

The information in this preliminary prospectus supplement and the accompanying base prospectus is not complete and may be changed. A registration statement relating to the securities has been declared effective by the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying base prospectus are not offers to sell these securities, and we are not soliciting offers to buy these securities in any state or jurisdiction where the offer or sale is not permitted.

Subject to Completion, dated July 19, 2018.

PRELIMINARY PROSPECTUS SUPPLEMENT
(to Prospectus dated June 22, 2017)

Shares



Common Stock

We are offering _____ shares of our common stock with an aggregate offering price of \$ _____. The public offering price is \$ _____ per share.

Our common stock is listed on The Nasdaq Global Market under the symbol "ZYNE." On July 18, 2018, the last reported sale price per share of our common stock was \$10.18 per share.

We are an "emerging growth company" as defined under the federal securities laws and, as such, have elected to comply with certain reduced public company reporting requirements.

Investing in our common stock involves risks. Before buying any shares, you should read the discussion of material risks of investing in our common stock in "Risk Factors" beginning on page S-10 of this prospectus supplement, on page 4 of the accompanying prospectus and in the documents incorporated by reference in this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	<u>PER SHARE</u>	<u>TOTAL</u>
Public offering price	\$ _____	\$ _____
Underwriting discounts and commissions (1)	\$ _____	\$ _____
Proceeds to us, before expenses	\$ _____	\$ _____

(1) We have agreed to reimburse the underwriters for certain of their reasonable out-of-pocket expenses. See "Underwriting" beginning on page S-16 for more information on this offering and the underwriting agreement.

Delivery of the shares of common stock in this offering is expected to be made on or about July _____, 2018. We have granted the underwriters an option for a period of 30 days to purchase up to _____ additional shares of our common stock. If the underwriters exercise this option in full, the total underwriting discounts and commissions payable by us will be \$ _____ and the total proceeds to us, before expenses, will be \$ _____.

Sole Book-Running Manager

Cantor

The date of this prospectus supplement is July _____, 2018

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying base prospectus are part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a “shelf” registration process. The prospectus supplement describes the specific terms of this offering and also adds to and updates the information contained in the accompanying base prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying base prospectus. The accompanying base prospectus gives more general information, some of which may not apply to this offering. If there is a difference between the information contained in this prospectus supplement and the information contained in the accompanying base prospectus or any document incorporated by reference having an earlier date than the date of this prospectus supplement, you should rely on the information in this prospectus supplement. Generally, when we refer to the prospectus, we are referring to this prospectus supplement and the accompanying base prospectus combined, together with the documents incorporated by reference herein or therein.

You should rely only on the information contained or incorporated by reference in this prospectus supplement, in the accompanying base prospectus, or contained in any free writing prospectus with respect to this offering filed by us with the SEC, including the additional information under the captions “Incorporation of Certain Information by Reference” and “Where You Can Find More Information” in this prospectus supplement. We have not, and the underwriters have not, authorized anyone to provide you with different information. You should assume that the information appearing in this prospectus supplement or the accompanying base prospectus and the documents incorporated by reference herein or therein, and in any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates.

We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying base prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying base prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying base prospectus outside the United States. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. This prospectus supplement and the accompanying base prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying base prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any filing that is incorporated or deemed to be incorporated by reference into this prospectus supplement or the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

Unless the context otherwise requires or as otherwise expressly stated, references in this prospectus supplement to the “Company,” “Zynerba,” “we,” “us,” “our” and similar terms refer to Zynerba Pharmaceuticals, Inc. and its subsidiary, Zynerba Pharmaceuticals Pty Ltd.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Any statements in this prospectus supplement, the base prospectus, or contained in any free writing prospectus with respect to this offering filed by us with the SEC, and the information incorporated herein and therein by reference relating to future financial or business performance, conditions or strategies and other financial and business matters that are not descriptions of historical facts, including expectations regarding future revenues and operating expenses and timing and outcome of our drug development programs, are forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Our forward-looking statements are based on management's estimates, assumptions, and projections that are subject to risks and uncertainties. These statements can generally be identified by the use of forward-looking words such as "believe," "expect," "intend," "may," "will," "should," "anticipate," "estimate" or similar terminology. Although we believe that the expectations reflected in our forward-looking statements are reasonable as of the date we make them, actual results could differ materially from those currently anticipated due to a number of factors, including risks relating to:

- our estimates regarding expenses, future revenue, capital requirements and timing and availability of and the need for additional financing;
- the results, cost and timing of our preclinical studies and clinical trials, including any delays to such clinical trials relating to enrollment or site initiation, as well as the number of required trials for regulatory approval and the criteria for success in such trials;
- our dependence on third parties in the conduct of our preclinical studies and clinical trials;
- legal and regulatory developments in the United States and foreign countries, including any actions or advice that may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional clinical trials;
- the difficulties and expenses associated with obtaining and maintaining regulatory approval of our product candidates, and the indication and labeling under any such approval;
- our plans and ability to develop and commercialize our product candidates;
- the successful development of our commercialization capabilities, including sales and marketing capabilities, whether alone or with potential future collaborators;
- the size and growth of the potential markets for our product candidates, the rate and degree of market acceptance of our product candidates and our ability to serve those markets;
- the success of competing therapies and products that are or become available;
- our ability to limit our exposure under product liability lawsuits;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- recently enacted and future legislation regarding the healthcare system, including changes to the Patient Protection and Affordable Care Act;
- our ability to obtain and maintain third-party manufacturing for our product candidates on commercially reasonable terms;

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- delays, interruptions or failures in the manufacture and supply of our product candidates;
- the performance of third parties upon which we depend, including contract research organizations, contract manufacturing organizations, contractor laboratories and independent contractors; and
- our ability to recruit or retain key scientific, commercial or management personnel or to retain our executive officers.

Further information on the factors and risks that could affect our business, financial condition and results of operations are set forth in this prospectus supplement under “Risk Factors” and in our filings with the SEC, which are available at <http://www.sec.gov>. Any forward-looking statement speaks only as of the date on which it is made, and we undertake no obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the date of this prospectus or the date of any later-filed free writing prospectus or documents incorporated by reference herein.

PROSPECTUS SUPPLEMENT SUMMARY

This summary description about us, our business and this offering highlights selected information contained elsewhere in this prospectus supplement or incorporated in this prospectus supplement by reference. This summary does not contain all of the information you should consider before deciding to invest in our common stock. You should carefully read this entire prospectus supplement, the accompanying base prospectus and any free writing prospectus with respect to this offering filed by us with the SEC, including each of the documents incorporated herein or therein by reference, before making an investment decision. Investors should carefully consider the information set forth under “Risk Factors” on page S-10 and in the documents incorporated by reference into this prospectus supplement or the accompanying base prospectus.

Company Overview

We are a clinical stage pharmaceutical company dedicated to the development and commercialization of pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders. We are committed to improving the lives of patients and their families living with severe, chronic health conditions including Fragile X syndrome, or FXS, and refractory epilepsies.

We are currently evaluating ZYN002, a patent protected transdermal cannabidiol, or CBD, gel for the treatment of FXS, developmental and epileptic encephalopathy, or DEE, and adult refractory epilepsy. In 2017, we completed three Phase 2 clinical trials for ZYN002 and two of those studies have open-label extensions that are ongoing. In April 2018, we initiated a Phase 2 clinical trial evaluating ZYN002 in DEE in pediatric and adolescent patients, and in July 2018, we initiated what we believe will be a pivotal clinical trial evaluating ZYN002 in children and adolescents with FXS. In 2018, we also plan to initiate an additional clinical trial evaluating ZYN002 for the treatment of refractory focal seizures in adults with epilepsy.

Our pipeline also includes ZYN001, a pro-drug of Δ^9 -tetrahydrocannabinol, or THC. We were previously evaluating ZYN001 and ZYN002 for pain indications and evaluating ZYN001 for the treatment of Tourette Syndrome, or TS. In January 2018, we decided to discontinue our development programs in the capital-intensive pain spaces and, in July 2018, following receipt of top line results from our Phase 1 study for ZYN001, we decided to focus our development efforts and investments on our development programs for ZYN002 for the treatment of FXS, DEE and refractory focal seizures in adults with epilepsy.

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 behavioral symptoms of FXS and epilepsy. We believe ZYN002 may potentially offer first-line therapies to patients suffering from FXS, DEE and focal seizures in adults with epilepsy.

ZYN002

ZYN002 is the first and only pharmaceutically-produced 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 of CBD when delivered transdermally. In addition, an in vitro study published in Cannabis and Cannabinoid Research in April 2016 demonstrated that CBD is degraded to THC in an acidic environment such as the stomach. We believe such degradation may lead to increased psychoactive effects if CBD is delivered orally and may be avoided 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 behavioral symptoms of FXS and DEE in pediatric and adolescent patients and refractory focal seizures in adults with epilepsy. We have been granted orphan drug designation from the FDA for the use of CBD for the treatment of FXS. In our Phase 1 program, ZYN002 was demonstrated to be safe

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and well tolerated, provided a favorable CBD pharmacokinetic profile, and no THC was detected in plasma or urine. The ZYN002 safety database across all clinical studies conducted by us includes data from 570 volunteers and patients. Across these clinical studies, ZYN002 has been well tolerated, consistent with previously reported clinical data.

In April, 2018, we initiated the Phase 2 BELIEVE 1 (Open Label Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Developmental and Epileptic Encephalopathy) clinical trial, a six-month open label multi-dose clinical trial designed to evaluate the efficacy and safety of ZYN002 in children and adolescents (three to <18 years) with DEE as classified by the International League Against Epilepsy (ILAE) (Scheffer et al. 2017). Approximately 50 patients with confirmed DEE will be enrolled in the clinical trial, approximately half of whom may have either Dravet or Lennox-Gastaut syndrome. Enrolled patients will receive weight-based initial doses of 125 mg BID (250 mg daily) or 250 mg BID (500 mg daily) of ZYN002 CBD gel. The primary endpoint is change in seizure frequency from baseline. We expect to report top line results from the BELIEVE 1 trial in 2019.

In July 2018 we initiated a randomized, double blind placebo controlled Clinical study of Cannabidiol (CBD) in Children and Adolescents with Fragile X (CONNECT-FX). The study will evaluate the efficacy and safety of ZYN002 in children ages three to 17 with full mutation FXS. Top line results are expected in the second half of 2019.

