealer Broadband Capital Management ("BCM") in connection with our termination of the BCM engagement, and $0.2 million of insurance costs. These increases were largely the result of our efforts to establish an infrastructure to support our product development activities and fees associated with becoming a public company. These increases were partially offset by a decrease in consulting costs of $2.1 million from 2014 to 2015, which primarily related to an engagement with BCM.

Comparison of the Years Ended December 31, 2014 and December 31, 2013

Revenue

Revenue decreased by $0.1 million or 14.2% to $0.8 million for the year ended December 31, 2014 from $0.9 million for the year ended December 31, 2013. The decrease was due to a $0.2 million decrease in grant revenue, which was partly offset by a $0.1 million increase in research services related to revenue received from a new contract entered into in November 2013.

Research and Development Expenses

Research and development expenses increased by $1.3 million, or 111.8%, to $2.4 million for the year ended December 31, 2014 from $1.1 million for the year ended December 31, 2013. The increase was primarily the result of increased consulting and compensation expense of $1.1 million for increased development activities, which was partly offset by decreased spending on university contracted services and lab supplies.

Our expenditures associated with ZYN002, ZYN001 and our other research and development projects in 2014 were $0.6 million, $0.6 million and $1.2 million, respectively. Our expenditures associated with ZYN001 and other research and development activities in 2013 were $0.3 million and $0.8 million, respectively; no expenditures were made for ZYN002 during the year ended December 31, 2013.

General and Administrative Expenses

General and administrative expenses increased by $3.6 million, or 817.5%, to $4.1 million for the year ended December 31, 2014 from $0.4 million for the year ended December 31, 2013. The increase was primarily the result of $1.9 million of non-cash expense for the issuance of common stock for services rendered by a related party and a third-party service provider in the year ended December 31, 2014 compared to $0 in the prior year. Additionally, during the year ended December 31, 2014, we expensed payments of $0.3 million to a related party for strategic advisory and consulting services and $0.5 million for the termination of a royalty agreement. The remaining increase is primarily due to legal costs and other administrative costs.

Liquidity and Capital Resources

Since our inception in 2007, we have devoted most of our cash resources to research and development and general and administrative activities. We have financed our operations primarily with the proceeds from the sale of equity securities (most notably our recent IPO, which is described below) 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, 2015, our principal sources of liquidity were our cash and cash equivalents, which totaled $41.5 million. Our working capital was $39.5 million as of December 31, 2015.

Equity Financings

In August 2015, we completed our IPO, selling 3,450,000 shares at an offering price of $14.00 per share resulting in gross proceeds of $48.3 million. Net proceeds received after underwriting fees and offering expenses were approximately $42.1 million. In connection with the closing of the IPO, all outstanding shares of our Series 1 convertible preferred stock were converted into an aggregate of 3,704,215 shares of common stock. Based on our current operating plans, we expect that the net proceeds from our IPO and our existing cash and cash equivalents will be sufficient to fund our operations and capital requirements through the end of 2017. We believe that these available funds will be sufficient to become Phase 3 ready, completing Phase 1 clinical trials for each of our product candidates and Phase 2a clinical trials for each of our five indications. However, it is difficult to predict our spending for our product candidates prior to obtaining FDA approval. 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. During the years ended December 31, 2014 and 2013, we received net proceeds of $13.2 million and $0.1 million, respectively, from the sale of convertible preferred stock.

Debt

We had no debt outstanding as of December 31, 2015 or 2014.

In April 2007, we were awarded a grant by the Kentucky Economic Development Finance Authority, or KEDFA, on behalf of the Commonwealth of Kentucky Department of Commercialization and Innovation, or DCI, in the form of a non-interest bearing forgivable loan in the amount of up to $500,000 to be used for the purchase of equipment. In September 2014, we repaid the forgivable loan balance of $499,996 and KEDFA released its security interest.

Future Capital Requirements

During the year ended December 31, 2015, net cash used in operating activities was $9.8 million, and our accumulated deficit as of December 31, 2015 was $22.6 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 make in the future. We have no current understandings, agreements or commitments for any material acquisitions or licenses of any products, businesses or technologies. We may need to raise substantial additional capital in order to engage in any of these types of transactions.

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 either of our product candidates, we will incur significant sales, marketing and outsourced 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 incur significant costs to comply with corporate governance, internal controls and similar requirements applicable to us as a public 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 develop or may in-license;

- the terms of any collaboration agreements we may choose to execute;
- the outcome, timing and cost of meeting regulatory requirements established by the DEA, the FDA, the EMA or other comparable foreign regulatory authorities;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the 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; 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.

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

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

Cash Flows

Years Ended December 31, 2015 and December 31, 2014 — The following table summarizes our cash flows from operating, investing and financing activities for the years ended December 31, 2015 and December 31, 2014.

	Year Ended December 31,	
	2015	2014
Statement of Cash Flows Data:		
Total net cash provided by (used in):		
Operating activities	$ (9,786,799)	$ (3,540,655)
Investing activities	(216,335)	(19,717)
Financing activities	42,185,513	12,736,358
Increase in cash and cash equivalents	$ 32,182,379	$ 9,175,986

Operating Activities

For the year ended December 31, 2015, cash used in operations was $9.8 million compared to $3.5 million for the year ended December 31, 2014. The increase from the comparable 2014 period was related to higher professional service costs incurred in connection with the preparation for our IPO, an increase in project and research and development costs associated with our preclinical studies and clinical trials that both reduced our prepaid preclinical trial expenses and increased our vendor payables, and an increase in accrued compensation, primarily associated with accrued bonuses at December 31, 2015.

We expect cash used in operating activities to continue to increase in 2016 as compared to 2015 due to an expected increase in our operating losses associated with ongoing development of our product candidates and the costs associated with being a public company.

Investing Activities

For the year ended December 31, 2015, cash used in investing activities was $0.2 million representing the cost of certain fabrication equipment, computer equipment, and furniture and fixtures associated with the establishment of our new corporate headquarters.

Financing Activities

Cash provided by financing activities was $42.2 million for the year ended December 31, 2015, primarily representing the net proceeds from our IPO. In the year ended December 31, 2014, cash provided by financing activities was $12.7 million, resulting from the issuance of shares of our Series 1 convertible preferred stock and Series B redeemable convertible preferred stock, partially offset by the repayment of a forgivable loan.

Years ended December 31, 2014 and December 31, 2013 — The following table summarizes our cash flows from operating, investing and financing activities for the years ended December 31, 2014 and December 31, 2013.

	Year ended December 31,	
	2014	2013
Statement of Cash Flows Data:		
Total net cash provided by (used in):		
Operating activities	$ (3,540,655)	$ (117,708)
Investing activities	(19,717)	(2,703)
Financing activities	12,736,358	109,458
Increase (decrease) in cash and cash equivalents	$ 9,175,986	$ (10,953)

Operating Activities

Net cash used in operating activities for the year ended December 31, 2014 was $3.5 million, including a net loss of $5.7 million, partly offset by $1.9 million of net noncash expenses and a $0.2 million net change in operating assets and liabilities. The net noncash expenses were predominantly related to the issuance of shares of common stock valued at $1.9 million for services rendered. The change in operating assets and liabilities was primarily due to a $0.4 million decrease in prepaid expenses and other assets and an increase in accounts payable and accrued expenses of $0.4 million partly offset by the timing of revenue of $0.6 million and expense recognition related to our research activities.

