

PROSPECTUS SUPPLEMENT
(To Prospectus dated August 13, 2019)



Up to \$75,000,000

Common Stock

We have entered into a Controlled Equity OfferingSM Sales Agreement, or the sales agreement, with Cantor Fitzgerald & Co., or Cantor, Canaccord Genuity LLC, or Canaccord Genuity, H.C. Wainwright & Co., LLC, or H.C. Wainwright & Co., and Ladenburg Thalmann & Co. Inc., or Ladenburg Thalmann, relating to shares of our common stock, par value \$0.001 per share, offered by this prospectus supplement and the accompanying base prospectus. We refer to each of Cantor, Canaccord Genuity, H.C. Wainwright & Co. and Ladenburg Thalmann as a "Sales Agent" and together as "Sales Agents."

Our common stock is traded on The Nasdaq Global Market under the symbol "ZYNE." On May 11, 2021, the last reported sale price per share of our common stock was \$4.16 per share.

Sales of our common stock, if any, under this prospectus supplement may be made in sales deemed to be an "at the market offering" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended, or the Securities Act. Subject to the terms of the sales agreement, the Sales Agents are not required to sell any specific number or dollar amount of securities. Each of the Sales Agents has agreed to use its commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us, consistent with its normal trading and sales practices, on mutually agreed terms among the Sales Agents and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The Sales Agents will be entitled to compensation under the terms of the sales agreement at a commission rate of up to 3.0% of the gross sales price of any shares sold under the sales agreement. See "Plan of Distribution" for additional information regarding compensation to be paid to the Sales Agents. In connection with the sale of our common stock on our behalf, each of the Sales Agents will be deemed to be an "underwriter" within the meaning of the Securities Act, and the compensation of the Sales Agents will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to the Sales Agents against certain civil liabilities, including liabilities under the Securities Act. See "Plan of Distribution."

Investing in our common stock involves risks. Before investing in our common stock, you should carefully read the discussion of material risks of investing in our common stock on page S-6 of this prospectus supplement under the heading "Risk Factors," as well as the risk factors discussed in the documents we file with the Securities and Exchange Commission pursuant to the Securities Exchange Act of 1934, and which we incorporate into this prospectus supplement by reference.

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

Cantor

Canaccord Genuity

H.C. Wainwright & Co.

Ladenburg Thalmann

The date of this prospectus supplement is May 12, 2021

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement 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”. 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 Sales Agents 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 Sales Agents 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 base 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, unless we state otherwise or the context indicates otherwise.

Zynerba[®], Zygel[™] and our logo are some of our trademarks used in this prospectus supplement. This prospectus supplement also includes trademarks, tradenames, and service marks that are the property of other organizations. Solely for convenience, our trademarks and tradenames referred to in this prospectus supplement appear without the [™] symbol, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks and tradenames.

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-6 and in the documents incorporated by reference into this prospectus supplement or the accompanying base prospectus.

Company Overview

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

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

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

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

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

CONNECT-FX Trial (FXS)

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

RECONNECT Trial (FXS)

In May 2021, following guidance received from the FDA regarding the regulatory path forward for Zygel, we announced that we will be conducting a pivotal, multi-national, confirmatory Phase 3 trial of Zygel in patients with FXS. The trial, which will be called RECONNECT (A Randomized, Double-Blind, Placebo-Controlled, Multiple-Center, Efficacy and Safety Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Fragile X Syndrome), is designed to evaluate the efficacy and safety of Zygel in children and adolescents with FXS. We believe that the results, if positive, from RECONNECT will be sufficient to support the submission of a New Drug Application for Zygel in patients with FXS.

The RECONNECT trial will be an 18-week trial which will enroll approximately 200 children and adolescents of which approximately 160 patients will have complete (100%) methylation of their *FMR1* gene and approximately 40 patients will have partial methylation of their *FMR1* gene. The primary endpoint for the trial will be the change in the Aberrant Behavior Checklist-Community FXS Specific (ABC-C_{FXS}) Social Avoidance subscale in patients who have complete methylation of their *FMR1* gene. All patients, including the cohort of partially methylated patients, will be included in a key secondary endpoint analysis.

We expect to initiate the RECONNECT trial in the third quarter of 2021. All patients will be eligible to enroll in our ongoing open-label extension after completing dosing in this clinical trial.

Phase 2 BRIGHT Trial (ASD)

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

Phase 2 INSPIRE Trial (22q)

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

Phase 2 BELIEVE Trial (DEE)

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

Zygel Clinical Development Timelines

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

We have never been profitable and have incurred net losses since inception. Our net losses were \$8.0 million and \$12.3 million for the three months ended March 31, 2021 and 2020, respectively. As of March 31, 2021, our accumulated deficit was \$210.1 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.

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.

THE OFFERING

Common stock to be offered by us	Shares of our common stock having an aggregate offering price of up to \$75,000,000.
Common stock to be outstanding after this offering	Up to 59,280,383 shares, assuming the issuance of up to 18,028,846 shares of our common stock based on an assumed sales price of \$4.16 per share, which was the closing price of our common stock on the Nasdaq Global Market on May 11, 2021. The actual number of shares issued will vary depending on the sales price under this offering.
Plan of Distribution	“At the market offering” that may be made from time to time through our Sales Agents. See “Plan of Distribution” on page S-14 of this prospectus supplement.
Use of Proceeds	We intend to use the net proceeds from this offering for working capital and general corporate purposes, including research and development expenses and capital expenditures. See “Use of Proceeds” on page S-11 of this prospectus supplement.
Risk Factors	Investing in our common stock involves a high degree of risk. See “Risk Factors” beginning on page S-6 of this prospectus supplement 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 that will be outstanding after this offering is based on 41,251,537 shares of common stock outstanding as of March 31, 2021, and excludes the following:

- 5,225,538 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2021 at a weighted-average exercise price of \$8.81 per share, of which 3,291,734 options were vested as of March 31, 2021; and
- 2,332,008 shares of our common stock available for future issuance as of March 31, 2021 under our Amended and Restated 2014 Omnibus Incentive Compensation Plan, or our 2014 Plan.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of the outstanding options described above.

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, 2020](#), as updated by other filings we have made and will make with the SEC incorporated by reference into this prospectus supplement. See “Incorporation by Reference” on page S-15.

Risks Related to This Offering

Management will have broad discretion over the use of the proceeds from this offering, and may not use the proceeds effectively.