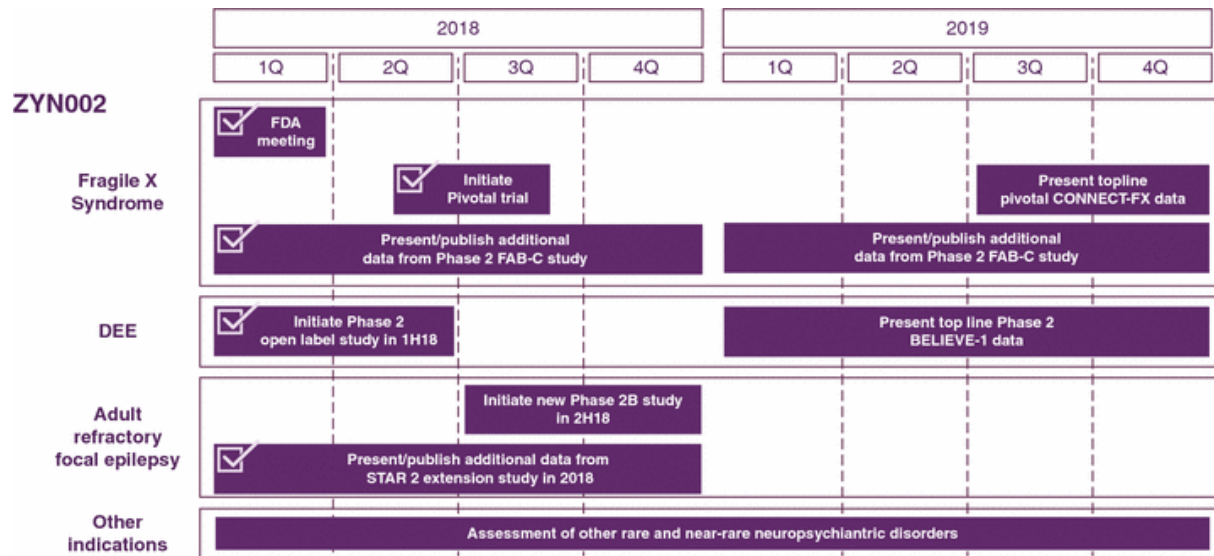
The CONNECT-FX study is a multi-national randomized, double-blind, placebo-controlled, 14-week study that will assess the efficacy and safety of ZYN002 for the treatment of children and adolescents with FXS. Approximately 200 male and female patients with FXS, confirmed with the full mutation of the FMR1 gene, will be enrolled at approximately 20 clinical sites in the United States, Australia, and New Zealand. Patients will be randomized 1:1 to either trial drug or placebo. Randomization will be stratified by gender, weight, and investigator geographic region. The primary endpoint is the change from baseline to the end of the treatment period in the Aberrant Behavior Checklist-Community FXS Specific (ABC-C_{FXS}) Social Avoidance subscale. Key secondary endpoints are the change from baseline to the end of the treatment period in the ABC-C_{FXS} Irritability subscale score, the ABC-C_{FXS} Socially Unresponsive/Lethargic subscale score, and improvement in Clinical Global Impression - Improvement (CGI-I) at the end of the treatment period. Based on discussions with the FDA, we will anchor the CGI-I scale to behavioral symptoms of FXS. Consistent with recent guidance from the FDA on capturing the voice of the patient in drug development, additional qualitative data on the clinical relevance of various FXS behaviors to caregivers and patients will be collected. If we obtain positive results from this trial, we plan to request a meeting with the FDA to determine the acceptability of these data as the basis for an NDA filing.

ZYN001

ZYN001 is a pro-drug of THC that was developed to enable transdermal delivery of THC 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 enzymatic process. In our preclinical animal studies, ZYN001 demonstrated effective skin permeation with sustained delivery and rapid conversion of ZYN001 to THC. These preclinical studies suggested increased bioavailability, consistent plasma levels and the avoidance of first-pass liver metabolism of ZYN001. In addition, preclinical testing showed no genotoxicity findings and safety pharmacology findings consistent with those seen with THC. ZYN001 was targeting treatment of TS. In July 2018, we announced top line results of our Phase 1 clinical trials in ZYN001, which indicated that target blood levels of 5 to 15 ng/ml THC were not achieved. As a result of these data, we have decided to focus our development efforts and investments on our development programs for ZYN002 for the treatment of FXS, DEE and refractory focal seizures in adults with epilepsy.

ZYN002 Clinical Development Timelines

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



Financial Information

We have never been profitable and have incurred net losses since inception. Our net losses were \$32.0 million, \$23.4 million and \$12.6 million for the years ended December 31, 2017, 2016 and 2015, respectively, and \$12.3 million and \$7.3 million for the three months ended March 31, 2018 and 2017, respectively. As of March 31, 2018, our accumulated deficit was \$90.3 million. We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability.

In June 2017, we entered into an Open Market Sales Agreement, or Sales Agreement, with Jefferies LLC, or Jefferies, pursuant to which we may sell, from time to time, up to \$50.0 million of our common stock. During 2017, we sold and issued 296,594 shares of common stock in the open market at a weighted average selling price of \$10.74 per share, for net proceeds of \$3.0 million. We have not sold any shares of common stock under the Sales Agreement during 2018.

Recent Developments

Financial Results as of June 30, 2018

Based on information currently available, we estimate that as of June 30, 2018 cash and cash equivalents were approximately \$43.1 million.

Our estimate of our cash and cash equivalents as of June 30, 2018 is preliminary and actual results may differ from this estimate due to the completion of our closing procedures with respect to the fiscal quarter ended June 30, 2018, final adjustments and other developments that may arise between now and the time the financial results for the fiscal quarter ended June 30, 2018 are finalized. As such, this estimate should not be viewed as a substitute for our interim unaudited financial statements for the fiscal quarter ended June 30, 2018 prepared in accordance with U.S. generally accepted accounting principles. Our expected results could change materially and are not necessarily indicative of the results to be achieved

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for the fiscal quarter ended June 30, 2018 or any future period. As a result of the foregoing considerations and the other limitations described herein, investors are cautioned not to place undue reliance on this preliminary financial information. We do not undertake any obligation to publicly update or revise this estimate, except as required by law.

Corporate Information

Our principal 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 <http://www.zynerba.com>. The information contained in, or that can be accessed through, our website is not part of this prospectus supplement. We make available free of charge on our website our annual, quarterly and current reports, including amendments to such reports, as soon as reasonably practicable after we electronically file such material with, or furnish such material to, the SEC.

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. We will remain an “emerging growth company” until the earliest of (1) the beginning of the first fiscal year following the fifth anniversary of our initial public offering, or January 1, 2021, (2) the beginning of the first fiscal year after our annual gross revenue is \$1.07 billion or more, (3) the date on which we have, during the previous three-year period, issued more than \$1.0 billion in non-convertible debt securities and (4) as of the end of any fiscal year in which the market value of our common stock held by non-affiliates exceeded \$700 million as of the end of the second quarter of that fiscal year. For as long as we remain an “emerging growth company”, we may take advantage of certain exemptions from various disclosure and reporting requirements that are applicable to other public companies that are not “emerging growth companies” including, but not limited to:

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

We 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 \$1.07 billion or we issue more than \$1.0 billion of non-convertible debt in any three-year period, we will cease to be an “emerging growth company” prior to the end of such period.

We have elected to take advantage of certain of the reduced disclosure obligations in the documents incorporated by reference into this prospectus supplement 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

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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.”

THE OFFERING

Common stock to be offered by us	shares
Common stock to be outstanding immediately following this offering	shares (or shares if the underwriters' option described below is exercised in full)
Option to purchase additional shares from us	We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to additional shares of our common stock.
Use of proceeds	We intend to use the net proceeds from this offering to support the clinical development of ZYN002, for additional research and development, and for general corporate purposes, which may include capital expenditures and funding our working capital needs. See "Use of Proceeds" on page S-13.
Risk Factors	Investing in our common stock involves a high degree of risk. See "Risk Factors" and other information included in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying base prospectus for a discussion of factors you should carefully consider before deciding to invest in shares of our common stock.
Nasdaq Global Market symbol	ZYNE

The number of shares of common stock outstanding immediately following this offering set forth above is based on 13,561,373 shares of our common stock outstanding as of June 30, 2018, and excludes:

- 3,222,413 shares of our common stock issuable upon the exercise of stock options outstanding as of June 30, 2018 at a weighted-average exercise price of \$12.27 per share, of which 1,591,565 options were vested as of June 30, 2018; and
- 1,086,663 shares of our common stock available for future issuance as of June 30, 2018 under our Amended and Restated 2014 Omnibus Incentive Compensation Plan, or the 2014 Plan.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of the outstanding options described above and no exercise by the underwriters of their option to purchase additional shares of our common stock.

RISK FACTORS

An investment in our common stock involves a high degree of risk. Our business, financial condition and results of operations could be materially and adversely affected by any of these risks. If any of these risks occur, the value of our common stock may decline and you may lose all or part of your investment. Before investing in our common stock, you should consider carefully the risk factors set forth in this prospectus supplement, the accompanying base prospectus and contained in any free writing prospectus with respect to this offering filed by us with the SEC, along with the risk factors described in “Item 1A. Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2017, as updated by other filings we make with the SEC incorporated by reference into this prospectus supplement.

Risks Related to This Offering

Our management team may invest or spend the proceeds of this offering in ways with which you may not agree or in ways which may not yield a significant return.

We currently intend to use the net proceeds from this offering to support the clinical development of ZYN002, for additional research and development, and for general corporate purposes, which may include capital expenditures and funding our working capital needs. However, we have not determined the specific allocation of the net proceeds among these potential uses. Our management will have broad discretion over the use and investment of the net proceeds of this offering, and, accordingly, investors in this offering will need to rely upon the judgment of our management with respect to the use of proceeds, with only limited information concerning our specific intentions. These proceeds could be applied in ways that do not improve our operating results or increase the value of your investment. Please see the section entitled “Use of Proceeds” on page S-13 of this prospectus supplement for further information.

If you purchase our common stock in this offering, you will experience immediate and substantial dilution in your investment.

Since the public offering price per share of our common stock is substantially higher than the net tangible book value per share of our common stock, you will suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering. Specifically, investors purchasing shares of common stock in this offering will incur immediate dilution of approximately \$ _____ per share, based upon our net tangible book value as of March 31, 2018, after giving effect to this offering. For a further description of the dilution that you will experience immediately after this offering, see the section in this prospectus supplement entitled “Dilution” on page S-15.