Net cash used in operating activities was $0.1 million for the year ended December 31, 2013 including a net loss of $0.6 million, partly offset by depreciation expense of less than $0.1 million and changes in operating assets and liabilities of $0.5 million primarily related to the timing of revenue and expense recognition for research activities.

Investing Activities

Cash used in investing activities in both the 2014 and 2013 annual periods related to the purchases of property and equipment.

Financing Activities

Cash provided by financing activities of $12.7 million for the year ended December 31, 2014 was primarily due to $12.9 million in net proceeds received on the sale of shares of our Series 1 convertible preferred stock and $0.3 million in net proceeds received on the sale of 250,000 shares of our Series B redeemable convertible preferred stock, partially offset by $0.5 million used to pay the note payable to KEDFA.

Cash provided by financing activities for the year ended December 31, 2013 was $0.1 million, reflecting proceeds on the issuance of shares of Series B redeemable convertible preferred stock and proceeds on the collection of stock subscription advances.

Off-Balance Sheet Arrangements

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

Contractual Obligations

The following table summarizes our contractual obligations as of December 31, 2015:

	Payments Due by Period				
	Total	2016	2017 and 2018	2019 and 2020	2021 and Thereafter
Operating lease obligations	$ 445,509	$ 97,626	$ 201,042	$ 146,841	$ -

Recent Accounting Pronouncements

In August 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2014-15, *Presentation of Financial Statements-Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, which defines management's responsibility to assess an entity's ability to continue as a going concern, and to provide related footnote disclosures if there is substantial doubt about its ability to continue as a going concern. The pronouncement is effective for annual reporting periods ending after December 15, 2016 with early adoption permitted. The adoption of this guidance is not expected to have a material impact on our financial statements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases*, which requires that lease arrangements longer than 12 months result in an entity recognizing an asset and liability. The pronouncement is effective for interim and annual periods beginning after December 15, 2018 with early adoption permitted. We are currently evaluating the impact we expect this guidance to have 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 and do not believe we are exposed to material market risk with respect to our cash and cash equivalents.

We currently have no operations outside the United States, but we have contracted with third parties to manufacture our product candidates in Canada and have begun to conduct Phase 1 clinical trials for ZYN002 in Australia. Manufacturing and research costs related to these operations are paid for in a combination of U.S. dollars and local currencies. Accordingly, we are subject to limited foreign currency exchange rate risk. We do not believe foreign currency exchange rate risk is a substantial risk at this time due to the limited extent of our operations, however, if we conduct additional clinical trials (we currently plan to conduct our Phase 2a clinical trials for ZYN002 in Australia) 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.

As of December 31, 2015, we had cash and cash equivalents of $41.5 million consisting primarily of cash and money market accounts. We do not engage in any hedging activities against changes in interest rates or foreign currency exchange rates. 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.

Item 8. Financial Statements and Supplementary Data

Our financial statements, together with the report of our independent registered public accounting firm, appear on pages F-1 through F-19 of this Report.

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, 2015. 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 SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by 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, 2015, 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

This Report does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for newly public companies.

Changes in Internal Control Over Financial Reporting

There has been no change in our internal control over financial reporting during the last fiscal quarter that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information called for by this item is incorporated herein by reference to the material under the captions "Board of Directors, Executive Officers and Corporate Governance," and "Security Ownership of Certain Beneficial Owners and Management – Section 16(a) Beneficial Ownership Reporting Compliance" in our proxy statement for the 2016 annual meeting of stockholders to be filed no later than 120 days after the end of our fiscal year ended December 31, 2015 (the "2016 Proxy Statement").

Item 11. Executive Compensation

The information called for 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 2016 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, 2015.

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	1,637,399	$ 10.49	216,762
Equity compensation plans not approved by security holders	—	—	—
Total	1,637,399	$ 10.49	216,762

Please see note (9) to our audited financial statements for a description of our 2014 Omnibus Incentive Compensation Plan.

The other information called for by this item is incorporated herein by reference to the material under the caption "Security Ownership of Certain Beneficial Owners and Management" in our 2016 Proxy Statement.

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

The information called for by this item is incorporated herein by reference to the material under the captions "Certain Relationships and Related Party Transactions" and "Board of Directors, Executive Officers and Corporate Governance – Policies and Procedures for Related Party Transactions" in our 2016 Proxy Statement.

Item 14. Principal Accounting Fees and Services

The information called for by this item is incorporated herein by reference to the material under the captions "Independent Auditors and Related Fees" in our 2016 Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Financial Statements.

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

Financial Statements

(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:

A list of exhibits to this Annual Report on Form 10-K is set forth on the Exhibit Index immediately preceding such exhibits and is incorporated herein by reference.

(b) Exhibits

See Exhibit Index.

(c) Not applicable

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 14, 2016

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 14, 2016
/s/ Richard A. Baron Richard A. Baron	Chief Financial Officer (Principal Financial Officer)	March 14, 2016
/s/ Warren D. Cooper, MB, BS, BSc, MPFM Warren D. Cooper, MB, BS, BSc, MPFM	Director	March 14, 2016
/s/ William J. Federici William J. Federici	Director	March 14, 2016
/s/ Thomas L. Harrison, LH.D Thomas L. Harrison, LH.D	Director	March 14, 2016
/s/ Daniel L. Kisner, MD Daniel L. Kisner, MD	Director	March 14, 2016
/s/ Kenneth I. Moch Kenneth I. Moch	Director	March 14, 2016
/s/ Cynthia A. Rask, MD Cynthia A. Rask, MD	Director	March 14, 2016

EXHIBIT INDEX

Exhibit No.	Exhibit Description
3.1	Sixth Amended and Restated Certificate of Incorporation of Zynerba Pharmaceuticals, Inc., effective August 10, 2015. Incorporated herein by reference to Exhibit 3.1 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 10, 2015.
3.2	Amended and Restated By-laws of Zynerba Pharmaceuticals, Inc., effective August 10, 2015. Incorporated herein by reference to Exhibit 3.2 to the registrant's Current Report on Form 8-K (File No. 001-37526) filed on August 10, 2015.
4.1	Form of Common Stock Certificate. Incorporated herein by reference to Exhibit 4.1 to the registrant's Registration Statement on Form S-1/A (File No. 333-205355) filed on July 31, 2015.
4.2	Third Amended and Restated Stockholders Agreement, dated May 6, 2014, by and among the registrant and certain stockholders. Incorporated herein by reference to Exhibit 4.2 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
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.
10.2+	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.
10.3+	Employment Agreement, dated October 2, 2014, by and between the registrant and Suzanne M. Hanlon. Incorporated herein by reference to Exhibit 10.4 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.4+	Employment Agreement, dated January 2, 2015, by and between the registrant and Richard A. Baron. Incorporated herein by reference to Exhibit 10.5 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.5	Severance Agreement and Release of Claims, dated September 26, 2014, by and between the registrant and Audra Stinchcomb. Incorporated herein by reference to Exhibit 10.6 to the registrant's Registration Statement on Form S-1 filed on June 30, 2015.
10.6	Patent Assignment, dated October 2, 2014, by and between the registrant and Audra Stinchcomb. Incorporated herein by reference to Exhibit 10.7 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.7	Agreement and Plan of Merger, dated May 6, 2014, by and among BCM X1 Holdings, LLC, BCM Partners IV, Corp., the registrant, Audra Stinchcomb and Steven Gailar. Incorporated herein by reference to Exhibit 10.10 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.8	Stock Transfer Agreement, dated September 26, 2014, by and between Michael Rapoport, Audra Stinchcomb and the registrant. Incorporated herein by reference to Exhibit 10.12 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.9	Grant no. 5RC2DA028984-02 dated September 17, 2010, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.13 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.10	Grant no. 1R43DA032161-01 dated July 14, 2011, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.14 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.