Because we have not designated the amount of net proceeds from this offering to be used for any particular purpose, our management will have broad discretion as to the application of the net proceeds from this offering and could use them for purposes other than those contemplated at the time of the offering. Our management may use the net proceeds for corporate purposes that may not improve our financial condition or market value. Pending use, we may invest any net proceeds from this offering in a manner that does not produce income or loses value. Please see the section entitled “Use of Proceeds” on page S-11 of this prospectus supplement for further information.

You may experience immediate and substantial dilution in the net tangible book value per share of the common stock you purchase.

The price per share of our common stock being offered may be higher than the net tangible book value per share of our common stock outstanding prior to this offering. Assuming that an aggregate of 18,028,846 shares are sold at a price of \$4.16 per share, the last reported sale price of our common stock on the Nasdaq Global Market on May 11, 2021, for aggregate gross proceeds of approximately \$75,000,000 in this offering, and after deducting commissions and estimated aggregate offering expenses payable by us, you will suffer immediate and substantial dilution of \$1.31 per share, representing the difference between the as adjusted net tangible book value per share of our common stock as of March 31, 2021 after giving effect to this offering at the assumed offering price. Please see the section entitled “Dilution” on page S-12 of this prospectus supplement for a more detailed illustration of the dilution you would incur if you participate in this offering.

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. In addition, as of March 31, 2021, there were options to purchase approximately 5,225,538 shares of our common stock outstanding at a weighted average exercise price of \$8.81. 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, stockholders may experience further dilution.

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. A substantial majority of the outstanding shares of our common stock are, and all of the shares sold in this offering upon issuance will be, freely tradable without restriction or further registration under the Securities Act, unless these shares are owned or purchased by “affiliates” as that term is defined in Rule 144 under the Securities Act. In addition, we have also registered the shares of common stock that we may issue under our equity incentive plans. As a result, these shares can be freely sold in the public market upon issuance, subject to restrictions under securities laws.

It is not possible to predict the actual number of shares we will sell under the Sales Agreement, or the gross proceeds resulting from those sales.

Subject to certain limitations in the sales agreement and compliance with applicable laws, we have the discretion to deliver a placement notice to the Sales Agents at any time throughout the term of the sales agreement. The number of shares that are sold through the Sales Agents after delivering a placement notice will fluctuate based on a number of factors, including the market price of our common stock during the term of the sales agreement, the limits we set with the Sales Agents in any applicable placement notice, and the demand for our common stock during the term of the sales agreement. Because the price per share of each share sold will fluctuate during the term of the sales agreement, it is not currently possible to predict the number of shares that will be sold or the gross proceeds to be raised in connection with the sales of shares of common stock offered under this prospectus.

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. To date during 2021, the trading price of our common stock has ranged from \$3.23 and \$9.00 per share. In addition, the trading volume of our common stock may fluctuate and cause significant price variations to occur. In addition to the factors discussed in this “Risk Factors” section and elsewhere in this prospectus supplement or the documents incorporated by reference herein, these factors include:

- results of clinical trials of Zygel or product candidates of our competitors;
- the success of competitive products;
- regulatory actions with respect to our product candidates or our competitors’ products and product candidates;
- actual or anticipated changes in our growth rate relative to our competitors;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to our preclinical and clinical development programs;
- the results of our efforts to in-license or acquire additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our common stock;
- 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. In addition, in the past, following periods of volatility in the overall market and decreases in the market price of a company's securities, securities class action litigation has often been instituted against these companies. We are subject to securities litigation, as described further in Part II of our [Annual Report on Form 10-K for the year ended December 31, 2020](#) in "Notes to Consolidated Financial Statements, Note 12. Commitments and Contingencies" and incorporated by reference in Part I, Item 3—*Legal Proceedings*. This litigation, and any other securities class actions that may be brought against us, could result in substantial costs and a diversion of our management's attention and resources.

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

- our ability to recruit or retain key scientific, commercial or management personnel or to retain our executive officers;
- the timing and outcome of current and future legal proceedings;
- our ability to maintain proper functionality and security of our internal computer and information systems and prevent or avoid cyberattacks, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption;
- the timing and outcome of the Australian Taxation Office's, or ATO, review regarding our eligibility to receive certain tax credits;
- the extent to which health epidemics and other outbreaks of communicable diseases, including the ongoing COVID-19 pandemic, could disrupt our operations or materially and adversely affect our business and financial conditions; and
- the other risks, uncertainties and factors discussed in our Annual Report on Form 10-K for the fiscal year ended December 31, 2020, under the caption "Item 1A. Risk Factors".

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 supplement or the date of any later-filed free writing prospectus or documents incorporated by reference herein.

USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate sales proceeds of up to \$75,000,000 from time to time. Because there is no minimum offering amount required in this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. There can be no assurance that we will sell any shares under or fully utilize the sales agreement with the Sales Agents as a source of financing.

We intend to use the net proceeds from the sale of the common stock offered by us hereunder, if any, for working capital and general corporate purposes, including research and development expenses and capital expenditures. We do not currently have specific plans or commitments with respect to the net proceeds from this offering and, accordingly, we are unable to quantify the allocations of such proceeds among the various potential uses. We will have broad discretion in the way we use the net proceeds of this offering.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted immediately 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 after this offering. As of March 31, 2021, our net tangible book value was \$95.7 million, or \$2.32 per share. Net tangible book value per share represents our total tangible assets (excluding deferred issuance costs) less our total liabilities, divided by the number of share outstanding.

After giving effect to the assumed sale of shares of our common stock in the aggregate amount of \$75,000,000 in this offering at an assumed offering price of \$4.16 per share, the last reported sale price of our common stock on the Nasdaq Global Market on May 11, 2021, and after deducting commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2021 would have been \$168.9 million, or \$2.85 per share. This amount would represent an immediate increase in net tangible book value of \$0.53 per share to existing stockholders and an immediate dilution in net tangible book value of \$1.31 per share to new investors purchasing common stock in this offering. We determine dilution by subtracting the assumed as adjusted net tangible book value per share after this offering from the assumed price per share paid by an investor in this offering.