Issuances of shares of common stock or securities convertible into or exercisable for shares of common stock following this offering, as well as the exercise of options, will dilute your ownership interests and may adversely affect the future market price of our common stock.

As a development stage company we will need additional capital to fund the development and commercialization of our 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, which may cause your ownership interest to be diluted. We may also sell substantial amounts of common stock under our Sales Agreement with Jefferies. In addition, as of June 30, 2018, there were options to purchase approximately 3.2 million shares of our common stock outstanding at a weighted average exercise price of \$12.27. If these securities are exercised, you may incur further dilution. Moreover, to the extent that we issue additional options to purchase, or securities convertible into or exchangeable for, shares of our common stock in the future and those options or other securities are exercised, converted or exchanged, you may experience further dilution.

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A substantial number of shares may be sold in the market following this offering, which may depress the market price for our common stock.

Sales of a substantial number of shares of our common stock in the public market following this offering could cause the market price of our common stock to decline. Upon completion of this offering, based on our shares outstanding as of June 30, 2018, we will have _____ shares of common stock outstanding, assuming no exercise of the underwriters' option to purchase additional shares of common stock. Of these shares, 620,743 shares are subject to a contractual lock-up with the underwriters for this offering for a period of 90 days following this offering. These shares can be sold, subject to any applicable volume limitations under federal securities laws, after the earlier of the expiration of, or release from, the 90-day lock-up period. The balance of our outstanding shares of common stock, including any shares purchased in this offering, may be resold into the public market immediately without restriction, unless these shares are owned or purchased by "affiliates" as that term is defined in Rule 144 under the Securities Act of 1933, as amended, or the Securities Act.

As of June 30, 2018, there were approximately 3.2 million shares subject to outstanding options granted pursuant to equity incentive arrangements and we have registered the exercise of these options and sale of the underlying shares of common stock under the Securities Act on a registration statement on Form S-8. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described above, to the extent applicable.

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 prospectus or the documents incorporated by reference herein, these factors include:

- results of clinical trials of our product candidates or product candidates of our competitors;
- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- the success of competitive products;
- actual or anticipated changes in our growth rate relative to our competitors;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to our preclinical and clinical development programs;

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- 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;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our common stock;
- announcements or expectations 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.

USE OF PROCEEDS

We estimate that the net proceeds we will receive from this offering will be approximately \$ million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds from this offering will be approximately \$ million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering to continue to support the clinical development of ZYN002, for additional research and development, and for general corporate purposes, which may include capital expenditures and funding our working capital needs.

We have not determined the amount of net proceeds to be used specifically for such purposes and, as a result, management will retain broad discretion over the allocation of net proceeds. The occurrence of unforeseen events, changed business conditions or numerous other factors, including our ability to gain access to additional financing, the relative success and cost of our research, preclinical and clinical development programs and whether we are able to enter into future licensing or collaboration arrangements, could result in the application of the net proceeds from this offering in a manner other than as described in this prospectus supplement. Pending their ultimate use, we intend to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

PRICE RANGE OF OUR COMMON STOCK

Our common stock has been traded on The Nasdaq Global Market since August 5, 2015 under the symbol “ZYNE.” The following table sets forth the range of high and low sales price of our common stock, as quoted on The Nasdaq Global Market, for the period indicated:

	<u>High</u>	<u>Low</u>
2018		
Third Quarter (through July 18, 2018)	\$ 10.88	\$ 7.65
Second Quarter	\$ 12.50	\$ 7.88
First Quarter	\$ 14.45	\$ 8.34
2017		
Fourth Quarter	\$ 15.14	\$ 8.39
Third Quarter	\$ 20.00	\$ 5.42
Second Quarter	\$ 25.95	\$ 16.27
First Quarter	\$ 23.75	\$ 15.80
2016		
Fourth Quarter	\$ 16.91	\$ 10.56
Third Quarter	\$ 14.44	\$ 6.62
Second Quarter	\$ 11.68	\$ 6.02
First Quarter	\$ 21.56	\$ 4.64

On July 18, 2018, the closing price of our common stock on The Nasdaq Global Market was \$10.18 per share. As of July 18, 2018, there were approximately 34 holders of record of our common stock. This does not include the number of persons whose stock is in nominee or “street name” accounts through brokers.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our stock and do not anticipate paying any cash dividends in the foreseeable future. We expect to retain available cash to finance ongoing operations and the potential growth of our business. Any future determination to pay dividends on our common stock will be at the discretion of our board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements, business prospects and other factors our board of directors may deem relevant, and subject to the restrictions contained in any future financing instruments.

DILUTION

Purchasers of our common stock in this offering will experience immediate dilution to the extent of the difference between the public offering price per share of our common stock and the as adjusted net tangible book value per share of our common stock upon closing of this offering. Net tangible book value per share of our common stock is determined at any date by subtracting our total liabilities from the amount of our total tangible assets (total assets less intangible assets) and dividing the difference by the number of shares of our common stock deemed to be outstanding at that date.

Our historical net tangible book value as of March 31, 2018 was \$50.3 million, or \$3.71 per share, based on 13,561,373 shares of common stock outstanding as of March 31, 2018. After giving effect to the sale of _____ shares of common stock in this offering at the public offering price of \$ _____ per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of March 31, 2018, would have been \$ _____ million, or \$ _____ per share. This amount represents an immediate increase in net tangible book value of \$ _____ per share of our common stock to existing stockholders and an immediate dilution in net tangible book value of \$ _____ per share of our common stock to investors participating in this offering.

The following table illustrates this per share dilution to new investors purchasing shares of common stock in this offering:

Public offering price per share		\$
Net tangible book value per share as of March 31, 2018	\$	3.71
Increase in net tangible book value per share attributable to investors participating in this offering		_____
Net tangible book value per share after this offering		_____
Dilution per share to investors participating in this offering		\$ _____

If the underwriters exercise their option to purchase additional shares in full, at the public offering price of \$ _____ per share, the net tangible book value will increase to \$ _____ per share, representing an immediate increase in net tangible book value to existing stockholders of \$ _____ per share and immediate dilution in net tangible book value of \$ _____ per share to investors participating in this offering.

The foregoing table and calculations are based on 13,561,373 shares of our common stock outstanding as of March 31, 2018, and excludes:

- 3,043,908 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2018 at a weighted-average exercise price of \$12.36 per share, of which 1,375,035 options were vested as of March 31, 2018; and
- 1,265,168 shares of our common stock available for future issuance as of March 31, 2018 under the 2014 Plan.

To the extent that any options are exercised, new options are issued under our equity incentive plans or we otherwise issue additional shares of common stock in the future at a price less than the public offering price, there may be further dilution to investors participating in this offering.

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement, dated July , 2018, between us and Cantor Fitzgerald & Co., 499 Park Avenue, New York, New York 10022, as the representative of the underwriters named below (the “Representative”) and the sole book-running manager of this offering, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the shares of common stock shown opposite its name below:

UNDERWRITER	NUMBER OF SHARES
Cantor Fitzgerald & Co.	
Total	

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers’ certificates and legal opinions and approval of certain legal matters by their counsel. The underwriting agreement provides that the underwriters will purchase all of the shares of common stock if any of them are purchased, other than the shares of our common stock that are subject to the option referred to below. We have agreed to indemnify the underwriters and certain of their controlling persons against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares of common stock subject to their acceptance of the shares of common stock from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Option to Purchase Additional Shares

We have granted to the underwriters an option, exercisable through and including the 30th day after the date of this prospectus supplement, to purchase, from time to time, in whole or in part, up to an aggregate of shares from us at the public offering price set forth on the cover page of this prospectus supplement, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to certain conditions, to purchase a number of additional shares approximately proportionate to that underwriter’s initial purchase commitment as indicated in the table above.

Commissions and Expenses

The underwriters have advised us that they propose to offer the shares of common stock to the public initially at the public offering price set forth on the cover page of this prospectus supplement and to certain dealers, which may include the underwriters, at that price less a concession not in excess of \$ per share of common stock. The underwriters may allow, and certain dealers may reallow, a discount from the concession not in excess of \$ per share of common stock to certain brokers and dealers. After the initial offering, the Representative may change the offering price and other selling terms.

The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters’ option to purchase additional shares.

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	PER SHARE		TOTAL	
	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares	Without Option to Purchase Additional Shares	With Option to Purchase Additional Shares
Public offering price	\$	\$	\$	\$
Underwriting discounts and commissions	\$	\$	\$	\$
Proceeds to us, before expenses	\$	\$	\$	\$

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately \$. We have also agreed to reimburse the underwriters for up to \$20,000 of certain of their counsels' fees and expenses, which reimbursed fee is deemed underwriting compensation for this offering by FINRA.

Listing

Our common stock is listed on The Nasdaq Global Market under the trading symbol "ZYNE."

No Sales of Similar Securities

We, our officers and our directors have agreed, subject to certain specified exceptions, not to directly or indirectly:

- sell, offer to sell, contract to sell or lend, pledge, hypothecate or grant any security interest in, transfer, effect any short sale or establish or increase a "put equivalent position" or liquidate or decrease "call equivalent position," each within the meaning of Rule 16a-1(h) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise dispose of any shares of common stock, options or warrants to acquire shares of common stock, or securities exchangeable or exercisable for or convertible into shares of common stock currently or hereafter owned either of record or beneficially, or
- engage in any swap, hedge or similar arrangement or agreement that transfers, in whole or in part, the economic risk of ownership of any shares of common stock, options, or warrants, regardless of whether any such transaction is to be settled in securities, in cash or otherwise, or
- make any demand for, or exercise any right with respect to, the registration under the Securities Act of the offer and sale of any shares of common stock, or securities exchangeable or exercisable for or convertible into shares of common stock, or cause to be filed a registration statement, prospectus or prospectus supplement (or an amendment or supplement thereto) with respect to any such registration, or
- publicly announce an intention to do any of the foregoing for a period of 90 days after the date of this prospectus without the prior written consent of Cantor Fitzgerald & Co.

This restriction terminates after the close of trading of the common stock on the 90th day after the date of this prospectus.

The exceptions to such agreements permit a party to the agreement, among other things and subject to restrictions, to: (a) make certain gifts and transfers upon death; (b) make certain transfers pursuant to a qualified domestic relations order; (c) exercise, convert or exchange any options, warrants or convertible securities into shares of common stock, provided, that these restrictions shall apply to any shares of common stock issued in connection with such exercise, conversion or exchange, except with respect to any shares withheld by us to cover tax liabilities; and (d) establish any trading plan pursuant to Rule

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10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that such plan does not provide for any sales to be made until the termination of these restrictions.