10.11	Grant no. 1RC2DA028984-01 dated September 30, 2009, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.15 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.12	Grant no. 1RC2DA028984-01, revised award letter dated June 9, 2011, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.16 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.13	Patent Assignment Consideration Agreement, dated August 21, 2014, by and between Albany College of Pharmacy and the registrant. Incorporated herein by reference to Exhibit 10.17 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.14	Termination and Release Agreement, dated October 1, 2014, by and between Buzzz Pharmaceuticals Ltd. and the registrant. Incorporated herein by reference to Exhibit 10.18 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.15(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.
10.15(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.
10.15(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.
10.15(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.
10.15(E)+	Form of Restricted Stock Grant Agreement under Amended and Restated 2014 Omnibus Incentive Compensation Plan. Incorporated herein by reference to Exhibit 10.19(E) to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.16+	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.
10.17	Grant Agreement No. KSTC-184-512-12-140 dated October 1, 2012 by and between Kentucky Science and Technology Corporation and the registrant. Incorporated herein by reference to Exhibit 10.21 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.18	Grant Agreement No. KSTC-184-512-11-114 dated September 29, 2011 by and between Kentucky Science and Technology Corporation and the registrant. Incorporated herein by reference to Exhibit 10.22 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.19	Grant Agreement No. KSTC-184-184-512-07-029 dated November 21, 2007 by and between Kentucky Science and Technology Corporation and the registrant. Incorporated herein by reference to Exhibit 10.23 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.20	Grant no. 5RC2DA028984-02, revised award letter dated May 9, 2012, from the National Institutes of Health to the registrant. Incorporated herein by reference to Exhibit 10.24 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.21	Termination of Letter Agreements, dated January 7, 2015, by and between Broadband Capital Management LLC and the registrant. Incorporated herein by reference to Exhibit 10.25 to the registrant's Registration Statement on Form S-1 (File No. 333-205355) filed on June 30, 2015.
10.22	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.
21.1	List of subsidiaries of the registrant
23.1	Consent of independent registered public accounting firm
31.1	Certifying Statement of the Chief Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certifying Statement of the Chief Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.

32.1	Certifying Statement of the Chief Executive Officer pursuant to Section 1350 of Title 18 of the United States Code.	
32.2	Certifying Statement of the Chief Financial Officer pursuant to Section 1350 of Title 18 of the United States Code.	
101 INS	XBRL Instance Document.	
101 SCH	XBRL Taxonomy Extension Schema Document.	
101 CAL	XBRL Taxonomy Extension Calculation Linkbase Document.	Filed herewith.
101 DEF	XBRL Taxonomy Extension Definition Linkbase Document.	Filed herewith.
101 LAB	XBRL Taxonomy Extension Label Linkbase Document.	Filed herewith.
101 PRE	XBRL Taxonomy Extension Presentation Linkbase Document.	Filed herewith.

+ Indicates management contract or compensatory plan.

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders
Zynerba Pharmaceuticals, Inc.:

We have audited the accompanying consolidated balance sheets of Zynerba Pharmaceuticals, Inc. and subsidiary (formerly AllTranz, Inc.) as of December 31, 2015 and 2014, and the related consolidated statements of operations, redeemable convertible preferred stock, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the years in the three-year period ended December 31, 2015. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Zynerba Pharmaceuticals, Inc. and subsidiary as of December 31, 2015 and 2014, and the results of their operations and their cash flows for each of the years in the three-year period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ KPMG LLP

Philadelphia, Pennsylvania
March 14, 2016

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS

	December 31, 2015	December 31, 2014
Assets		
Current assets:		
Cash and cash equivalents	$ 41,513,060	$ 9,330,681
Deferred offering costs	—	1,080,199
Prepaid expenses and other current assets	1,902,635	1,183,949
Total current assets	43,415,695	11,594,829
Property and equipment, net	227,646	19,642
Other assets	200	2,200
Total assets	$ 43,643,541	$ 11,616,671
Liabilities, Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current Liabilities:		
Accounts payable	$ 823,401	$ 313,937
Accrued expenses	2,272,991	1,711,473
Deferred grant revenue	841,225	1,120,125
Total current liabilities	3,937,617	3,145,535
Commitments and contingencies (note 11)		
Convertible Preferred Stock:		
Series 1 convertible preferred stock, $0.001 par value; 7,807,502 shares authorized; 6,964,053 shares issued and outstanding at December 31, 2014	—	16,522,811
Stockholders' equity (deficit):		
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; 9,199,919 shares and 2,029,747 shares issued and outstanding at December 31, 2015 and December 31, 2014, respectively	9,200	2,030
Additional paid-in capital	62,276,779	1,975,000
Accumulated deficit	(22,580,055)	(10,028,705)
Total stockholders' equity (deficit)	39,705,924	(8,051,675)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 43,643,541	$ 11,616,671

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS

	Year ended December 31,		
	2015	2014	2013
Revenue	$ 278,900	$ 810,012	$ 943,904
Operating expenses:			
Research and development	7,445,669	2,401,406	1,134,041
General and administrative	5,364,390	4,076,339	444,302
Total operating expenses	12,810,059	6,477,745	1,578,343
Loss from operations	(12,531,159)	(5,667,733)	(634,439)
Other income (expense):			
Interest income (expense), net	7,352	(1,844)	(2,351)
Loss before income taxes	(12,523,807)	(5,669,577)	(636,790)
Income tax expense	(27,543)	—	—
Net loss	(12,551,350)	(5,669,577)	(636,790)
Accretion of redeemable convertible preferred stock	—	(87,954)	(161,834)
Net loss applicable to common stockholders	$ (12,551,350)	$ (5,757,531)	$ (798,624)
Net loss per share basic and diluted	$ (2.82)	$ (6.44)	$ (1.63)
Basic and diluted weighted average shares outstanding	4,457,719	894,575	490,760

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF REDEEMABLE CONVERTIBLE PREFERRED STOCK, CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
YEARS ENDED DECEMBER 31, 2013, 2014 and 2015