The following table illustrates this dilution:

Assumed public offering price per share		\$	4.16
Net tangible book value per share as of March 31, 2021	\$	2.32	
Increase in net tangible book value per share attributable to new investors purchasing shares in this offering		<u>0.53</u>	
As adjusted net tangible book value per share after giving effect to this offering			2.85
Dilution per share to new investors in this offering	\$		<u>1.31</u>

The table above assumes, for illustrative purposes, that an aggregate of 18,028,846 shares of our common stock are sold at a price of \$4.16 per share, the last reported sale price of our common stock on the Nasdaq Global Market on May 11, 2021, for aggregate gross proceeds of \$75,000,000. The shares sold in this offering, if any, will be sold from time to time at various prices. An increase of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$4.16 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$75,000,000 is sold at that price, would increase our as adjusted net tangible book value per share after the offering to \$3.03 per share and would result in an increase in the dilution in net tangible book value per share to new investors in this offering of \$0.82 per share to \$2.13 per share, after deducting commissions and estimated offering expenses payable by us. A decrease of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$4.16 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$75,000,000 is sold at that price, would decrease our as adjusted net tangible book value per share after the offering to \$2.60 per share and would result in a decrease in the dilution in net tangible book value per share to new investors in this offering of \$0.75 per share to \$0.56 per share, after deducting commissions and estimated offering expenses payable by us.

The foregoing table and calculations are based on 41,251,537 shares of our common stock outstanding as of March 31, 2021, and exclude:

- 5,225,538 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2021 at a weighted-average exercise price of \$8.81 per share, of which 3,291,734 options were vested as of March 31, 2021; and
- 2,332,008 shares of our common stock available for future issuance as of March 31, 2021 under our 2014 Plan.

To the extent that outstanding options are exercised, investors purchasing shares in this offering could experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or equity-based securities, the issuance of these securities could result in further dilution to our stockholders.

PLAN OF DISTRIBUTION

We have entered into the sales agreement with the Sales Agents, under which we may offer and sell up to \$75,000,000 of shares of our common stock from time to time through the Sales Agents, acting as agents. Sales of the shares of common stock, if any, may be made at market prices by any method deemed to be an “at the market” offering as defined in Rule 415(a)(4) under the Securities Act, including, without limitation, sales made directly on the Nasdaq Global Market or any other existing trading market for our common stock.

We may instruct the Sales Agents not to sell our common stock if the sales cannot be effected at or above the price designated by us from time to time. We or the Sales Agents may suspend or terminate the offering of our common stock upon notice and subject to other conditions.

We will pay the Sales Agents commissions, in cash, for their services for acting as a Sales Agent in the sale of our common stock. The Sales Agents will be entitled to compensation at a commission rate of up to 3.0% of the gross sales price per share sold. We have also agreed to reimburse a portion of the Sales Agents’ expenses, including reasonable and documented legal fees, in connection with this offering up to a maximum of \$50,000. In accordance with FINRA Rule 5110 these reimbursed fees and expenses are deemed sales compensation to the Sales Agents in connection with this offering. We estimate that the total expenses for the offering, excluding commissions and expense reimbursement payable to the Sales Agents under the terms of the sales agreement, will be approximately \$50,000. Because there is no minimum offering amount required as a condition to this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time.

Settlement for sales of shares of our common stock will occur on the second trading day following the date on which any sales are made (or such earlier day as is industry practice for regular-way trading), in return for payment of the net proceeds to us. Sales of our common stock as contemplated in this prospectus supplement will be settled through the facilities of The Depository Trust Company or by such other means as we and the Sales Agents may agree upon. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

The Sales Agents will use their commercially reasonable efforts, consistent with their sales and trading practices, to solicit offers to purchase shares of our common stock under the terms and subject to the conditions set forth in the sales agreement. In connection with the sale of shares of our common stock on our behalf, each of the Sales Agents will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation of the Sales Agents may be deemed to be underwriting commissions or discounts. We have agreed to provide indemnification and contribution to the Sales Agents against certain civil liabilities, including liabilities under the Securities Act.

The offering pursuant to the sales agreement will terminate upon the earlier of (1) the sale of all shares of our common stock subject to the sales agreement, (2) the termination of the sales agreement as permitted therein, or (3) the third anniversary of the date of the sales agreement. We and the Sales Agents may each terminate the sales agreement at any time upon ten days’ prior notice.

The Sales Agents and their affiliates may in the future provide various investment banking, commercial banking and other financial services for us and our affiliates, for which services they may in the future receive customary fees. To the extent required by Regulation M, the Sales Agents will not engage in any market making activities involving our common stock while the offering is ongoing under this prospectus supplement.

This prospectus supplement and the accompanying base prospectus in electronic format may be made available on a website maintained by each of the Sales Agents and the Sales Agents may distribute this prospectus supplement and the accompanying base prospectus electronically.

LEGAL MATTERS

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

EXPERTS

The consolidated financial statements of Zynerva Pharmaceuticals, Inc. and subsidiary as of December 31, 2020 and 2019 and for each of the years in the three-year period ended December 31, 2020, 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 supplement is part of a registration statement we filed with the SEC. This prospectus supplement 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 supplement, 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 supplement 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 supplement or any sale of the securities offered by this prospectus supplement.

We are currently subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and in accordance therewith file periodic reports, proxy statements and other information with the SEC. Our SEC filings are 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 BY REFERENCE

We incorporate information into this prospectus supplement 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 supplement, except to the extent superseded by information contained in this prospectus supplement. This prospectus supplement 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, 2020, filed with the SEC on March 10, 2021 \(including the portions of our proxy statement for our 2021 annual meeting of stockholders incorporated by reference therein\);](#)
- [our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2021, filed with the SEC on May 12, 2021;](#)
- 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 [March 10, 2021](#) and [May 5, 2021](#); 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 supplement 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 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.

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. 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



\$300,000,000
Common Stock
Preferred Stock
Debt Securities
Warrants
Purchase Contracts
Units
Subscription Rights

We may from time to time in one or more offerings offer and sell up to \$300,000,000 in the aggregate of the securities identified above. This prospectus provides you with a general description of the securities.

We may offer these securities separately or together as units. Each time we offer and sell securities, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the securities. The supplement may also add, update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement before you invest in any of our securities.

We may offer and sell the securities described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If any underwriters, dealers or agents are involved in the sale of any of the securities, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus entitled, "About this Prospectus" and "Plan of Distribution" for more information. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such securities.