Cantor Fitzgerald & Co. may, in its sole discretion and at any time or from time to time before the termination of the 90-day period release all or any portion of the securities subject to lock-up agreements. There are no existing agreements between the underwriters and any of our shareholders who will execute a lock-up agreement, providing consent to the sale of shares prior to the expiration of the lock-up period.

Market Making, Stabilization and Other Transactions

The underwriters may make a market in the common stock as permitted by applicable laws and regulations. However, the underwriters are not obligated to do so, and the underwriters may discontinue any market-making activities at any time without notice in their sole discretion. Accordingly, no assurance can be given as to the liquidity of the trading market for the common stock, that you will be able to sell any of the common stock held by you at a particular time or that the prices that you receive when you sell will be favorable.

The underwriters have advised us that they, pursuant to Regulation M under the Securities Exchange Act of 1934, as amended, and certain persons participating in the offering may engage in short sale transactions, stabilizing transactions, syndicate covering transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the common stock at a level above that which might otherwise prevail in the open market. Establishing short sales positions may involve either “covered” short sales or “naked” short sales.

“Covered” short sales are sales made in an amount not greater than the underwriters’ option to purchase additional shares of our common stock in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares of our common stock or purchasing shares of our common stock in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares.

“Naked” short sales are sales in excess of the option to purchase additional shares of our common stock. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of shares of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the common stock. A syndicate covering transaction is the bid for or the purchase of shares of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. Similar to other purchase transactions, the underwriters’ purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the common stock originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

Neither we, nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. The underwriters are not obligated to engage in these activities and, if commenced, may end any of these activities at any time.

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Passive Market Making

The underwriters may also engage in passive market making transactions in our common stock on The NASDAQ Global Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of those transactions. The underwriters are not required to engage in passive market making and, if commenced, may end passive market making activities at any time.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or on the web sites or through online services maintained by one or more of the underwriters or their affiliates. The underwriters may agree with us to allocate a specific number of shares of common stock for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters' web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus supplement, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

The underwriters and certain of their affiliates are full service financial institutions engaged in a wide range of activities for their own accounts and the accounts of customers, which may include, among other things, corporate finance, mergers and acquisitions, merchant banking, equity and fixed income sales, trading and research, derivatives, foreign exchange, futures, asset management, custody, clearance and securities lending. The underwriters and certain of their affiliates have, from time to time, performed, and may in the future perform, various investment banking and financial advisory services for us and our affiliates, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their businesses, the underwriters and their respective affiliates may, directly or indirectly, hold long or short positions, trade and otherwise conduct such activities in or with respect to debt or equity securities and/or bank debt, and/or derivative products. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Stamp Taxes

If you purchase shares of common stock offered in this prospectus supplement, you may be required to pay stamp taxes and other charges under the laws and practices of the country of purchase, in addition to the offering price listed on the cover page of this prospectus supplement.

NOTICE TO INVESTORS

Canada

This prospectus supplement constitutes an "exempt offering document" as defined in and for the purposes of applicable Canadian securities laws. No prospectus has been filed with any securities commission or similar regulatory authority in Canada in connection with the offer and sale of the common stock. No securities commission or similar regulatory authority in Canada has reviewed or in any way

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passed upon this prospectus supplement or on the merits of the common stock and any representation to the contrary is an offence.

Canadian investors are advised that this prospectus supplement has been prepared in reliance on section 3A.3 of National Instrument 33-105 *Underwriting Conflicts* (“NI 33-105”). Pursuant to section 3A.3 of NI 33-105, this prospectus supplement is exempt from the requirement that we and the underwriter(s) provide investors with certain conflicts of interest disclosure pertaining to “connected issuer” and/or “related issuer” relationships that may exist between us and the underwriter(s) as would otherwise be required pursuant to subsection 2.1(1) of NI 33-105.

Resale Restrictions

The offer and sale of the common stock in Canada is being made on a private placement basis only and is exempt from the requirement that we prepare and file a prospectus under applicable Canadian securities laws. Any resale of the common stock acquired by a Canadian investor in this offering must be made in accordance with applicable Canadian securities laws, which may vary depending on the relevant jurisdiction, and which may require resales to be made in accordance with Canadian prospectus requirements, pursuant to a statutory exemption from the prospectus requirements, in a transaction exempt from the prospectus requirements or otherwise under a discretionary exemption from the prospectus requirements granted by the applicable local Canadian securities regulatory authority. These resale restrictions may under certain circumstances apply to resales of the common stock outside of Canada.

Representations of Purchasers

Each Canadian investor who purchases the common stock will be deemed to have represented to us and the underwriter(s) that the investor (i) is purchasing the common stock as principal, or is deemed to be purchasing as principal in accordance with applicable Canadian securities laws, for investment only and not with a view to resale or redistribution; (ii) is an “accredited investor” as such term is defined in section 1.1 of National Instrument 45-106 *Prospectus Exemptions* (“NI 45-106”) or, in Ontario, as such term is defined in section 73.3(1) of the *Securities Act* (Ontario); and (iii) is a “permitted client” as such term is defined in section 1.1 of National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*.

Taxation and Eligibility for Investment

Any discussion of taxation and related matters contained in this prospectus supplement does not purport to be a comprehensive description of all of the tax considerations that may be relevant to a Canadian investor when deciding to purchase the common stock and, in particular, does not address any Canadian tax considerations. No representation or warranty is hereby made as to the tax consequences to a resident, or deemed resident, of Canada of an investment in the common stock or with respect to the eligibility of the common stock for investment by such investor under relevant Canadian federal and provincial legislation and regulations.

Rights of Action for Damages or Rescission

Securities legislation in certain of the Canadian jurisdictions provides certain purchasers of securities pursuant to an offering memorandum (such as this prospectus supplement), including where the distribution involves an “eligible foreign security” as such term is defined in Ontario Securities Commission Rule 45-501 *Ontario Prospectus and Registration Exemptions* and in Multilateral Instrument 45-107 *Listing Representation and Statutory Rights of Action Disclosure Exemptions*, as applicable, with a remedy for damages or rescission, or both, in addition to any other rights they may have at law, where the offering memorandum, or other offering document that constitutes an offering memorandum, and any amendment thereto, contains a “misrepresentation” as defined under applicable Canadian securities laws. These remedies, or notice with respect to these remedies, must be exercised or delivered, as the

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case may be, by the purchaser within the time limits prescribed under, and are subject to limitations and defences under, applicable Canadian securities legislation. In addition, these remedies are in addition to and without derogation from any other right or remedy available at law to the investor.

Language of Documents

Upon receipt of this document, each Canadian investor hereby confirms that it has expressly requested that all documents evidencing or relating in any way to the sale of the securities described herein (including for greater certainty any purchase confirmation or any notice) be drawn up in the English language only. *Par la réception de ce document, chaque investisseur Canadien confirme par les présentes qu'il a expressément exigé que tous les documents faisant foi ou se rapportant de quelque manière que ce soit à la vente des valeurs mobilières décrites aux présentes (incluant, pour plus de certitude, toute confirmation d'achat ou tout avis) soient rédigés en anglais seulement.*

Australia

This prospectus is not a disclosure document for the purposes of Australia's Corporations Act 2001 (Cth) of Australia, or Corporations Act, has not been lodged with the Australian Securities & Investments Commission and is only directed to the categories of exempt persons set out below. Accordingly, if you receive this prospectus in Australia:

You confirm and warrant that you are either:

- a "sophisticated investor" under section 708(8)(a) or (b) of the Corporations Act;
- a "sophisticated investor" under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to the company which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made; or
- a "professional investor" within the meaning of section 708(11)(a) or (b) of the Corporations Act.

To the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor or professional investor under the Corporations Act any offer made to you under this prospectus is void and incapable of acceptance.

You warrant and agree that you will not offer any of the shares issued to you pursuant to this prospectus for resale in Australia within 12 months of those securities being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

European Economic Area

In relation to each member state of the European Economic Area which has implemented the Prospectus Directive, each referred to herein as a Relevant Member State, with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, referred to herein as the Relevant Implementation Date, no offer of any securities which are the subject of the offering contemplated by this prospectus has been or will be made to the public in that Relevant Member State other than any offer where a prospectus has been or will be published in relation to such securities that has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the relevant competent authority in that Relevant Member State in accordance with the Prospectus Directive, except that with effect from and including the Relevant Implementation Date, an offer of such securities may be made to the public in that Relevant Member State:

- to any legal entity which is a "qualified investor" as defined in the Prospectus Directive;
- to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors) as

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defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives of the underwriters for any such offer; or

- in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of securities shall require us or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

For the purposes of this provision, the expression an “offer to the public” in relation to any securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe the securities, as the same may be varied in that Relevant Member State by any measure implementing the Prospectus Directive in that Relevant Member State and the expression “Prospectus Directive” means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State and the expression “2010 PD Amending Directive” means Directive 2010/73/EU.

Hong Kong

No securities have been offered or sold, and no securities may be offered or sold, in Hong Kong, by means of any document, other than to persons whose ordinary business is to buy or sell shares or debentures, whether as principal or agent; or to “professional investors” as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or in other circumstances which do not result in the document being a “prospectus” as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32) of Hong Kong. No document, invitation or advertisement relating to the securities has been issued or may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance.

This prospectus has not been registered with the Registrar of Companies in Hong Kong. Accordingly, this prospectus may not be issued, circulated or distributed in Hong Kong, and the securities may not be offered for subscription to members of the public in Hong Kong. Each person acquiring the securities will be required, and is deemed by the acquisition of the securities, to confirm that he is aware of the restriction on offers of the securities described in this prospectus and the relevant offering documents and that he is not acquiring, and has not been offered any securities in circumstances that contravene any such restrictions.

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Japan

The offering has not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948 of Japan, as amended), or FIEL, and the Initial Purchaser will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means, unless otherwise provided herein, any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the FIEL and any other applicable laws, regulations and ministerial guidelines of Japan.

Singapore

This prospectus has not been and will not be lodged or registered with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or the invitation for subscription or purchase of the securities may not be issued, circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to the public or any member of the public in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person as defined under Section 275(2), or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions, specified in Section 275 of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of any other applicable provision of the SFA.