	Redeemable convertible preferred stock				Convertible preferred stock		Stockholders' equity (deficit)				
	Series A		Series B		Series 1		Common stock		Additional paid-capital	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at December 31, 2012	**720,002**	**$ 1,569,764**	**955,253**	**$ 1,358,817**	**—**	**$ —**	**490,760**	**$ 49**	**$ 108,432**	**$ (3,668,936)**	**$ (3,560,455)**
Issuance of Series B redeemable convertible preferred stock, net of stock issuance costs of $3,040	—	—	42,856	71,958	—	—	—	—	—	—	—
Accretion of redeemable convertible preferred stock to redemption value	—	76,415	—	85,419	—	—	—	—	(108,432)	(53,402)	(161,834)
Net loss	—	—	—	—	—	—	—	—	—	(636,790)	(636,790)
Balance at December 31, 2013	**720,002**	**1,646,179**	**998,109**	**1,516,194**	**—**	**—**	**490,760**	**49**	**—**	**(4,359,128)**	**(4,359,079)**
Issuance of Series B redeemable convertible preferred stock, net of stock issuance costs of $3,089	—	—	250,000	347,411	—	—	—	—	—	—	—
Accretion of redeemable convertible preferred stock to redemption value	—	25,443	—	62,511	—	—	—	—	(87,954)	—	(87,954)
Issuance of Series 1 convertible preferred stock, net of offering costs of $289,878	—	—	—	—	6,244,051	12,925,034	—	—	—	—	—
Issuance of common stock (pre recapitalization)	—	—	—	—	—	—	74,923	7	125,360	—	125,367
Forfeiture of common stock (pre recapitalization)	—	—	—	—	—	—	(359,042)	(36)	36	—	—
Recapitalization transactions (Note 8)	(720,002)	(1,671,622)	(1,248,109)	(1,926,116)	720,002	3,597,777	591,230	778	791,183	—	791,961
Issuance of common stock (post recapitalization)	—	—	—	—	—	—	693,661	694	1,146,913	—	1,147,607
Forfeiture of common stock (post recapitalization)	—	—	—	—	—	—	(41,667)	(42)	42	—	—
Issuance of restricted stock	—	—	—	—	—	—	579,882	580	(580)	—	—
Net loss	—	—	—	—	—	—	—	—	—	(5,669,577)	(5,669,577)
Balance at December 31, 2014	**—**	**—**	**—**	**—**	**6,964,053**	**16,522,811**	**2,029,747**	**2,030**	**1,975,000**	**(10,028,705)**	**(8,051,675)**
Conversion of Series 1 convertible preferred stock	—	—	—	—	(6,964,053)	(16,522,811)	3,704,215	3,704	16,519,107	—	16,522,811
Issuance of common stock, net of issuance costs	—	—	—	—	—	—	3,450,000	3,450	42,118,554	—	42,122,004
Exercise of stock options	—	—	—	—	—	—	15,957	16	63,493	—	63,509
Stock-based compensation expense	—	—	—	—	—	—	—	—	1,600,625	—	1,600,625
Net loss	—	—	—	—	—	—	—	—	—	(12,551,350)	(12,551,350)
Balance at December 31, 2015	**—**	**$ —**	**—**	**$ —**	**—**	**$ —**	**9,199,919**	**$ 9,200**	**$62,276,779**	**$(22,580,055)**	**$ 39,705,924**

See accompanying notes to consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year ended December 31,		
	2015	2014	2013
Cash flows from operating activities:			
Net loss	$ (12,551,350)	$ (5,669,577)	$ (636,790)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	26,027	27,063	49,392
Forgiveness of accounts payable	—	(180,782)	—
Common stock issued for services	—	2,063,565	—
Stock-based compensation	1,600,625	—	—
Loss on disposal of equipment	—	22,550	—
Changes in operating assets and liabilities:			
Grant receivables	—	34,514	102,120
Prepaid expenses and other assets	(716,686)	437,691	(1,599,580)
Deferred grant revenue	(278,900)	(641,321)	1,838,334
Accounts payable	536,354	140,105	86,233
Accrued expenses	1,597,131	225,537	42,583
Net cash used in operating activities	(9,786,799)	(3,540,655)	(117,708)
Cash flows from investing activities:			
Purchases of property and equipment	(216,335)	(19,717)	(2,703)
Net cash used in investing activities	(216,335)	(19,717)	(2,703)
Cash flows from financing activities:			
Proceeds from issuance of Series B redeemable convertible preferred stock, net	—	309,911	71,958
Proceeds from issuance of Series 1 convertible preferred stock, net	—	12,925,034	—
Proceeds from the issuance of common stock, net of offering costs	42,122,004	1,409	—
Proceeds from the exercise of stock options	63,509	—	—
Proceeds from stock subscription advances	—	—	37,500
Repayment of borrowings	—	(499,996)	—
Net cash provided by financing activities	42,185,513	12,736,358	109,458
Net increase (decrease) in cash and cash equivalents	32,182,379	9,175,986	(10,953)
Cash and cash equivalents at beginning of period	9,330,681	154,695	165,648
Cash and cash equivalents at end of period	$ 41,513,060	$ 9,330,681	$ 154,695
Supplemental disclosures of cash flow information:			
Accrued dividends on redeemable convertible preferred stock	$ —	$ 48,078	$ 88,681
Accretion of redeemable convertible preferred stock	—	39,876	73,153
Deferred offering costs included in accounts payable and accrued expenses	—	1,080,199	—
Property and equipment acquired but not yet paid	17,696	1,748	—
Cash paid for interest	—	1,920	2,378

See accompanying notes to unaudited 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 (the "Company", "we"), is a specialty pharmaceutical company focused on developing and commercializing proprietary next-generation synthetic cannabinoid therapeutics formulated for transdermal delivery. The Company was incorporated on January 31, 2007 under the laws of the State of Delaware as AllTranz, Inc. and changed its name to Zynerba Pharmaceuticals, Inc. in August 2014. The Company operated in Lexington, Kentucky until October 2014 when it moved its operations to Pennsylvania.

The Company has incurred losses and negative cash flows from operations since inception and has an accumulated deficit of $22.6 million as of December 31, 2015. 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 and convertible promissory notes.

In August 2015, the Company completed its Initial Public Offering (IPO) of common stock selling 3,450,000 shares at an offering price of $ 14.00 per share, resulting in gross proceeds of $48.3 million. Net proceeds received after underwriting fees and offering expenses were $42.1 million. In connection with the IPO, all outstanding shares of Series 1 convertible preferred stock converted into 3,704,215 shares of common stock. Management believes that current cash and cash equivalents are sufficient to fund operations through the end of 2017. Substantial additional financings will be needed by the Company to fund its operations, to complete clinical development of and to commercially develop its product candidates. There is no assurance that such financing will be available when needed or on acceptable terms.