INVESTING IN OUR SECURITIES INVOLVES RISK. SEE THE "RISK FACTORS" ON PAGE 3 OF THIS PROSPECTUS AND ANY SIMILAR SECTION CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

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 August 5, 2019, the last reported sale price per share of our common stock was \$9.79 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.

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 August 13, 2019

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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 \$300,000,000.

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. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement or free writing prospectus may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement or free writing prospectus, you should rely on the information in the prospectus supplement or free writing prospectus, as applicable. You should read both this prospectus and any prospectus supplement together with the additional information described under the heading “Where You Can Find More Information; Incorporation 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 mentioned above 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 any information or to make any representations other than those contained in this prospectus, any applicable prospectus supplement or any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you.

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, that the information appearing in any applicable free writing prospectus is accurate at any date other than the date of that free writing prospectus, or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference. Our business, financial condition, results of operations and prospects may have changed since those dates. This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. In addition, the market and industry data and forecasts that may be included or incorporated by reference in this prospectus, any prospectus supplement or any applicable free writing prospectus may involve estimates, assumptions and other risks and uncertainties and are subject to change based on various factors, including those discussed under the heading “Risk Factors” contained in this prospectus, the applicable prospectus supplement and any applicable free writing prospectus, and under similar headings in other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

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.

Zynerba®, Zygel™ and our logo are some of our trademarks used in this prospectus. This prospectus also includes trademarks, tradenames, and service marks that are the property of other organizations. Solely for convenience, our trademarks and tradenames referred to in this prospectus appear without the™ symbol, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks and tradenames.

WHERE YOU CAN FIND MORE INFORMATION

Available Information

We are currently subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and in accordance therewith file periodic reports, proxy statements and other information with the SEC. Our SEC filings are 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.

Incorporation 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, 2018, filed with the SEC on March 11, 2019 \(including the portions of our proxy statement for our 2019 annual meeting of stockholders incorporated by reference therein\);](#)
- our Quarterly Reports on Form 10-Q for the fiscal quarter ended [March 31, 2019](#), filed with the SEC on [May 8, 2019](#) and for the fiscal quarter ended [June 30, 2019](#), filed with the SEC on [August 6, 2019](#);
- 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 4, 2019](#), [February 20, 2019](#), [February 26, 2019](#), [March 7, 2019](#), [May 6, 2019 \(two filings\)](#), [May 29, 2019](#), and [June 12, 2019](#); 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 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. 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

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.

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, tax credits and timing and availability of and the need for additional financing;
- the results, cost and timing of our preclinical studies and clinical trials, including any delays to such clinical trials relating to enrollment or site initiation, as well as the number of required trials for regulatory approval and the criteria for success in such trials;
- our dependence on third parties in the conduct of our preclinical studies and clinical trials;
- legal and regulatory developments in the United States and foreign countries, including any actions or advice that may affect the design, initiation, timing, continuation, progress or outcome of clinical trials or result in the need for additional clinical trials;
- the difficulties and expenses associated with obtaining and maintaining regulatory approval of our product candidates, and the indication and labeling under any such approval;
- our plans and ability to develop and commercialize our product candidates;
- the successful development of our commercialization capabilities, including medical affairs and sales and marketing capabilities, whether alone or with potential future collaborators;
- the size and growth of the potential markets for our product candidates, the rate and degree of market acceptance of our product candidates and our ability to serve those markets;
- the coverage and reimbursement status for our product candidates from third-party payors;
- the success of competing therapies and products that are or become available;
- our ability to limit our exposure under product liability lawsuits;
- 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;
- delays, interruptions or failures in the manufacture and supply of our product candidates;
- the performance of third parties upon which we depend, including third-party contract research organizations, contract manufacturing organizations, contractor laboratories and independent contractors;
- our ability to recruit or retain key scientific, commercial or management personnel or to retain our executive officers;
- our ability to maintain proper functionality and security of our internal computer and information systems and prevent or avoid cyberattacks, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption;
- the other risks, uncertainties and factors discussed in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q, under the caption “Item 1A. Risk Factors.”

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 ZYNERBA PHARMACEUTICALS

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, Autism Spectrum Disorder, or ASD, 22q11.2 Deletion Syndrome, or 22q, and a heterogeneous group of rare and ultra-rare epilepsies known as developmental and epileptic encephalopathies, or DEE.

We are currently evaluating Zygel™, a patent-protected, pharmaceutically produced transdermal cannabidiol, or CBD, gel for the treatment of FXS, DEE, ASD and 22q. In 2017, we completed three Phase 2 clinical trials for Zygel and two of those studies have open-label extensions that are ongoing. In April 2018, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with DEE, and in July 2018, we initiated what we believe will be a pivotal clinical trial evaluating Zygel in children and adolescent patients with FXS. In March 2019, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with ASD and in May 2019, we initiated an open-label Phase 2 clinical trial evaluating Zygel in children and adolescent patients with 22q.

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

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 Section 2(a) of the Securities Act of 1933, as amended, or the Securities Act, as modified by the Jumpstart Our Business Startups Act of 2012, or JOBS Act. For as long as we remain an “emerging growth company”, we may take advantage of certain exemptions from various disclosure and reporting requirements that are applicable to other public companies that are not “emerging growth companies” including, but not limited to:

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

We will remain an “emerging growth company” until the earliest of (1) the last day of the fiscal year (a) following the fifth anniversary of our initial public offering (b) in which we have annual gross revenue of at least \$1.07 billion, or (c) in which we are deemed to be an accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the last day of the prior second quarter and (2) the date on which we have, during the previous three-year period, issued more than \$1.0 billion in non-convertible debt securities.

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.”

USE OF PROCEEDS

We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes unless the applicable prospectus supplement provides otherwise. General corporate purposes may include, and are not limited to, research and development costs, including funding of clinical trial programs, costs to commercialize any approved product candidates, manufacturing costs, working capital and capital expenditures.

We may temporarily invest the net proceeds in a variety of capital preservation instruments, including investment grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government, or may hold such proceeds as cash, until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

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. As of August 2, 2019, there were 23,198,010 shares of our common stock outstanding held by approximately 30 stockholders of record.

Common Stock

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 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

Some provisions of Delaware law and our charter and bylaws contain provisions that could make the following transactions more difficult: acquisition of us by means of a tender offer; acquisition of us by means of a proxy contest or otherwise; or removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions that might result in a premium over the market price for our shares.