Where the securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- a corporation (which is not an accredited investor as defined under Section 4A of the SFA) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor,

shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for six months after that corporation or that trust has acquired the Offer Shares under Section 275 of the SFA except:

- to an institutional investor under Section 274 of the SFA or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than \$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions, specified in Section 275 of the SFA;
- where no consideration is given for the transfer; or
- where the transfer is by operation of law.

Switzerland

The securities may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This prospectus has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or

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regulated trading facility in Switzerland. Neither this prospectus nor any other offering or marketing material relating to the securities or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this prospectus nor any other offering or marketing material relating to the offering, we or the securities have been or will be filed with or approved by any Swiss regulatory authority. In particular, this prospectus will not be filed with, and the offer of securities will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of securities has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of securities.

Israel

This document does not constitute a prospectus under the Israeli Securities Law, 5728-1968, or the Securities Law, and has not been filed with or approved by the Israel Securities Authority. In the State of Israel, this document is being distributed only to, and is directed only at, and any offer of the shares is directed only at, investors listed in the first addendum, or the Addendum, to the Israeli Securities Law, consisting primarily of joint investment in trust funds, provident funds, insurance companies, banks, portfolio managers, investment advisors, members of the Tel Aviv Stock Exchange, underwriters, venture capital funds, entities with equity in excess of NIS 50 million and “qualified individuals”, each as defined in the Addendum (as it may be amended from time to time), collectively referred to as qualified investors (in each case purchasing for their own account or, where permitted under the Addendum, for the accounts of their clients who are investors listed in the Addendum). Qualified investors will be required to submit written confirmation that they fall within the scope of the Addendum, are aware of the meaning of same and agree to it.

United Kingdom

This prospectus is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors (as defined in the Prospectus Directive) that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, referred to herein as the Order, and/or (ii) high net worth entities falling within Article 49(2)(a) to (d) of the Order and other persons to whom it may lawfully be communicated. Each such person is referred to herein as a Relevant Person.

This prospectus and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a Relevant Person should not act or rely on this document or any of its contents.

MIFID II Product Governance

Any distributor subject to Directive 2014/65/EU, as amended (“MiFID II”) that is offering, selling or recommending the shares of common stock is responsible for undertaking its own target market assessment in respect of the shares of common stock and determining its own distribution channels for the purposes of the MiFID II product governance rules under Commission Delegated Directive (EU) 2017/593 (“Delegated Directive”). Neither the Company nor the underwriters make any representations or warranties as to a distributor’s compliance with the Delegated Directive.

LEGAL MATTERS

The legal validity of the securities offered by this prospectus supplement will be passed upon for us by Pepper Hamilton LLP, Philadelphia, Pennsylvania. Covington & Burling LLP, New York, New York is counsel for the underwriters in connection with this offering.

EXPERTS

The consolidated financial statements of Zynerva Pharmaceuticals, Inc. and subsidiary as of December 31, 2017 and 2016 and for each of the years in the three-year period ended December 31, 2017, have been incorporated by reference herein in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement we filed with the SEC. This prospectus does not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. You should rely only on the information contained in this prospectus or incorporated by reference. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus supplement is accurate as of any date other than the date on the front page of this prospectus supplement, regardless of the time of delivery of this prospectus or any sale of the securities offered by this prospectus.

We are currently subject to the reporting requirements of the Exchange Act, and in accordance therewith file periodic reports, proxy statements and other information with the SEC. You may read and copy any such reports, proxy statements and other information at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the public reference room. Our SEC filings are also available to you on the SEC's website at <http://www.sec.gov> and in the "Investor Relations" section of our website at <http://www.zynerba.com>. Our website and the information contained on that site, or connected to that site, are not incorporated into and are not a part of this prospectus supplement.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

We incorporate information into this prospectus by reference, which means that we disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, except to the extent superseded by information contained in this prospectus or in later-filed documents incorporated by reference in this prospectus. This prospectus incorporates by reference the documents set forth below, the file number for each of which is 001-37526, that have been previously filed with the SEC (other than, in each case, documents or information deemed to have been "furnished" and not "filed" in accordance with SEC rules):

- our Annual Report on Form 10-K for the year ended December 31, 2017, filed with the SEC on March 12, 2018 (including the portions of our proxy statement for our 2018 annual meeting of stockholders incorporated by reference therein);
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2018, filed with the SEC on May 8, 2018;
- our Current Reports on Form 8-K (other than portions thereof furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits accompanying such reports that are related to such

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items, unless specifically stated to the contrary) filed with the SEC on January 4, 2018, January 30, 2018, March 5, 2018, April 10, 2018, April 16, 2018, April 25, 2018, June 7, 2018, July 5, 2018, July 9, 2018 and July 12, 2018; and

- the description of our common stock contained in our registration statement on Form 8-A filed under the Exchange Act on July 30, 2015, including any amendment or report filed for the purpose of updating such description.

In addition, all documents that we file with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and before the termination of the offering of our securities shall be deemed incorporated by reference into this prospectus supplement and to be a part of this prospectus supplement from the respective dates of filing such documents; provided, however, that we are not incorporating any information furnished under Item 2.02 or Item 7.01 of any Current Report on Form 8-K.

Any statement contained in a document incorporated by reference in this prospectus supplement shall be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or in any other subsequently filed document that also is or is deemed to be incorporated by reference in this prospectus supplement modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement.

You may obtain copies of any of these filings by contacting us at the address and telephone number indicated below or by contacting the SEC as described below under the section entitled "Where You Can Find More Information." Documents incorporated by reference are available from us without charge, excluding all exhibits unless an exhibit has been specifically incorporated by reference into this prospectus supplement, by requesting them in writing or by telephone at:

Zynerba Pharmaceuticals, Inc.
Attention: Corporate Secretary
80 W. Lancaster Avenue, Suite 300
Devon, PA 19333
(484) 581-7505

PROSPECTUS



\$250,000,000
Common Stock
Preferred Stock
Debt Securities
Warrants
Purchase Contracts
Units
Subscription Rights

We may from time to time offer and sell up to \$250,000,000 in total of:

- shares of our common stock, par value \$0.001 per share;
- shares of our preferred stock, par value \$0.001 per share;
- debt securities consisting of debentures, notes or other evidences of indebtedness;
- warrants to purchase shares of common stock, preferred stock and/or debt securities;
- purchase contracts to purchase common stock or preferred stock;
- units consisting of a combination of the foregoing securities;
- subscription rights to purchase any of the foregoing securities; or
- any combination of these securities.

We may offer common stock, preferred stock, debt securities, warrants, purchase contracts, units or subscription rights separately or together, in separate series, in amounts, at prices and on terms to be set forth in one or more supplements to this prospectus. The preferred stock, debt securities, warrants, or subscription rights we may offer may be convertible into or exercisable or exchangeable for common or preferred stock or other securities of ours or equity securities of one or more other entities. We refer to our common stock, preferred stock, debt securities, warrants, purchase contracts, units and subscription rights collectively as the "securities." When we decide to issue securities, we will provide you with the specific terms and the public offering price of the securities in prospectus supplements. In the case of shares of preferred stock, these terms will include, as applicable, the specific title and stated value, and any dividend, liquidation, redemption, conversion, voting and other rights. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement. You should read this prospectus and any applicable prospectus supplement carefully before you invest. This prospectus may not be used to offer or sell securities unless accompanied by a prospectus supplement.

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We may sell these securities to or through underwriters and also to other purchasers or through agents. We will set forth the names of any underwriters or agents in an accompanying prospectus supplement, if applicable.

Our common stock is traded on The NASDAQ Global Market, or NASDAQ, under the symbol “ZYNE.” None of the other securities are currently publicly traded. On June 8, 2017, the last reported sale price per share of our common stock was \$18.38 per share.

We are an “emerging growth company” as defined under the federal securities laws and, as such, have elected to comply with certain reduced public company reporting requirements.

You should read carefully this prospectus, the documents incorporated by reference in this prospectus and any prospectus supplement before you invest. Investing in our common stock involves risks. Please see “Risk Factors” on page 4 for more information.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is June 22, 2017

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ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement that we filed with the U.S. Securities and Exchange Commission, or the SEC, using a “shelf” registration process. Under this shelf registration process, we may offer to sell any of the securities, or any combination of the securities, described in this prospectus, in each case in one or more offerings, up to a total dollar amount of \$250,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities pursuant to this prospectus, we will provide a prospectus supplement or free writing prospectus that will contain specific information about the terms of that offering. The prospectus supplement or free writing prospectus may also add, update or change information contained in this prospectus. Therefore, if there is any inconsistency between the information in this prospectus and the prospectus supplement, you should rely on the information in the prospectus supplement. You should read both this prospectus and any prospectus supplement together with the additional information described under the headings “Where You Can Find More Information” and “Incorporation of Certain Information by Reference,” and any free writing prospectus that we may prepare and distribute.

The registration statement that contains this prospectus, including the exhibits to the registration statement and the information incorporated by reference, contains additional information about the securities offered under this prospectus. That registration statement can be read at the SEC website or at the SEC offices mentioned below under the heading “Where You Can Find More Information.”

You should rely only on the information provided in this prospectus and in any prospectus supplement, including the information incorporated by reference. We have not authorized anyone to provide you with different information.

Neither this prospectus nor any accompanying prospectus supplement constitutes an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor does this prospectus or any prospectus supplement constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction.

You should not assume that the information in this prospectus or any supplement to this prospectus is accurate at any date other than the date indicated on the cover page of these documents or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference.

Unless the context otherwise requires or as otherwise expressly stated, references in this prospectus to the “Company,” “Zynerba,” “we,” “us,” “our” and similar terms refer to Zynerba Pharmaceuticals, Inc. and its subsidiary, Zynerba Pharmaceuticals Pty Ltd, unless we state otherwise or the context indicates otherwise.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Any statements in this prospectus, any accompanying prospectus supplement and the information incorporated herein and therein by reference relating to future financial or business performance, conditions or strategies and other financial and business matters, including expectations regarding future revenues and operating expenses, are forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements that are not descriptions of historical facts are forward-looking statements and are based on management's estimates, assumptions, and projections that are subject to risks and uncertainties. These statements can generally be identified by the use of forward-looking words such as "believe," "expect," "intend," "may," "will," "should," "anticipate," "estimate" or similar terminology. Although we believe that the expectations reflected in our forward-looking statements are reasonable as of the date we make them, actual results could differ materially from those currently anticipated due to a number of factors, including risks relating to:

- 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, the rate and degree of market acceptance of ZYN002 and ZYN001 and our ability to serve those markets;
- legal and regulatory developments in the United States and foreign countries;
- the success of competing therapies and products that are or become available;
- our ability to limit our exposure under product liability lawsuits;
- our use of the proceeds from our initial public offering, or IPO, and subsequent offerings, including any offering pursuant to this prospectus and any accompanying prospectus supplement;
- our ability to obtain and maintain intellectual property protection for ZYN002 and ZYN001;
- recently enacted and future legislation regarding the healthcare system, including changes to the Affordable Care Act that may be made in the 115th United States Congress;
- our ability to obtain and maintain third-party manufacturing for our product candidates on commercially reasonable terms;
- the performance of third parties upon which we depend, including our ability to obtain and maintain third-party manufacturing for our product candidates on commercially reasonable terms;

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- the performance of third parties upon which we depend, including third-party contract research organizations and third-party manufacturers; and
- our ability to recruit or retain key scientific or management personnel or to retain our executive officers.