The Company is subject to those risks associated with any specialty 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 financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities at the date of the financial statements and reported amounts of revenue and expenses during the reporting period. Actual results could differ from such estimates.

c. Fair Value of Financial Instruments

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

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, 2015 and 2014, the Company invested a portion of its cash balances in money market funds, which has been included as cash equivalents on the consolidated balance sheets.

e. Prepaid Expenses and Other Assets

Prepaid expenses primarily consist of prepaid preclinical trial expenses of $1.2 million and $1.1 million as of December 31, 2015 and 2014, respectively. Prepaid expenses as of December 31, 2015 includes a receivable of $0.4 million related to the expected tax incentive refund of certain research and development costs incurred in Australia.

f. Property and Equipment

Property and equipment are recorded at cost and are depreciated on a straight-line basis over their estimated useful lives. The Company estimates a life of three years for computer equipment and five years for furniture and fixtures and lab equipment. 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 operating expenses. Repairs and maintenance costs are expensed as incurred.

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 impairment may have occurred. If indicators of 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, 2015, 2014 and 2013, 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 (CROs), consultants and employee related expenses including salaries and benefits.

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 vesting period of the award. Stock-based awards issued to non-employees are revalued until the award vests.

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

The expected life of stock options was estimated using the "simplified method," as the Company has no historical information to develop reasonable expectations about future exercise patters and post vesting employment termination

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

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 stock price volatility, the Company uses comparable public companies as a basis for its expected volatility to calculate the fair value of option grants. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected life of the option.

j. Revenue Recognition

Revenue related to research grants and research services for third party product development are recognized when persuasive evidence of an arrangement exists, delivery has occurred or services have been rendered, the price is fixed and determinable, and collectability is reasonably assured. Research services revenue of $0, $0.1 million and $0.1 million in 2015, 2014 and 2013, respectively, represents fees for research and development activities. The remaining revenue represents grant revenue. Grant revenue received is deferred until the related expenditures are incurred.

k. Income Taxes

The Company recognizes deferred tax assets and liabilities for temporary differences between the financial reporting basis and the tax basis of the Company's assets and liabilities and the expected benefits of net operating loss carryforwards. The impact of changes in tax rates and laws on deferred taxes, if any, applied during the years in which temporary differences are expected to be settled, is reflected in the financial statements in the period of enactment. The measurement 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, 2015 and 2014, the Company has concluded that a full valuation allowance is necessary for their net deferred tax assets. The Company had no material amounts recorded for uncertain tax positions, interest or penalties in the accompanying financial statements.

l. Net Loss Per Share

Basic loss per share is computed by dividing net loss applicable to common stockholders by the weighted average number of shares of common stock outstanding during each period. Diluted loss per share includes the effect, if any, from the potential exercise or conversion of securities, such as redeemable convertible preferred stock, convertible preferred stock, restricted stock, and stock options, which would result in the issuance of incremental shares of common stock. In computing the basic and diluted net loss per share applicable to common stockholders, the weighted average number of shares remains the same for both calculations due to the fact that when a net loss exists, dilutive shares are not included in the calculation as the impact is anti-dilutive.

The following potentially dilutive securities outstanding as of December 31, 2015, 2014 and 2013 have been excluded from the computation of diluted weighted average shares outstanding, as they would be anti-dilutive:

	December 31,		
	2015	2014	2013
Redeemable convertible preferred stock	—	—	913,873
Convertible preferred stock	—	3,704,126	—
Stock options	1,637,399	542,550	196,726
Unvested restricted stock	398,671	579,882	—
	2,036,070	4,826,558	1,110,599

Amounts in the table reflect the common stock equivalents of the noted instruments.

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

m. Recapitalization

On July 22, 2015, the Board of Directors approved a reverse stock split of the Company's common stock at a ratio of one share for every 1.88 shares previously held. The reverse stock split was effected July 30, 2015. All common stock share and per share data included in the financial statements reflect the reverse stock split.

n. Segment Information

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

o. Recent Accounting Pronouncements

In August 2014, the Financial Accounting Standard Board (FASB) issued Accounting Standards Update (ASU) No. 2014-15, *Presentation of Financial Statements-Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, which defines management's responsibility to assess an entity's ability to continue as a going concern, and to provide related footnote disclosures if there is substantial doubt about its ability to continue as a going concern. The pronouncement is effective for annual reporting periods ending after December 15, 2016 with early adoption permitted. The adoption of this guidance is not expected to have a material impact on the Company's consolidated financial statements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases*, which requires that lease arrangements longer than 12 months result in an entity recognizing an asset and liability. The pronouncement is effective for interim and annual periods beginning after December 15, 2018 with early adoption permitted. The Company is currently evaluating the impact this guidance is expected to have on its consolidated financial statements.

(3) Fair Value Measurements

The Company utilizes a valuation hierarchy that prioritizes fair value measurements based on the types of inputs used for the various valuation techniques related to its financial assets and financial liabilities. The three levels of inputs used to measure fair value are described as follows:

Level 1 — Unadjusted quoted prices in active markets for identical assets or liabilities.

Level 2 — Observable inputs and quoted prices in active markets for similar assets and liabilities.

Level 3 — 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 cash equivalents measured at fair value on a recurring basis:

		Fair Value Measurement as of December 31, 2015		
	Carrying value as of December 31, 2015	Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 41,032,351	$ 41,032,351	$ —	$ —
Certificate of deposit (included in prepaid expenses and other current assets)	20,000	20,000	—	—
	$ 41,052,351	$ 41,052,351	$ —	$ —

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

	Carrying value as of December 31, 2014	Fair Value Measurement as of December 31, 2014		
		Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 9,004,991	$9,004,991	$ —	$ —
	$ 9,004,991	$9,004,991	$ —	$ —

(4) Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist of the following as of December 31, 2015 and 2014:

	December 31, 2015	December 31, 2014
Prepaid development expenses	$ 1,211,668	$ 1,143,308
Prepaid insurance	282,440	18,491
Tax incentive receivable	356,718	—
Other	51,809	22,150
Total prepaid expenses and other current assets	$ 1,902,635	$ 1,183,949

(5) Property and Equipment

Property and equipment consisted of the following:

	Estimated useful life (in years)	December 31, 2015	December 31, 2014
Equipment	5	$ 139,526	$ 4,325
Computer equipment	3	23,632	17,139
Furniture and fixtures	5	94,118	1,781
Total cost		257,276	23,245
Less accumulated depreciation		(29,630)	(3,603)
Property and equipment, net		$ 227,646	$ 19,642

Depreciation expense was $26,027, $27,063 and $49,392 for the years ended December 31, 2015, 2014 and 2013 respectively.

(6) Accrued Expenses

Accrued expenses consisted of the following:

	December 31, 2015	December 31, 2014
Accrued compensation	$ 1,047,530	$ 37,045
Accrued research and development	943,295	—
Deferred offering costs	—	1,080,199
Grants payable	—	400,000
Other	282,166	194,229
Total accrued expenses	$ 2,272,991	$ 1,711,473

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

(7) Debt

In April 2007, the Company was awarded a grant by the Kentucky Economic Development Finance Authority (KEDFA) on behalf of the Commonwealth of Kentucky Department of Commercialization and Innovation (DCI) in the form of a non interest bearing forgivable loan in the amount of up to $500,000 to be used for the purchase of equipment. In January 2014, the Company granted KEDFA liens on certain of its patents as security for the forgivable loan. In September 2014, the Company repaid the forgivable loan balance of $499,996 as management determined they would not meet the performance criteria associated with the grant and KEDFA released its security interest.