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

Delaware Anti-Takeover Statute

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

Undesignated Preferred Stock

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

Board Size and Vacancies

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

Elimination of Stockholder Action by Written Consent

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

Requirements for Advance Notification of Stockholder Nominations and Proposals

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

Special Stockholder Meetings

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

Choice of Forum

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

Amendment of Charter Provisions

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

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

The following description, together with the additional information we include in any applicable prospectus supplement or free writing prospectus, summarizes certain general terms and provisions of the debt securities that we may offer under this prospectus. When we offer to sell a particular series of debt securities, we will describe the specific terms of the series in a supplement to this prospectus. We will also indicate in the supplement to what extent the general terms and provisions described in this prospectus apply to a particular series of debt securities.

We may issue debt securities either separately, or together with, or upon the conversion or exercise of or in exchange for, other securities described in this prospectus. Debt securities may be our senior, senior subordinated or subordinated obligations and, unless otherwise specified in a supplement to this prospectus, the debt securities will be our direct, unsecured obligations and may be issued in one or more series.

The debt securities will be issued under an indenture between us and a third party to be identified therein as trustee. We have summarized select portions of the indenture below. The summary is not complete. The form of the indenture has been filed as an exhibit to the registration statement and you should read the indenture for provisions that may be important to you. In the summary below, we have included references to the section numbers of the indenture so that you can easily locate these provisions. Capitalized terms used in the summary and not defined herein have the meanings specified in the indenture.

We may offer under this prospectus up to an aggregate principal amount of \$300,000,000 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 \$300,000,000. 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.

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in a resolution of our board of directors, in an officer's certificate or by a supplemental indenture. (Section 2.2) We can issue an unlimited amount of debt securities under the indenture that may be issued in one or more series. Unless otherwise set forth in a resolution of our board of directors, a supplemental indenture or an officer's certificate detailing the adopt of a series of debt securities, all securities in a series shall be identical. Debt securities may differ between series with respect to any term, provided, that all series of debt securities shall be equally and ratably entitled to the benefits of the indenture. (Section 2.1)

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;

- 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 obligation, if any, of the Company to redeem or repurchase the debt securities of a series pursuant to any sinking fund or analogous provision or at the option of a holder of the debt securities, and the period or periods within which, the price or prices at which and the terms and conditions upon which debt securities of a series shall be redeemed or purchased, in whole or in part, pursuant to such obligation;
- 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;
- the terms and conditions, if any, upon which the debt securities shall be subordinated in right of payment to other indebtedness of the Company; and
- if the debt securities of a series, in whole or any specified part, shall be defeasible. (Section 2.2)

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of and any premium and interest on any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you with information on the restrictions, elections, general tax considerations, specific terms and other information with respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

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. (Section 2.2)

Transfer and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, or the Depository, or a nominee of the Depository (we will refer to any debt security represented by a global debt security as a book-entry debt security), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a certificated debt security) as set forth in the applicable prospectus supplement. Except as set forth under the heading “Global Debt Securities and Book-Entry System” below, book-entry debt securities will not be issuable in certificated form.

Certificated Debt Securities. You may transfer or exchange certificated debt securities in accordance with the terms of the indenture. (Section 2.4) 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. (Section 2.7)

You may effect the transfer of certificated debt securities and the right to receive the principal of, premium and interest on certificated debt securities only by surrendering the certificate representing those certificated debt securities and either reissuance by us or the trustee of the certificate to the new holder or the issuance by us or the trustee of a new certificate to the new holder. (Section 2.7)

Global Securities. Each global debt security representing book-entry debt securities will be deposited with, or on behalf of, the Depository, and registered in the name of the Depository or a nominee of the Depository. Please see “Global Securities.”

No Protection in the Event of Change of Control

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions which may afford holders of the debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control) which could adversely affect holders of debt securities.

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. (Article 4)

Consolidation, Merger and Sale of Assets

We may not consolidate with or merge with or into, or sell, assign, convey, transfer, lease or otherwise dispose of all or substantially all of our properties and assets to any person, or a successor person, unless:

- the indenture shall remain in full force and effect and either we are the surviving corporation or the successor person (if other than us) is a corporation organized and validly existing under the laws of any U.S. domestic jurisdiction or a corporation or comparable legal entity organized under the laws of a foreign jurisdiction and expressly assumes by a supplemental indenture executed and delivered to the trustee, all of our obligations on the debt securities and under the indenture; and
- immediately after giving effect to the transaction, no Default or Event of Default, shall have occurred and be continuing. (Section 5.1)

Defaults and Notice

Unless otherwise specified in the resolution of our board of directors, supplemental indenture or officer's certificate establishing a series of debt securities, "Event of Default" means with respect to any series of debt securities, any of the following:

- failure to pay the principal of, or premium, if any, on any debt security when the same becomes due and payable at Maturity, upon acceleration, redemption or otherwise;
- failure to make a payment of any interest on any debt security of such series when due and payable, and the default continues for a period of 30 days;
- failure to perform or observe any other covenants or agreements in the indenture with respect to the debt securities of the series or in the Indenture for 60 days after written notice from the trustee or the holders of not less than 25% of the aggregate principal amount of the debt securities of the series then outstanding, with such notice specifying the default, demanding that it be remedied and stating that the notice is a "Notice of Default";
- certain events relating to our bankruptcy, insolvency or reorganization or the bankruptcy, insolvency or reorganization of a Significant Subsidiary;
- certain cross defaults, if and as applicable; and
- any other Event of Default specified in the resolution of our board of directors, supplemental indenture or officer's certificate establishing such series of debt securities. (Section 6.1)

No Event of Default with respect to a particular series of debt securities necessarily constitutes an Event of Default with respect to any other series of debt securities. (Section 6.2) The occurrence of certain Events of Default or an acceleration under the indenture may constitute an event of default under certain indebtedness of ours or our subsidiary outstanding from time to time.

If an Event of Default with respect to debt securities of any series at the time outstanding (except as to certain events of bankruptcy, insolvency or reorganization) occurs and is continuing, then the trustee or the holders of not less than 25% in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal of, and accrued and unpaid interest, if any, on, all debt securities of that series. In the case of an Event of Default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all Events of Default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture and such rescission would not conflict with any judgment or decree. (Section 6.2) We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an Event of Default.