Further information on the factors and risks that could affect our business, financial condition and results of operations are set forth in this prospectus under “Risk Factors” and in our filings with the SEC, which are available at <http://www.sec.gov>. Any forward-looking statement speaks only as of the date on which it is made, and we undertake no obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the date of this prospectus or the date of documents incorporated by reference in this prospectus.

ABOUT THE COMPANY

Company Overview

We are a clinical stage specialty pharmaceutical company dedicated to developing and commercializing innovative transdermal synthetic cannabinoid treatments for patients with high unmet needs. We are evaluating two patent protected product candidates, ZYN002 and ZYN001, in five indications. We are studying ZYN002 in adult patients with refractory epileptic focal seizures (formerly known as complex partial seizures) and osteoarthritis, or OA, and in pediatric patients with 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. In 2016, we completed a Phase 1 program for ZYN002 in which it was demonstrated to be safe and well tolerated in both healthy volunteers and patients with epilepsy. We are currently conducting Phase 2 clinical trials for ZYN002 in adult patients with refractory epileptic focal seizures, adult patients with OA and pediatric patients with FXS. We expect to initiate Phase 1 clinical trials for ZYN001 in the first half of 2017.

ZYN002 is the first and only synthetic cannabidiol, or 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 of CBD when delivered transdermally. In addition, an in vitro study published in Cannabis and Cannabinoid Research in April 2016 demonstrated that CBD is degraded to Δ^9 -tetrahydrocannabinol, or THC, in an acidic environment such as the stomach. We believe such degradation may lead to increased psychoactive effects if CBD is delivered orally and may be avoided 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 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 of THC 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. We are working with a development partner, LTS LOHMANN Therapie-Systeme AG, to optimize the formulation of ZYN001 into a state of the art drug-adhesive matrix transdermal patch to be used in clinical studies. 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 of ZYN001. In addition, preclinical testing 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, which collectively currently represent multi-billion dollar markets.

Corporate Information

Our principal 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 <http://www.zynerba.com>. The information contained in, or that can be accessed through, our website is not part of this prospectus. We make available free of charge on our website our annual, quarterly and current reports, including amendments to such reports, as soon as reasonably practicable after we electronically file such material with, or furnish such material to, the SEC.

Implications of Being an Emerging Growth Company

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earliest of (1) the beginning of the first fiscal year following the fifth anniversary of our initial public offering, or January 1, 2021, (2) the beginning of the first

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fiscal year after our annual gross revenue is \$1.0 billion or more, (3) the date on which we have, during the previous three-year period, issued more than \$1.0 billion in non-convertible debt securities and (4) as of the end of any fiscal year in which the market value of our common stock held by non-affiliates exceeded \$700 million as of the end of the second quarter of that fiscal year.

For as long as we remain an “emerging growth company,” we may take advantage of certain exemptions from various reporting requirements that are applicable to 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, reduced disclosure obligations regarding executive compensation and financial statements in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote to approve executive compensation and shareholder approval of any golden parachute payments not previously approved. We will take advantage of these reporting exemptions until we are no longer an “emerging growth company.”

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.”

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider and evaluate all of the information contained in this prospectus, any accompanying prospectus supplement, and in the documents we incorporate by reference in this prospectus before you decide to purchase our securities. In particular, you should carefully consider and evaluate the risks and uncertainties described in “Part I — Item 1A. Risk Factors” of our most recent Form 10-K, as updated by the additional risks and uncertainties set forth in other filings we make with the SEC or any accompanying prospectus supplement. Any of the risks and uncertainties set forth therein could materially and adversely affect our business, results of operations and financial condition, which in turn could materially and adversely affect the trading price or value of our securities. As a result, you could lose all or part of your investment.

USE OF PROCEEDS

Unless otherwise indicated in a prospectus supplement, we anticipate that the net proceeds from our sale of any securities will be used to fund the development of our clinical programs, for other research and development activities and for general corporate purposes, which may include capital expenditures and funding our working capital needs.

The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from the offering and progress with our clinical development programs. Expenditures will also depend upon the establishment of collaborative arrangements with other companies, the availability of additional financing and other factors. Investors will be relying on the judgment of our management regarding the application of the proceeds of any sale of securities.

RATIO OF EARNINGS TO FIXED CHARGES

The following table sets forth our ratio of earnings to fixed charges and the ratio of our combined fixed charges and preferred dividends to earnings for each of the periods indicated. The following table is qualified by the more detailed information appearing in the computation table set forth in Exhibit 12.1 to the registration statement of which this prospectus is part and the historical financial statements, including the notes to those financial statements, incorporated by reference in this prospectus.

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(Amounts shown are in thousands, except for ratios)	Year Ended December 31,				Three Months Ended
	2013	2014	2015	2016	March 31, 2017
Ratio of earnings to fixed charges	N/A	N/A	N/A	N/A	N/A
Ratio of combined fixed charges and preferred dividends to earnings	N/A	N/A	N/A	N/A	N/A
Deficiency of earnings available to cover fixed charges	\$ (655)	\$ (5,691)	\$ (12,547)	\$ (23,450)	\$ (7,273)
Deficiency of earnings available to cover combined fixed charges and preferred stock dividends	\$ (744)	\$ (5,739)	\$ (12,547)	\$ (23,450)	\$ (7,273)

For purposes of computing the ratio of earnings to fixed charges and the ratio of our combined fixed charges and preferred dividends to earnings, earnings consist of income (loss) from continuing operations before income taxes plus fixed charges. Fixed charges consist of interest expense and an estimate of the interest within rental expense. We did not record earnings for any of the years ended December 31, 2016, 2015, 2014 and 2013 or the three months ended March 31, 2017. Accordingly, our earnings were insufficient to cover fixed charges for such periods and we are unable to disclose a ratio of earnings to fixed charges for such periods.

DESCRIPTION OF OUR CAPITAL STOCK

The following, together with the additional information we include in the applicable prospectus supplement, describes the common stock and preferred stock that we may offer under this prospectus, including the material provisions of our sixth amended and restated certificate of incorporation, or our charter, and our amended and restated bylaws, or our bylaws, and certain provisions of the Delaware General Corporation Law, or the DGCL. Because the following is only a summary, it does not contain all of the information that may be important to you. For a complete description, you should refer to our charter and our bylaws, copies of which have been filed as exhibits to the registration statement of which this prospectus is a part, as well as the relevant provisions of the DGCL.

General

Our charter authorizes us to issue up to 210,000,000 shares, 200,000,000 of which are designated as common stock with a par value of \$0.001 per share and 10,000,000 of which are designated as preferred stock with a par value of \$0.001 per share.

Common Stock

Outstanding Shares

As of June 8, 2017 there were 13,249,779 shares of our common stock issued and outstanding and options to purchase 2,373,845 shares of our common stock outstanding.

Voting Rights

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

Dividends

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

No Preemptive or Other Rights

Holders of our common stock have no preemptive rights and have no other rights to subscribe for additional securities under Delaware law. Nor does our common stock have any conversion rights or rights of redemption (or, if any such rights have been granted in relation to our common stock, any such rights have been waived). Upon liquidation, all holders of our common stock are entitled to participate pro rata in our assets available for distribution, subject to the rights of any class of preferred stock then outstanding.

Preferred Stock

Under our charter, our board of directors has the authority, subject to limitations prescribed by Delaware law, to issue preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of its

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qualifications, limitations and restrictions. Our board of directors also can increase or decrease the number of shares of any series, but not below the number of shares of that series then outstanding.

Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of the common stock. The issuance of preferred stock could delay, defer or prevent a change in control of our company and may adversely affect the market price of our common stock and the voting and other rights of the holders of common stock. We have no current plan to issue any shares of preferred stock.

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

Delaware Anti-Takeover Law

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

Certificate of Incorporation and Bylaws

Our charter and bylaws contain provisions that may delay or discourage transactions involving an actual or potential change of control or change in our management, and could adversely affect the price of our common stock. Among other things, these provisions of our charter and bylaws:

- 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;
- provide that the authorized number of directors may be changed only by the resolution of our board of directors;
- provide that special meetings of our stockholders may be called only by the board of directors or by such person or persons requested by a majority of the board of directors to call such meetings;
- provide that the Court of Chancery of the State of Delaware is the exclusive forum in which we and our directors may be sued by our stockholders; and
- provide that our certificate of incorporation and bylaws can only be amended to remove or revise the anti-takeover measures discussed above upon consent of 66 ²/₃% of the outstanding capital stock.

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Listing on the NASDAQ Global Market

Our common stock is listed on the NASDAQ Global Market under the symbol “ZYNE.”

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer and Trust Company, LLC.

DESCRIPTION OF DEBT SECURITIES

This section describes the general terms and provisions of the debt securities that we may offer under this prospectus, any of which may be issued as convertible or exchangeable debt securities. We will set forth the particular terms of the debt securities we offer in a prospectus supplement. The extent, if any, to which the following general provisions apply to particular debt securities will be described in the applicable prospectus supplement. The following description of general terms relating to the debt securities and the indenture under which the debt securities will be issued are summaries only and therefore are not complete. You should read the indenture and the prospectus supplement regarding any particular issuance of debt securities.

We will issue any debt under an indenture to be entered into between us and the trustee identified in the applicable prospectus supplement. The terms of the debt securities will include those stated in the indenture and those made part of the indenture by reference to the Trust Indenture Act of 1939, as in effect on the date of the indenture. We have filed or will file a copy of the form of indenture as an exhibit to the registration statement in which this prospectus is included. The indenture will be subject to and governed by the terms of the Trust Indenture Act of 1939.