(8) Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)

Series A and Series B Redeemable Convertible Preferred Stock

In connection with the Company's recapitalization in 2014, all $0.0001 par value Series A Participating Preferred Stock (Series A) and $0.0001 par value Series B Participating Preferred Stock (Series B) were converted to Series 1 convertible preferred stock (see below).

The Series B ranked senior to the Series A and the common stock in liquidation. The Series A and B were convertible into common stock at the option of the holder, automatically converted into common stock upon a public offering of stock with a public offering price of not less than $25,000,000, or the consent of a majority of the holders and had a liquidation value of $1.75 per share plus unpaid dividends. Dividends were cumulative, accrued beginning in June 2008 and October 2013 for the Series A and Series B, respectively, at a rate of 6% per year and became payable upon declaration by the board of directors of the Company, redemption or liquidation.

At the earlier of a Company Default (as defined) or August 30, 2017, the Series A and B Preferred Stock were redeemable at the option of a majority of the holders at the greater of a price per share of $1.75 plus unpaid dividends, if any, or the then fair market value. Total accretion of the Series A unamortized issuance cost towards redemption value was $1,309 and $3,930 for the years ended December 31, 2014 and 2013, respectively. Total accretion of the Series A dividends towards the redemption value was $24,134 and $72,485 for the years ended December 31, 2014 and 2013, respectively.

Total accretion of the Series B unamortized issuance cost and beneficial conversion feature towards the redemption value was $38,568 and $69,223 for the years ended December 31, 2014 and 2013, respectively. Total accretion of the Series B dividends towards the redemption value was $23,943 and $16,196 for the years ended December 31, 2014 and 2013, respectively.

In January 2014, the Company issued 200,002 shares of Series B and warrants to purchase 49,998 shares of Series B for total proceeds of $350,000 less stock issuance costs of $3,089 for net proceeds to the Company of $346,911. In April 2014, the warrants to purchase 49,998 shares of Series B were exercised for total proceeds to the Company of $500. Since the Series B underlying the warrants could have been redeemed for cash upon an event that is not within the Company's control, these warrants were classified as a derivative liability with changes to fair value, if any, recorded through earnings at each reporting period through the exercise date.

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

Recapitalization Transactions

In May 2014, a series of transactions, referred to as the Recapitalization Transactions, were executed resulting in the issuance of 720,002 shares of Series 1 convertible preferred stock (Series 1) and 797,871 shares of new common stock, as follows:

- A shareholder who was an original founder of the Company elected to forfeit 359,042 shares of the original common stock. The forfeited shares were canceled and retired by the Company.
- All outstanding options that were previously issued were cancelled.
- The Company issued 74,923 shares of common stock to certain existing investors and employees for total proceeds of $1,409. As a result of the issuance, the Company recognized $123,958 of noncash general and administrative expense during the year ended December 31, 2014.
- Prior to the recapitalization, all outstanding shares of the Series A and the Series B were converted into shares of common stock. The Company converted 720,002 shares of Series A and 1,248,109 shares of Series B into 1,046,847 shares of common stock.
- On May 6, 2014, the Company recapitalized. In connection with the recapitalization, each share of common stock was exchanged into shares of Series 1 by multiplying each share of common stock issued and outstanding immediately prior to the recapitalization by 0.57434. As a result, 720,002 shares of Series 1 were issued pursuant to such exchange.
- In connection with the recapitalization, 478,723 shares of new common stock were issued to a new investor (New Investor). The Company recognized $792,000 of noncash general and administrative expense during the year ended December 31, 2014 as a result of the issuance. In addition, the Company issued 319,148 shares of new common stock to the same shareholder that forfeited 359,042 shares of common stock prior to the recapitalization.

Series 1 Convertible Preferred Stock

From May 2014 through October 2014, the Company issued an aggregate of 6,244,051 shares of Series 1 for total proceeds of $13,214,912 less stock issuance costs of $289,878 for net proceeds of $12,925,034. The Series 1 converted into 3,704,215 shares of common stock in connection with the IPO.

Voting

Holder of the Series 1, voting as a class, were entitled to elect four members of the board of directors. Holders of the common stock, voting as a single class, were entitled to elect one member of the board of directors.

Dividends

Holders of Series 1 were entitled to receive a dividend on each outstanding share of Series 1, if and when declared by the board of directors, issuable upon the conversion of a share of Series 1 on the record date in the case of a dividend on common stock or any class or series convertible into common stock.

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

Liquidation

In the event of a liquidation, dissolution, or winding-up, or in the event the Company was merged with, or was acquired by another entity, the holders of each share of Series 1 were entitled to receive an amount equal to the greater of the $3.98 per share plus any dividends declared but unpaid thereon or such amount per share as would have been payable had all shares of Series 1 been converted to common stock immediately prior to such liquidation. With respect to the liquidation preference, after payment has been made to the holders of Series 1, the remaining assets available for distribution would have been distributed to the holders of common stock.

Redemption

The Series 1 was subject to redemption under certain "deemed liquidation events" and as such, the Series 1 was considered contingently redeemable for financial accounting purposes. The Company concluded that none of these events were probable at December 31, 2014.

Common Stock Transactions

In September 2014, the Company issued 579,614 shares of common stock to the New Investor for providing certain advisory service, including management services. The Company recognized $958,914 of noncash general and administrative expense for these issuances during the year ended December 31, 2014. An additional 114,047 shares of common stock were issued to third parties for providing consulting services. As a result of the issuances, the Company recognized $188,693 of noncash general and administrative expense during the year ended December 31, 2014.

In October 2014, the New Investor forfeited 41,667 shares of common stock.

In August 2015, the Company completed its IPO, selling 3,450,000 shares at an offering price of $14.00 per share, resulting in gross proceeds of $48.3 million. Net proceeds received after underwriting fees and offering expenses were approximately $42.1 million.

(9) Stock-Based Compensation

During May 2014, all outstanding stock options under the 2007 stock option plan (the 2007 Plan) were cancelled in connection with the recapitalization (Note 8).

The Company maintains the Amended and Restated 2014 Omnibus Incentive Compensation Plan (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 purchase an aggregate of 2,450,000 shares of the Company's common stock to employees, officers, directors, consultants, and advisors, 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, commencing on January 1, 2017, equal to the lesser of 1.5 million shares and 10% of the number of shares of common stock outstanding on the last trading day of December of the preceding year. In addition, the 2014 Plan provides selected executive employees with the opportunity to receive bonus awards that are considered qualified performance-based compensation. As of December 31, 2015, 216,762 shares are available for 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-employees.