The trustee is entitled 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. (Section 6.6) 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. (Section 6.5) However, the trustee 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. (Section 6.5)

No holder of any debt security of any series will have any right to institute any proceeding or pursue any remedy, with respect to the indenture or a series of debt securities, unless:

- that holder has previously given to the trustee written notice of a continuing Event of Default with respect to debt securities of that series; and
- the holders of not less than 25% in principal amount of the outstanding debt securities of that series have made written request, and offered indemnity or security satisfactory to the trustee, to the trustee to institute the proceeding as trustee, and the trustee has failed to institute the proceeding within 60 days and has not received from the holders of not less than a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request within such 60 day periods. (Section 6.6)

No holder of debt securities under the indenture may use the indenture to prejudice the rights of another holder or to obtain a preference or priority over another holder of debt securities. (Section 6.6)

Notwithstanding any other provision in the indenture, the holder of any debt security will have an absolute and unconditional right to receive payment of the principal of, premium and any interest on that debt security on or after the due dates expressed in that debt security and to institute suit for the enforcement of payment. (Section 6.7)

The indenture requires us, within 120 days after the end of our fiscal year, to furnish to the trustee a statement as to compliance with the indenture. (Section 4.4) If a Default or Event of Default occurs and is continuing with respect to the securities of any series and if it is known to a responsible officer of the trustee, the trustee shall mail to each holder of the securities of that series notice of a Default or Event of Default within 90 days after it occurs or, if later, after a responsible officer of the trustee has knowledge of such Default or Event of Default (except if such Default or Event of Default has been validly cured or waived before the trustee gives such notice). The indenture provides that the trustee may withhold notice to the holders of debt securities of any series of any Default or Event of Default (except in payment on any debt securities of that series) with respect to debt securities of that series if the trustee determines in good faith that withholding notice is in the interest of the holders of those debt securities. (Section 7.5)

Modification of the Indenture

We and the trustee may modify, amend or supplement the indenture or the debt securities of any series without the consent of any holder of any debt security:

- to comply with covenants in the indenture described above under the heading “Consolidation, Merger and Sale of Assets”; to provide for uncertificated securities in addition to or in place of certificated securities;
- to provide for certificated debt securities in addition to uncertificated debt securities;
- to comply with requirements of the SEC in order to effect or maintain the qualification of the indenture under the Trust Indenture Act;
- to cure any ambiguity, defect or inconsistency or make any other change to the indenture or the debt securities that does not materially and adversely affect the rights of any holder of our debt securities under the indenture;
- to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture; or
- to effect the appointment of a successor trustee with respect to the debt securities of any series and to add to or change any of the provisions of the indenture to provide for or facilitate administration by more than one trustee. (Section 8.1)

We may also modify or supplement the indenture with the written consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or supplement. The holders of at least a majority in principal amount of the outstanding debt securities of each such series affected by the modifications or supplement may waive compliance by us in a particular instance with any provision of the indenture or the debt securities of such affected series of debt securities without notice to any holder of our debt securities. We may not make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

- reduce the amount of debt securities whose holders must consent to an amendment, supplement or waiver;
- reduce the rate of or change the time for payment of interest (including default interest) on any debt security;
- reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;
- make the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security;
- change the amount or time of any payment required by any debt security, or reduce the premium payable upon any redemption of any debt securities, or change the time before which no such redemption may be made;
- waive a default in the payment of the principal of, or interest or premium, if any, on, any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);
- waive a redemption payment with respect to any debt security, or change any of the provisions with respect to the redemption of any debt securities;
- reduce the principal amount of discount securities payable upon acceleration of maturity; or
- make any change to certain provisions of the indenture relating to the rights of holders to institute suit with respect to the indenture or the debt securities of a series and the modification or supplement of the indenture or the debt securities of any series requiring the consent of holders of our debt securities. (Section 8.2)

The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series (Section 6.4); provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration. (Section 6.2)

Defeasance; Satisfaction and Discharge

Legal Defeasance. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, we may be discharged from any and all obligations in respect of the debt securities of any series (subject to certain exceptions). We will be so discharged upon the irrevocable deposit with the trustee, in trust, of money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money or U.S. government obligations in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities.

This discharge may occur only if, among other things, we have delivered to the trustee an opinion of counsel stating that we have received from, or there has been published by, the United States Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable United States federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit, defeasance and discharge and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit, defeasance and discharge had not occurred. (Section 9.4)

Defeasance of Certain Covenants. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, upon compliance with certain conditions:

- we may omit to comply with the covenant described under the heading “Consolidation, Merger and Sale of Assets” and certain other covenants set forth in the indenture, as well as any additional covenants which may be set forth in the applicable prospectus supplement; and
- any omission to comply with those covenants will not constitute a Default or an Event of Default with respect to the debt securities of that series.

This is referred to as covenant defeasance. The conditions include:

- depositing with the trustee money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities; and
- delivering to the trustee an opinion of counsel to the effect that the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit and related covenant defeasance and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit and related covenant defeasance had not occurred. (Section 9.3)

No Personal Liability of Directors, Officers, Employees or Stockholders

None of our past, present or future directors, officers, employees or stockholders, as such, will have any liability for any of our obligations under the debt securities or the indenture or for any claim based on, or in respect or by reason of, such obligations or their creation. By accepting a debt security, each holder waives and releases all such liability. This waiver and release is part of the consideration for the issue of the debt securities. However, this waiver and release may not be effective to waive liabilities under U.S. federal securities laws, and it is the view of the SEC that such a waiver is against public policy. (Section 10.9)

Governing Law

The indenture and the debt securities, including any claim or controversy arising out of or relating to the indenture or the securities, will be governed by the laws of the State of New York. (Section 10.8)

DESCRIPTION OF WARRANTS

We may issue warrants for the purchase of shares of our common stock or preferred stock or of debt securities. We may issue warrants independently or together with other securities, and the warrants may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and the investors or a warrant agent. The following summary of material provisions of the warrants and warrant agreements are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement and warrant certificate applicable to a particular series of warrants. The terms of any warrants offered under a prospectus supplement may differ from the terms described below. We urge you to read the applicable prospectus supplement and any related free writing prospectus, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants.