We may offer under this prospectus up to an aggregate principal amount of \$250,000,000 in debt securities, or if debt securities are issued at a discount, or in a foreign currency, foreign currency units or composite currency, the principal amount as may be sold for an aggregate initial public offering price of up to \$250,000,000. Unless otherwise specified in the applicable prospectus supplement, the debt securities will represent direct, unsecured obligations of the Company and will rank equally with all of our other unsecured indebtedness.

The following statements relating to the debt securities and the indenture are summaries, qualified in their entirety by reference to the detailed provisions of the indenture and the final form indenture as may be filed with a future prospectus supplement.

The prospectus supplement will set forth, to the extent required, the following terms of the debt securities in respect of which the prospectus supplement is delivered:

- the title of the series;
- the aggregate principal amount;
- the issue price or prices, expressed as a percentage of the aggregate principal amount of the debt securities;
- any limit on the aggregate principal amount;
- the date or dates on which principal is payable;
- the interest rate or rates (which may be fixed or variable) or, if applicable, the method used to determine such rate or rates;
- the date or dates from which interest, if any, will be payable and any regular record date for the interest payable;

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- the place or places where principal and, if applicable, premium and interest, is payable;
- the terms and conditions upon which we may, or the holders may require us to, redeem or repurchase the debt securities;
- the denominations in which such debt securities may be issuable, if other than denominations of \$1,000 or any integral multiple of that number;
- whether the debt securities are to be issuable in the form of certificated securities (as described below) or global securities (as described below);
- the portion of principal amount that will be payable upon declaration of acceleration of the maturity date if other than the principal amount of the debt securities;
- the currency of denomination;
- the designation of the currency, currencies or currency units in which payment of principal and, if applicable, premium and interest, will be made;
- if payments of principal and, if applicable, premium or interest, on the debt securities are to be made in one or more currencies or currency units other than the currency of denomination, the manner in which the exchange rate with respect to such payments will be determined;
- if amounts of principal and, if applicable, premium and interest may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index, then the manner in which such amounts will be determined;
- the provisions, if any, relating to any collateral provided for such debt securities;
- any addition to or change in the covenants and/or the acceleration provisions described in this prospectus or in the indenture;
- any events of default, if not otherwise described below under “Defaults and Notice”;
- the terms and conditions, if any, for conversion into or exchange for shares of our common stock or preferred stock;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents; and
- the terms and conditions, if any, upon which the debt securities shall be subordinated in right of payment to other indebtedness of the Company.

We may issue discount debt securities that provide for an amount less than the stated principal amount to be due and payable upon acceleration of the maturity of such debt securities in accordance with the terms of the indenture. We may also issue debt securities in bearer form, with or without coupons. If we issue discount debt securities or debt securities in bearer form, we will describe material U.S. federal income tax considerations and other material special considerations which apply to these debt securities in the applicable prospectus supplement. We may issue debt securities denominated in or payable in a foreign currency or currencies or a foreign currency unit or units. If we do, we will describe the restrictions, elections and general tax considerations relating to the debt securities and the foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

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Exchange and/or Conversion Rights

We may issue debt securities which can be exchanged for or converted into shares of our common stock or preferred stock. If we do, we will describe the terms of exchange or conversion in the prospectus supplement relating to these debt securities.

Transfer and Exchange

We may issue debt securities that will be represented by either:

- “book-entry securities,” which means that there will be one or more global securities registered in the name of a depositary or a nominee of a depositary; or
- “certificated securities,” which means that they will be represented by a certificate issued in definitive registered form.

We will specify in the prospectus supplement applicable to a particular offering whether the debt securities offered will be book-entry or certificated securities.

Certificated Debt Securities

If you hold certificated debt securities issued under an indenture, you may transfer or exchange such debt securities in accordance with the terms of the indenture. You will not be charged a service charge for any transfer or exchange of certificated debt securities but may be required to pay an amount sufficient to cover any tax or other governmental charge payable in connection with such transfer or exchange.

Global Securities

The debt securities of a series may be issued in the form of one or more global securities that will be deposited with a depositary or its nominees identified in the prospectus supplement relating to the debt securities. In such a case, one or more global securities will be issued in a denomination or aggregate denominations equal to the portion of the aggregate principal amount of outstanding debt securities of the series to be represented by such global security or securities.

Unless and until it is exchanged in whole or in part for debt securities in definitive registered form, a global security may not be registered for transfer or exchange except as a whole by the depositary for such global security to a nominee of the depositary and except in the circumstances described in the prospectus supplement relating to the debt securities. The specific terms of the depositary arrangement with respect to a series of debt securities will be described in the prospectus supplement relating to such series.

Protection in the Event of Change of Control

Any provision in an indenture that governs our debt securities covered by this prospectus that includes any covenant or other provision providing for a put or increased interest or otherwise that would afford holders of our debt securities additional protection in the event of a recapitalization transaction, a change of control of the Company, or a highly leveraged transaction will be described in the applicable prospectus supplement.

Covenants

Unless otherwise indicated in this prospectus or the applicable prospectus supplement, our debt securities may not have the benefit of any covenant that limits or restricts our business or operations, the pledging of our assets or the incurrence by us of indebtedness. We will describe in the applicable prospectus supplement any material covenants in respect of a series of debt securities.

Consolidation, Merger and Sale of Assets

We may agree in any indenture that governs the debt securities of any series covered by this prospectus that

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we will not consolidate with or merge into any other person or convey, transfer, sell or lease our properties and assets substantially as an entirety to any person, unless such person and such proposed transaction meets various criteria, which we will describe in detail in the applicable prospectus supplement.

Defaults and Notice

The debt securities of any series will contain events of default to be specified in the applicable prospectus supplement, which may include, without limitation:

- failure to pay the principal of, or premium or make-whole amount, if any, on any debt security of such series when due and payable (whether at maturity, by call for redemption, through any mandatory sinking fund, by redemption at the option of the holder, by declaration or acceleration or otherwise);
- failure to make a payment of any interest on any debt security of such series when due;
- failure to perform or observe any other covenants or agreements in the indenture with respect to the debt securities of such series;
- certain events relating to our bankruptcy, insolvency or reorganization; and
- certain cross defaults, if and as applicable.

If an event of default with respect to debt securities of any series shall occur and be continuing, we may agree that the trustee or the holders of at least 25% in aggregate principal amount of the then outstanding debt securities of such series may declare the principal amount (or, if the debt securities of such series are issued at an original issue discount, such portion of the principal amount as may be specified in the terms of the debt securities of such series) of all debt securities of such series or such other amount or amounts as the debt securities or supplemental indenture with respect to such series may provide, to be due and payable immediately. Any provisions pertaining to events of default and any remedies associated therewith will be described in the applicable prospectus supplement.

Any indenture that governs our debt securities covered by this prospectus may require that the trustee under such indenture shall, within 90 days after the occurrence of a default, give to holders of debt securities of any series notice of all uncured defaults with respect to such series known to it. However, in the case of a default that results from the failure to make any payment of the principal of, premium or make-whole amount, if any, or interest on the debt securities of any series, or in the payment of any mandatory sinking fund installment with respect to debt securities of such series, if any, the trustee may withhold such notice if it in good faith determines that the withholding of such notice is in the interest of the holders of debt securities of such series. Any terms and provisions relating to the foregoing types of provisions will be described in further detail in the applicable prospectus supplement.

Any indenture that governs our debt securities covered by this prospectus will contain a provision entitling the trustee to be indemnified by holders of debt securities before proceeding to exercise any trust or power under the indenture at the request of such holders. Any such indenture may provide that the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of any series may direct the time, method and place of conducting any proceedings for any remedy available to the trustee for such series, or of exercising any trust or power conferred upon the trustee with respect to the debt securities of such series. However, the trustee under any such indenture may decline to follow any such direction that conflicts with law or the indenture, or that the trustee determines may be unduly prejudicial to the holders of the debt securities of such series not joining in such direction.

Any indenture that governs our debt securities covered by this prospectus may endow the holders of such debt securities to institute a proceeding with respect to such indenture, subject to certain conditions, which will be specified in the applicable prospectus supplement and which may include, that the holders of at least a majority in aggregate principal amount of the debt securities of such series then outstanding make a written request upon the

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trustee to exercise its power under the indenture, indemnify the trustee and afford the trustee reasonable opportunity to act. Even so, such holders may have an absolute right to receipt of the principal, premium or make-whole amount, if any, and interest when due, with respect to such debt securities, to require conversion or exchange of debt securities if such indenture provides for convertibility or exchangeability at the option of the holder and to institute suit for the enforcement of such rights. Any terms and provisions relating to the foregoing types of provisions will be described in further detail in the applicable prospectus supplement.

Modification of the Indenture

We and the trustee may modify any indenture that governs our debt securities of any series covered by this prospectus with or without the consent of the holders of such debt securities, under certain circumstances to be described in a prospectus supplement.

Investors may hold their interests in a global security directly through DTC if they are DTC participants, or indirectly through organizations that are DTC participants. Except in the limited circumstances described below, holders of debt securities represented by interests in a global security will not be entitled to receive their debt securities in fully registered certificated form.

Defeasance; Satisfaction and Discharge

The prospectus supplement will outline the conditions under which we may elect to have certain of our obligations under the indenture discharged and under which the indenture obligations will be deemed to be satisfied.

Regarding the Trustee

We will identify the trustee and any relationship that we may have with such trustee, with respect to any series of debt securities, in the prospectus supplement relating to the applicable debt securities. You should note that if the trustee becomes a creditor of Zynerva Pharmaceuticals, Inc., the indenture and the Trust Indenture Act of 1939 limit the rights of the trustee to obtain payment of claims in certain cases, or to realize on certain property received in respect of any such claim, as security or otherwise. The trustee and its affiliates may engage in, and will be permitted to continue to engage in, other transactions with us and our affiliates. If, however, the trustee acquires any “conflicting interest” within the meaning of the Trust Indenture Act of 1939, it must eliminate such conflict or resign.

Governing Law

The law governing the indenture and the debt securities will be identified in the prospectus supplement relating to the applicable indenture and debt securities.

DESCRIPTION OF WARRANTS

The following, together with the additional information we may include in the applicable prospectus supplement, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants we may offer, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement.

As of the date of this prospectus, there are no outstanding warrants.