In October and December 2014, the Company entered into employment contracts and agreements in connection with the hiring of its key executives and certain consultants and issued stock options to purchase 542,550 shares of common stock

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

with an exercise price of $3.98 per share and 579,882 shares of restricted common stock that have certain performance-based and time-based vesting criteria. The stock options and restricted stock awards vested 25% upon the closing of the Company's IPO and then ratably over three years following the closing of the Company's IPO. Accordingly, prior to the Company's IPO in August 2015, no expense had been recorded for the stock option grants and restricted stock awards.

During the year ended December 31, 2015, the Company granted 1,110,806 stock options, which included 1,001,977 stock options that were granted to employees and the Company's Board of Directors at the time of the Company's IPO. The stock options granted to the Company's employees at the time of the IPO, primarily vest in sixteen equal quarterly increments from the IPO date. The stock options granted to the Company's Board of Directors at the time of the IPO vest in equal one-third increments on the anniversary of the of the Company's IPO for three consecutive years. All other stock options granted during 2015 vest 25% upon the first anniversary of the relative grant date and quarterly over three years thereafter.

During the year ended December 31, 2015, the Company recorded stock-based compensation expense related to its stock option grants and restricted stock awards, as follows:

	Research and Development	General and Administrative	Total
Stock option grants	$ 403,395	$ 860,281	$1,263,676
Restricted stock awards	142,506	194,443	336,949
	$ 545,901	$ 1,054,724	$1,600,625

The following table summarizes the stock option activity under the 2014 Plan.

	Options	Weighted Average Grant Date Fair Value	Weighted Average Exercise Price
Outstanding as of December 31, 2013	—	$ —	$ —
Granted	542,550	$ 0.84	$ 3.98
Outstanding as of December 31, 2014	542,550	$ 0.84	$ 3.98
Granted	1,110,806	$ 9.13	$ 13.58
Exercised	(15,957)	$ 0.84	$ 3.98
Outstanding as of December 31, 2015	1,637,399	$ 6.47	$ 10.49

As of December 31, 2015, there was $9.3 million of unrecognized stock-based compensation expense related to stock options, which is expected to be recognized over a weighted-average period of 3.38 years. As of December 31, 2015, 240,234 stock options with a weighted average grant date fair value of $2.68 per share were exercisable. The Company expects all 1,397,165 unvested stock options to vest. As of December 31, 2015, the Company's outstanding stock options had a weighted average contractual life of 9.3 years and an intrinsic value of zero.

The weighted average grant date fair value of stock options granted during the year ended December 31, 2015 was estimated using the Black-Scholes option pricing model with the following ranges of assumptions: expected volatility of 76%- 77%, risk free interest rate of 1.7%- 2.0%, expected term of 5.75 years to 6.25 years and 0% expected dividend yield. The weighted average grant date fair value of stock options granted during the year ended December 31, 2014 was estimated using the Black-Scholes option pricing model with the following ranges of assumptions: expected volatility of 76%, risk free interest rate of 2.0%, expected term of 6 years and 0% expected dividend yield. Due to the stage of the Company and its recent IPO in August 2015, the Company currently computes volatility using a basket of peer companies rather its own historical experience.

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

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

	Shares	Weighted Average Grant Date Fair Value
Unvested as of December 31, 2013	—	$ —
Granted	579,882	$ 1.65
Unvested as of December 31, 2014	579,882	$ 1.65
Vested	(181,211)	$ 1.65
Unvested as of December 31, 2015	398,671	$ 1.65

As of December 31, 2015, there was $0.6 million of unrecognized stock-based compensation expense related to unvested restricted stock awards as of December 31, 2015, which is expected to be recognized over a weighted-average period of 2.59 years, and the Company expects all 398,671 unvested restricted stock awards to vest.

(10) Income Taxes

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

	Year ended December 31,		
	2015	2014	2013
United States	$(12,145,964)	$(5,669,577)	$(636,790)
Foreign	(377,843)	—	—
Total	$(12,523,807)	$(5,669,577)	$(636,790)

As of December 31, 2015 and 2014, the Company has $2.3 million of start-up expenses capitalized for income tax purposes. Additionally, the Company has approximately $17.7 million and $6.9 million of federal net operating loss carryforwards and $0.4 million and $0.2 million of research tax credit carryforwards as of December 31, 2015 and 2014, respectively. The net operating loss carryforwards and research tax credit carryforwards begin to expire in 2028 and 2027, respectively.

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.

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

The components of the net deferred income tax asset as of December 31, 2015 and 2014 are as follows:

	December 31, 2015	December 31, 2014
Deferred tax assets:		
Net operating loss carry-forwards	$ 6,531,375	$ 2,411,209
Startup costs	817,052	916,994
Research and development credit carry-forwards	425,282	161,174
Deferred revenue	304,264	454,697
Stock-based compensation	227,093	—
Gross deferred tax assets	8,305,066	3,944,074
Deferred tax liabilities:		
Accumulated depreciation	(18,519)	(4,262)
Stock-based compensation	—	(389,438)
Gross deferred tax liabilities	(18,519)	(393,700)
Less valuation allowance	(8,286,547)	(3,550,374)
Net deferred tax asset	$ —	$ —

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, 2015 and 2014, 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 $4.7 million and $2.0 million during the years ended December 31, 2015 and 2014, respectively, due primarily to the generation of net operating loss carryforwards during those years.

The Company does not have unrecognized tax benefits as of December 31, 2015 and 2014, respectively. The Company recognizes interest and penalties accrued on any unrecognized tax benefits as a component of income tax expense.

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

	Year ended December 31,		
	2015	2014	2013
Federal income tax benefit at statutory rate	34.0 %	34.0 %	34.0 %
State income tax, net of federal benefit	2.9 %	(0.3)%	6.3 %
Foreign tax rate differential	(0.1)%	— %	— %
Permanent differences	(1.2)%	(0.7)%	— %
Research and development credit benefit	2.0 %	1.6 %	7.1 %
Change in valuation allowance	(37.8)%	(34.6)%	(47.4)%
Effective income tax rate	(0.2)%	— %	— %

The Company files income tax returns in the U.S. federal jurisdiction and various state jurisdictions. The Company's 2011 to 2015 tax years remain open and subject to examination.

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

(11) Commitments and Contingencies

a. Federal Grants

One U.S. Federal agency provided 85% and 91% of grant revenue during the years ended December 31, 2014 and 2013, respectively. There was no grant revenue received during the year ended December 31, 2015. When received, grant revenue is deferred until the related expenditures are incurred.

As of December 31, 2015 and 2014, there was $0.8 million and $1.1 million, respectively, included in deferred revenue and $0.8 million and $1.1 million, respectively, included in prepaid expenses and other assets for prepaid research and development contracts related to the federal grant "ARRA — Transdermal Cannabinoid Prodrug Treatment for Cannabis Withdrawal and Dependence."