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

The particular terms of any issue of warrants will be described in the prospectus supplement relating to the issue. Those terms may include:

- the number of shares of common stock or preferred stock purchasable upon the exercise of warrants to purchase such shares and the price at which such number of shares may be purchased upon such exercise;
- the designation, stated value and terms (including, without limitation, liquidation, dividend, conversion and voting rights) of the series of preferred stock purchasable upon exercise of warrants to purchase preferred stock;
- the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;
- the date, if any, on and after which the warrants and the related debt securities, preferred stock or common stock will be separately transferable;
- the terms of any rights to redeem or call the warrants;
- the date on which the right to exercise the warrants will commence and the date on which the right will expire; United States Federal income tax consequences applicable to the warrants; and
- any additional terms of the warrants, including terms, procedures, and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

- to vote, consent or receive dividends;
- receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or
- exercise any rights as stockholders of Zynherba Pharmaceuticals, Inc.

Each warrant will entitle its holder to purchase the principal amount of debt securities or the number of shares of preferred stock or common stock at the exercise price set forth in, or calculable as set forth in, the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

A holder of warrant certificates may exchange them for new warrant certificates of different denominations, present them for registration of transfer and exercise them at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Until any warrants to purchase debt securities are exercised, the holder of the warrants will not have any rights of holders of the debt securities that can be purchased upon exercise, including any rights to receive payments of principal, premium or interest on the underlying debt securities or to enforce covenants in the applicable indenture. Until any warrants to purchase common stock or preferred stock are exercised, the holders of the warrants will not have any rights of holders of the underlying common stock or preferred stock, including any rights to receive dividends or payments upon any liquidation, dissolution or winding up on the common stock or preferred stock, if any.

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.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

- 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.

GLOBAL SECURITIES

Book-Entry, Delivery and Form

Unless we indicate differently in any applicable prospectus supplement or free writing prospectus, the securities initially will be issued in book-entry form and represented by one or more global notes or global securities, or, collectively, global securities. The global securities will be deposited with, or on behalf of, The Depository Trust Company, New York, New York, as depository, or DTC, and registered in the name of Cede & Co., the nominee of DTC. Unless and until it is exchanged for individual certificates evidencing securities under the limited circumstances described below, a global security may not be transferred except as a whole by the depository to its nominee or by the nominee to the depository, or by the depository or its nominee to a successor depository or to a nominee of the successor depository.

DTC has advised us that it is:

- a limited-purpose trust company organized under the New York Banking Law;
- a “banking organization” within the meaning of the New York Banking Law; a member of the Federal Reserve System;
- a “clearing corporation” within the meaning of the New York Uniform Commercial Code; and
- a “clearing agency” registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC holds securities that its participants deposit with DTC. DTC also facilitates the settlement among its participants of securities transactions, such as transfers and pledges, in deposited securities through electronic computerized book-entry changes in participants’ accounts, thereby eliminating the need for physical movement of securities certificates. “Direct participants” in DTC include securities brokers and dealers, including underwriters, banks, trust companies, clearing corporations and other organizations. DTC is a wholly-owned subsidiary of The Depository Trust & Clearing Corporation, or DTCC. DTCC is the holding company for DTC, National Securities Clearing Corporation and Fixed Income Clearing Corporation, all of which are registered clearing agencies. DTCC is owned by the users of its regulated subsidiaries. Access to the DTC system is also available to others, which we sometimes refer to as indirect participants, that clear through or maintain a custodial relationship with a direct participant, either directly or indirectly. The rules applicable to DTC and its participants are on file with the SEC.

Purchases of securities under the DTC system must be made by or through direct participants, which will receive a credit for the securities on DTC’s records. The ownership interest of the actual purchaser of a security, which we sometimes refer to as a beneficial owner, is in turn recorded on the direct and indirect participants’ records. Beneficial owners of securities will not receive written confirmation from DTC of their purchases. However, beneficial owners are expected to receive written confirmations providing details of their transactions, as well as periodic statements of their holdings, from the direct or indirect participants through which they purchased securities. Transfers of ownership interests in global securities are to be accomplished by entries made on the books of participants acting on behalf of beneficial owners. Beneficial owners will not receive certificates representing their ownership interests in the global securities, except under the limited circumstances described below.

To facilitate subsequent transfers, all global securities deposited by direct participants with DTC will be registered in the name of DTC’s partnership nominee, Cede & Co., or such other name as may be requested by an authorized representative of DTC. The deposit of securities with DTC and their registration in the name of Cede & Co. or such other nominee will not change the beneficial ownership of the securities. DTC has no knowledge of the actual beneficial owners of the securities. DTC’s records reflect only the identity of the direct participants to whose accounts the securities are credited, which may or may not be the beneficial owners. The participants are responsible for keeping account of their holdings on behalf of their customers.

So long as the securities are in book-entry form, you will receive payments and may transfer securities only through the facilities of the depository and its direct and indirect participants. We will maintain an office or agency in the location specified in the prospectus supplement for the applicable securities, where notices and demands in respect of the securities and the indenture may be delivered to us and where certificated securities may be surrendered for payment, registration of transfer or exchange.

Conveyance of notices and other communications by DTC to direct participants, by direct participants to indirect participants and by direct participants and indirect participants to beneficial owners will be governed by arrangements among them, subject to any legal requirements in effect from time to time.

Redemption notices will be sent to DTC. If less than all of the securities of a particular series are being redeemed, DTC's practice is to determine by lot the amount of the interest of each direct participant in the securities of such series to be redeemed.

Neither DTC nor Cede & Co. (or such other DTC nominee) will consent or vote with respect to the securities. Under its usual procedures, DTC will mail an omnibus proxy to us as soon as possible after the record date. The omnibus proxy assigns the consenting or voting rights of Cede & Co. to those direct participants to whose accounts the securities of such series are credited on the record date, identified in a listing attached to the omnibus proxy.

So long as securities are in book-entry form, we will make payments on those securities to the depository or its nominee, as the registered owner of such securities, by wire transfer of immediately available funds. If securities are issued in definitive certificated form under the limited circumstances described below and unless if otherwise provided in the description of the applicable securities herein or in the applicable prospectus supplement, we will have the option of making payments by check mailed to the addresses of the persons entitled to payment or by wire transfer to bank accounts in the United States designated in writing to the applicable trustee or other designated party at least 15 days before the applicable payment date by the persons entitled to payment, unless a shorter period is satisfactory to the applicable trustee or other designated party.