We may issue warrants for the purchase of common stock, debt securities, preferred stock or any combination of the foregoing securities. Warrants may be issued independently or together with our securities offered by any prospectus supplement. Series of warrants may be issued under a separate warrant agreement. The applicable prospectus supplement will describe the terms of the warrants offered, including but not limited to the following:

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- the number of warrants offered;
- the price or prices at which the warrants will be issued;
- the currency or currencies in which the prices of the warrants may be payable;
- securities for which the warrants are exercisable;
- whether the warrants will be issued with any other securities and, if so, the amount and terms of these securities;
- the amount of securities purchasable upon exercise of each warrant and the price at which and the currency or currencies in which the securities may be purchased upon such exercise, and the events or conditions under which the amount of securities may be subject to adjustment;
- the date on which the right to exercise such warrants shall commence and the date on which such right shall expire;
- the circumstances, if any, which will cause the warrants to be deemed to be automatically exercised;
- the minimum or maximum amount of such warrants, if any, that may be exercised at any one time;
- any material risk factors relating to such warrants; and
- any other material terms of such warrants.

Prior to the exercise of any warrants, holders of such warrants will not have any rights of holders of the securities purchasable upon such exercise, including the right to receive payments of dividends, or the right to vote such underlying securities.

Prospective purchasers of warrants should be aware that special United States federal income tax, accounting and other considerations may be applicable to instruments such as warrants. The applicable prospectus supplement will describe such considerations, to the extent they are material, as they apply generally to purchasers of such warrants.

DESCRIPTION OF PURCHASE CONTRACTS

We may issue purchase contracts, including contracts obligating holders to purchase from or sell to us, and obligating us to sell to or purchase from the holders, a specified number of shares of our common stock or preferred stock at a future date or dates, which we refer to in this prospectus as purchase contracts. The price per share of common stock or preferred stock and the number of shares of each may be fixed at the time the purchase contracts are issued or may be determined by reference to a specific formula set forth in the purchase contracts. The purchase contracts may be issued separately or as part of units, consisting of one or more purchase contracts and beneficial interests in debt securities or any other securities described in the applicable prospectus supplement or any combination of the foregoing, securing the holders' obligations to purchase the common stock or preferred stock under the purchase contracts.

The purchase contracts may require us to make periodic payments to the holders of the units or vice versa, and these payments may be unsecured or prefunded on some basis. The purchase contracts may require holders to secure their obligations under those contracts in a specified manner, including pledging their interest in another purchase contract.

The applicable prospectus supplement will describe the terms of the purchase contracts, including, if applicable, collateral or depositary arrangements.

DESCRIPTION OF UNITS

The following, together with the additional information we may include in the applicable prospectus supplement, summarizes the material terms and provisions of the units that we may offer under this prospectus. While the terms summarized below will apply generally to any units we may offer, we will describe the particular terms of any series of units in more detail in the applicable prospectus supplement.

We may, from time to time, issue units comprised of one or more of the other securities that may be offered under this prospectus, in any combination. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately at any time, or at any time before a specified date.

Any applicable prospectus supplement will describe:

- the material terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any material provisions relating to the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units; and
- any material provisions of the governing unit agreement that differ from those described above.

DESCRIPTION OF SUBSCRIPTION RIGHTS

As specified in any applicable prospectus supplement, we may issue subscription rights consisting of one or more debt securities, shares of preferred stock, shares of common stock or any combination of such securities.

PLAN OF DISTRIBUTION

We may sell the securities being offered by this prospectus separately or together:

- directly to purchasers;
- through agents;
- to or through underwriters;
- through dealers;
- through a block trade in which the broker or dealer engaged to handle the block trade will attempt to sell the securities as agent, but may position and resell a portion of the block as principal to facilitate the transaction; or
- through a combination of any of these methods of sale.

In addition, we may issue the securities being offered by this prospectus as a dividend or distribution. We may effect the distribution of the securities from time to time in one or more transactions:

- at a fixed price or prices, which may be changed from time to time;
- at market prices prevailing at the times of sale;
- at prices related to prevailing market prices; or
- at negotiated prices.

For example, we may engage in at-the-market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. We may also sell securities through a rights offering, forward contracts or similar arrangements. In any distribution of subscription rights to stockholders, if all of the underlying securities are not subscribed for, we may then sell the unsubscribed securities directly to third parties or may engage the services of one or more underwriters, dealers or agents, including standby underwriters, to sell the unsubscribed securities to third parties.

The securities issued and sold under this prospectus will have no established trading market, other than our common stock, which is listed on NASDAQ. Any shares of our common stock sold pursuant to this prospectus will be eligible for listing and trading on the NASDAQ, subject to official notice of issuance. Any underwriters to whom securities are sold by us for public offering and sale may make a market in the securities, but the underwriters will not be obligated to do so and may discontinue any market making at any time without notice. The securities, other than our common stock, may or may not be listed on a national securities exchange or other trading market.

We will set forth in a prospectus supplement:

- the terms of any underwriting or other agreement that we reach relating to sales under this prospectus;
- the method of distribution of the securities;
- the names of any agents, underwriters or dealers, including any managing underwriters, used in the offering of securities;
- the terms of any direct sales, including the terms of any bidding or auction process, or the terms of any other transactions;

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- the compensation payable to agents, underwriters and dealers, which may be in the form of discounts, concessions or commissions;
- any activities that may be undertaken by agents, underwriters and dealers to stabilize, maintain or otherwise affect the price of the securities; and
- any indemnification and contribution obligations owing to agents, underwriters and dealers.

If we sell directly to institutional investors or others, they may be deemed to be underwriters within the meaning of the Securities Act with respect to any resale of the securities. Unless otherwise indicated in a prospectus supplement, if we sell through an agent, such agent will be acting on a best efforts basis for the period of its appointment. Any agent may be deemed to be an “underwriter” of the securities as that term is defined in the Securities Act. If a dealer is used in the sale of the securities, we or an underwriter will sell securities to the dealer, as principal. The dealer may resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

We may authorize agents, underwriters and dealers to solicit offers by certain institutional investors to purchase offered securities under contracts providing for payment and delivery on a future date specified in a prospectus supplement. The prospectus supplement will also describe the public offering price for the securities and the commission payable for solicitation of these delayed delivery contracts. Delayed delivery contracts will contain definite fixed price and quantity terms. The obligations of a purchase under these delayed delivery contracts will be subject to only two conditions:

- that the institution’s purchase of the securities at the time of delivery of the securities is not prohibited under the law of any jurisdiction to which the institution is subject; and
- that we shall have sold to the underwriters the total principal amount of the offered securities, less the principal amount covered by the delayed contracts.

To the extent permitted by and in accordance with Regulation M under the Securities Exchange Act of 1934, as amended, or the Exchange Act, in connection with an offering an underwriter may engage in over-allotments, stabilizing transactions, short covering transactions and penalty bids. Over-allotments involve sales in excess of the offering size, which creates a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would be otherwise. If commenced, the underwriters may discontinue any of the activities at any time.

To the extent permitted by and in accordance with Regulation M under the Exchange Act, any underwriters who are qualified market makers on NASDAQ may engage in passive market making transactions in the securities on NASDAQ during the business day prior to the pricing of an offering, before the commencement of offers or sales of the securities. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker’s bid, however, the passive market maker’s bid must then be lowered when certain purchase limits are exceeded.

The specific terms of any lock-up provisions in respect of any given offering will be described in the applicable prospectus supplement.

In compliance with the guidelines of the Financial Industry Regulatory Authority, Inc., or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker-dealer may not exceed 8% of the aggregate proceeds of the offering.

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The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business for which they receive compensation.

No securities may be sold under this prospectus without delivery, in paper format or in electronic format, or both, of the applicable prospectus supplement describing the method and terms of the offering.

LEGAL MATTERS

The legal validity of the securities offered by this prospectus will be passed upon for us by Hogan Lovells US LLP, Philadelphia, Pennsylvania.

EXPERTS

The consolidated financial statements of Zynerva Pharmaceuticals, Inc. and subsidiary as of December 31, 2016 and 2015 and for each of the years in the three-year period ended December 31, 2016, have been incorporated by reference herein in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

We incorporate information into this prospectus by reference, which means that we disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, except to the extent superseded by information contained in this prospectus. This prospectus incorporates by reference the documents set forth below, the file number for each of which is 001-37526, that have been previously filed with the SEC (other than, in each case, documents or information deemed to have been “furnished” and not “filed” in accordance with SEC rules):

- our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on March 27, 2017 (including the portions of our proxy statement for our 2017 annual meeting of stockholders incorporated by reference therein);
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2017, filed with the SEC on May 9, 2017;
- our Current Reports on Form 8-K (other than portions thereof furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits accompanying such reports that are related to such items, unless specifically stated to the contrary) filed with the SEC on January 6, 2017, January 18, 2017, January 19, 2017, February 6, 2017, February 9, 2017, March 13, 2017, March 27, 2017, May 1, 2017 and June 8, 2017; and
- the description of our common stock contained in our registration statement on Form 8-A filed under the Exchange Act on July 30, 2015, including any amendment or report filed for the purpose of updating such description.

In addition, all documents that we file with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of the initial registration statement of which this prospectus is a part and prior to the effectiveness of such registration statement and all such documents that we file with the SEC after the date of this prospectus and before the termination of the offering of our securities shall be deemed incorporated by reference into this prospectus and to be a part of this prospectus from the respective dates of filing such documents.

Any statement contained in a document incorporated by reference in this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or in any other subsequently filed document that also is or is deemed to be incorporated by reference in this prospectus modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so

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modified or superseded, to constitute a part of this prospectus.

You may obtain copies of any of these filings by contacting us at the address and telephone number indicated below or by contacting the SEC as described below under the section entitled “Where You Can Find More Information.” Documents incorporated by reference are available from us without charge, excluding all exhibits unless an exhibit has been specifically incorporated by reference into this prospectus, by requesting them in writing or by telephone at:

Zynerba Pharmaceuticals, Inc.
Attention: Corporate Secretary
80 W. Lancaster Avenue, Suite 300
Devon, PA 19333
(484) 581-7505

WHERE YOU CAN FIND MORE INFORMATION

We are currently subject to the reporting requirements of the Exchange Act, and in accordance therewith file periodic reports, proxy statements and other information with the SEC. You may read and copy any such reports, proxy statements and other information at the SEC’s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the public reference room. Our SEC filings are also available to you on the SEC’s website at <http://www.sec.gov> and in the “Investor Relations” section of our website at <http://www.zynerba.com>. Our website and the information contained on that site, or connected to that site, are not incorporated into and are not a part of this prospectus.

Shares



Common Stock

PROSPECTUS SUPPLEMENT

Sole Book-Running Manager

Cantor

July , 2018