During 2007 through 2013, the Company received an aggregate amount of $400,000 related to grants received from the Kentucky Science and Technology Corporation (KSTC), a shareholder of the Company. As part of the grant agreement, the Company was required to have its principal office of operations and 51% of its property and payroll located in Kentucky for at least 60 months after the final disbursement of grant funds, which occurred in October 2013. Upon transfer of the Company's office of operations to another state, a default would occur and all funds received prior to the date of default would be required to be repaid to KSTC. As a result of this contingency, the Company recorded the $400,000 in grant funds as deferred revenue at December 31, 2013. Due to the Company's relocation to Pennsylvania in 2014, this amount was reflected in accrued expenses at December 31, 2014. In February 2015, the Company repaid the KSTC grants in full.

b. Research and Development Agreement

In August 2014, the Company entered into a patent assignment consideration agreement with Albany College of Pharmacy (ACP) pursuant to which the Company paid $500,000 in exchange for the termination of a royalty agreement that was executed in December 2004. This payment was expensed and included in general and administrative expenses for the year ended December 31, 2014.

c. Employee Retirement Plan

The Company has established a retirement plan authorized by section 401(k) of the Internal Revenue Code. In accordance with the plan, all employees are eligible to participate in the plan after 90 days of full-time employment and attainment of age 21 or older. Each employee can contribute a percentage of compensation up to a maximum of the statutory limits per year. The Company has the option to make discretionary matching contributions and profit sharing contributions. The Company made no contributions during 2015, 2014 or 2013.

d. Leases

The Company has entered into lease agreements for office space in Pennsylvania and Kentucky. In February 2015, the Company entered into the current lease for its Pennsylvania headquarters, which commenced in June 2015. The lease expires in 2020 and provides for minimum lease commitments of $97,626, $99,556, $101,486, $103,416 and $43,425 for the years ended December 31, 2016, 2017, 2018, 2019 and 2020, respectively. The Company is party to a month-to-month lease for office space in Kentucky for which it pays a nominal monthly rent.

Total lease expense during the years ended December 31, 2015, 2014 and 2013 was $77,192, $63,880 and $52,665, respectively.

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

e. Employment Agreements

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

f. 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. The Company believes there are no matters pending or threatened that will have a material impact to the Company's financial position or results of operations.

(12) Related Party Transactions

The Company paid affiliates of the New Investor $250,000 for the reimbursement of stock issuance costs during the year ended December 31, 2014. Additionally, the Company paid $250,000 for various services, including management services, rendered in 2014. Furthermore, the Company paid legal expenses on the behalf of the New Investor totaling $200,000, of which, $37,366 related to stock issuance costs. In January 2015, the Company entered into a termination agreement with the New Investor pursuant to which certain agreements will be terminated upon payment of $500,000. The Company paid the New Investor $500,000 prior to the closing of the Company's August 2015 IPO.

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

(13) Quarterly Financial Data (unaudited)

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

	2015			
	First Quarter (1)	Second Quarter (1)	Third Quarter	Fourth Quarter
Revenue	$ 14,828	$ 15,390	$ 199,407	$ 49,275
Operating expenses:				
Research and development	853,704	1,010,989	2,271,968	3,309,008
General and administrative	653,773	631,474	1,922,755	2,156,388
Total operating expenses	1,507,477	1,642,463	4,194,723	5,465,396
Loss from operations	(1,492,649)	(1,627,073)	(3,995,316)	(5,416,121)
Other income (expense):				
Interest income (expense), net	680	697	1,572	4,403
Loss before income taxes	(1,491,969)	(1,626,376)	(3,993,744)	(5,411,718)
Income tax expense	—	—	—	(27,543)
Net loss	(1,491,969)	(1,626,376)	(3,993,744)	(5,439,261)
Accretion of redeemable convertible preferred stock	—	—	—	—
Net loss applicable to common stockholders	$ (1,491,969)	$ (1,626,376)	$ (3,993,744)	$ (5,439,261)
Net loss per share basic and diluted	$ (1.03)	$ (1.12)	$ (0.66)	$ (0.62)
Basic and diluted weighted average shares outstanding	1,449,865	1,449,865	6,045,211	8,787,855

	2014			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 146,287	$ 64,097	$ 525,471	$ 74,157
Operating expenses:				
Research and development	285,725	367,296	932,838	815,547
General and administrative	99,704	1,206,188	2,107,520	662,927
Total operating expenses	385,429	1,573,484	3,040,358	1,478,474
Loss from operations	(239,142)	(1,509,387)	(2,514,887)	(1,404,317)
Other income (expense):				
Interest income (expense), net	(1,217)	(268)	(359)	—
Net loss	(240,359)	(1,509,655)	(2,515,246)	(1,404,317)
Accretion of redeemable convertible preferred stock	(87,954)	—	—	—
Net loss applicable to common stockholders	$ (328,313)	$ (1,509,655)	$ (2,515,246)	$ (1,404,317)
Net loss per share basic and diluted	$ (0.67)	$ (2.29)	$ (2.64)	$ (0.96)
Basic and diluted weighted average shares outstanding	490,760	659,944	954,167	1,462,101

The sum of the quarterly per share amounts may not equal per share amounts reported for the year due to rounding.

(1) The Company has corrected the amounts above to exclude contingently redeemable shares from the net loss per share basic and diluted and basic and diluted weighted average shares outstanding calculations for the first and second quarter. The Company had previously disclosed $0.74 net loss per share basic and diluted for the three months ended March 31, 2015 in the Company's Form S-1 and $0.80 net loss per share basic and diluted for the three months ended June 30, 2015 in the second quarter Form 10-Q.

Exhibit 21.1

Subsidiaries of Zynerba Pharmaceuticals, Inc.

Subsidiary	Jurisdiction of Incorporation
Zynerba Pharmaceuticals Pty Ltd	Australia

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors
Zynerba Pharmaceuticals, Inc.:

We consent to the incorporation by reference in the registration statement on Form S-8 (No. 333-207973) of Zynerba Pharmaceuticals, Inc. (formerly AllTranz, Inc.) of our report dated March 14, 2016, with respect to the consolidated balance sheets of Zynerba Pharmaceuticals, Inc. as of December 31, 2015 and 2014, and the related consolidated statements of operations, redeemable convertible preferred stock, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the years in the three-year period ended December 31, 2015, which report appears in the December 31, 2015 annual report on Form 10-K of Zynerba Pharmaceuticals, Inc.

/s/ KPMG LLP

Philadelphia, Pennsylvania
March 14, 2016

Exhibit 31.1

CERTIFICATION

I, Armando Anido, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: March 14, 2016

Exhibit 31.2

CERTIFICATION

I, Richard A. Baron, certify that:

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

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

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

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

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

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

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

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

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

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

By: /s/ Richard A. Baron
Name: Richard A. Baron
Title: Chief Financial Officer and Treasurer

Dated: March 14, 2016

Exhibit 32.1

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

In connection with the annual report of Zynerba Pharmaceuticals, Inc. (the "Company") on Form 10-K for the fiscal year ended December 31, 2015 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Armando Anido, Chairman and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

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

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

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

Dated: March 14, 2016

Exhibit 32.2

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

In connection with the annual report of Zynerba Pharmaceuticals, Inc. (the "Company") on Form 10-K for the fiscal year ended December 31, 2015 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Richard A. Baron, Chief Financial Officer and Treasurer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

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

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

/s/ Richard A. Baron
Richard A. Baron
Chief Financial Officer and Treasurer

Dated: March 14, 2016