Redemption proceeds, distributions and dividend payments on the securities will be made to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC. DTC's practice is to credit direct participants' accounts upon DTC's receipt of funds and corresponding detail information from us on the payment date in accordance with their respective holdings shown on DTC records. Payments by participants to beneficial owners will be governed by standing instructions and customary practices, as is the case with securities held for the account of customers in bearer form or registered in "street name." Those payments will be the responsibility of participants and not of DTC or us, subject to any statutory or regulatory requirements in effect from time to time. Payment of redemption proceeds, distributions and dividend payments to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC, is our responsibility, disbursement of payments to direct participants is the responsibility of DTC, and disbursement of payments to the beneficial owners is the responsibility of direct and indirect participants.

Except under the limited circumstances described below, purchasers of securities will not be entitled to have securities registered in their names and will not receive physical delivery of securities. Accordingly, each beneficial owner must rely on the procedures of DTC and its participants to exercise any rights under the securities and the indenture.

The laws of some jurisdictions may require that some purchasers of securities take physical delivery of securities in definitive form. Those laws may impair the ability to transfer or pledge beneficial interests in securities.

DTC may discontinue providing its services as securities depository with respect to the securities at any time by giving reasonable notice to us. Under such circumstances, in the event that a successor depository is not obtained, securities certificates are required to be printed and delivered.

As noted above, beneficial owners of a particular series of securities generally will not receive certificates representing their ownership interests in those securities. However, if:

- DTC notifies us that it is unwilling or unable to continue as a depository for the global security or securities representing such series of securities or if DTC ceases to be a clearing agency registered under the Exchange Act at a time when it is required to be registered and a successor depository is not appointed within 90 days of the notification to us or of our becoming aware of DTC's ceasing to be so registered, as the case may be;
- we determine, in our sole discretion, not to have such securities represented by one or more global securities; or
- an Event of Default has occurred and is continuing with respect to such series of securities,

we will prepare and deliver certificates for such securities in exchange for beneficial interests in the global securities. Any beneficial interest in a global security that is exchangeable under the circumstances described in the preceding sentence will be exchangeable for securities in definitive certificated form registered in the names that the depository directs. It is expected that these directions will be based upon directions received by the depository from its participants with respect to ownership of beneficial interests in the global securities.

Euroclear and Clearstream

If so provided in the applicable prospectus supplement, you may hold interests in a global security through Clearstream Banking S.A., which we refer to as “Clearstream,” or Euroclear Bank S.A./N.V., as operator of the Euroclear System, which we refer to as “Euroclear,” either directly if you are a participant in Clearstream or Euroclear or indirectly through organizations which are participants in Clearstream or Euroclear. Clearstream and Euroclear will hold interests on behalf of their respective participants through customers’ securities accounts in the names of Clearstream and Euroclear, respectively, on the books of their respective U.S. depositories, which in turn will hold such interests in customers’ securities accounts in such depositories’ names on DTC’s books.

Clearstream and Euroclear are securities clearance systems in Europe. Clearstream and Euroclear hold securities for their respective participating organizations and facilitate the clearance and settlement of securities transactions between those participants through electronic book-entry changes in their accounts, thereby eliminating the need for physical movement of certificates.

Payments, deliveries, transfers, exchanges, notices and other matters relating to beneficial interests in global securities owned through Euroclear or Clearstream must comply with the rules and procedures of those systems. Transactions between participants in Euroclear or Clearstream, on one hand, and other participants in DTC, on the other hand, are also subject to DTC’s rules and procedures.

Investors will be able to make and receive through Euroclear and Clearstream payments, deliveries, transfers and other transactions involving any beneficial interests in global securities held through those systems only on days when those systems are open for business. Those systems may not be open for business on days when banks, brokers and other institutions are open for business in the United States.

Cross-market transfers between participants in DTC, on the one hand, and participants in Euroclear or Clearstream, on the other hand, will be effected through DTC in accordance with the DTC’s rules on behalf of Euroclear or Clearstream, as the case may be, by their respective U.S. depositories; however, such cross-market transactions will require delivery of instructions to Euroclear or Clearstream, as the case may be, by the counterparty in such system in accordance with the rules and procedures and within the established deadlines (European time) of such system. Euroclear or Clearstream, as the case may be, will, if the transaction meets its settlement requirements, deliver instructions to its U.S. depository to take action to effect final settlement on its behalf by delivering or receiving interests in the global securities through DTC, and making or receiving payment in accordance with normal procedures for same-day fund settlement. Participants in Euroclear or Clearstream may not deliver instructions directly to their respective U.S. depositories.

Due to time zone differences, the securities accounts of a participant in Euroclear or Clearstream purchasing an interest in a global security from a direct participant in DTC will be credited, and any such crediting will be reported to the relevant participant in Euroclear or Clearstream, during the securities settlement processing day (which must be a business day for Euroclear or Clearstream) immediately following the settlement date of DTC. Cash received in Euroclear or Clearstream as a result of sales of interests in a global security by or through a participant in Euroclear or Clearstream to a direct participant in DTC will be received with value on the settlement date of DTC but will be available in the relevant Euroclear or Clearstream cash account only as of the business day for Euroclear or Clearstream following DTC’s settlement date.

Other

The information in this section of this prospectus concerning DTC, Clearstream, Euroclear and their respective book-entry systems has been obtained from sources that we believe to be reliable, but we do not take responsibility for this information. This information has been provided solely as a matter of convenience. The rules and procedures of DTC, Clearstream and Euroclear are solely within the control of those organizations and could change at any time. Neither we nor the trustee nor any agent of ours or of the trustee has any control over those entities and none of us takes any responsibility for their activities. You are urged to contact DTC, Clearstream and Euroclear or their respective participants directly to discuss those matters. In addition, although we expect that DTC, Clearstream and Euroclear will perform the foregoing procedures, none of them is under any obligation to perform or continue to perform such procedures and such procedures may be discontinued at any time. Neither we nor any agent of ours will have any responsibility for the performance or nonperformance by DTC, Clearstream and Euroclear or their respective participants of these or any other rules or procedures governing their respective operations.

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 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;

- 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 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.

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 Pepper Hamilton LLP, Philadelphia, Pennsylvania. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Zynerva Pharmaceuticals, Inc. and subsidiary as of December 31, 2018 and 2017 and for each of the years in the three-year period ended December 31, 2018, 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.



Up to \$75,000,000

Common Stock

Prospectus Supplement

Cantor

Canaccord Genuity

H.C. Wainwright & Co.

Ladenburg Thalmann

May 12, 2021
