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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended September 30, 2021

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number: 001-37526

Zynerba Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

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

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

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

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

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

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

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

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

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

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

As of November 11, 2021, the registrant had 41,217,537 shares of common stock, $0.001 par value per share, outstanding.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

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

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

- our expectations, projections and estimates regarding expenses, future revenue, capital requirements, 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, or our 2020 Annual Report, and our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2021 and June 30, 2021, under the caption "Item 1A. Risk Factors".

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

PART I – FINANCIAL INFORMATION

Item 1. Consolidated Financial Statements (Unaudited)

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(UNAUDITED)

	September 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 75,642,498	$ 59,157,187
Incentive and tax receivables	8,535,607	9,042,586
Prepaid expenses and other current assets	3,880,014	5,166,401
Total current assets	88,058,119	73,366,174
Property and equipment, net	447,728	585,403
Incentive and tax receivables	868,083	—
Right-of-use assets	622,240	105,199
Total assets	$ 89,996,170	$ 74,056,776
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 2,636,350	$ 2,522,716
Accrued expenses	8,053,949	11,280,843
Lease liabilities	207,635	109,689
Total current liabilities	10,897,934	13,913,248
Lease liabilities, long-term	411,237	—
Total liabilities	11,309,171	13,913,248
Stockholders' equity:		
Preferred stock, $0.001 par value; 10,000,000 shares authorized; no shares issued or outstanding	—	—
Common stock, $0.001 par value; 200,000,000 shares authorized; 41,281,537 shares issued and outstanding at September 30, 2021 and 29,975,264 shares issued and outstanding at December 31, 2020	41,282	29,975
Additional paid-in capital	309,312,130	262,286,008
Accumulated deficit	(230,666,413)	(202,172,455)
Total stockholders' equity	78,686,999	60,143,528
Total liabilities and stockholders' equity	$ 89,996,170	$ 74,056,776

See accompanying notes to unaudited consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(UNAUDITED)

	Three months ended September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
Operating expenses:				
Research and development	$ 6,341,171	$ 5,805,948	$ 16,402,129	$ 30,038,582
General and administrative	3,869,481	3,425,831	11,531,824	11,834,434
Total operating expenses	10,210,652	9,231,779	27,933,953	41,873,016
Loss from operations	(10,210,652)	(9,231,779)	(27,933,953)	(41,873,016)
Other income (expense):				
Interest income	5,038	10,781	16,614	239,066
Foreign exchange (loss) gain	(376,637)	172,467	(576,619)	(85,171)
Total other expense	(371,599)	183,248	(560,005)	153,895
Net loss	$ (10,582,251)	$ (9,048,531)	$ (28,493,958)	$ (41,719,121)
Net loss per share basic and diluted	$ (0.26)	$ (0.31)	$ (0.73)	$ (1.59)
Basic and diluted weighted average shares outstanding	40,092,128	29,243,375	38,933,209	26,258,626

See accompanying notes to unaudited consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(UNAUDITED)

	Nine months ended September 30, 2021				
	Common stock		Additional paid-in capital	Accumulated deficit	Total stockholders' equity
	Shares	Amount			
Balance at December 31, 2020	**29,975,264**	**$ 29,975**	**$ 262,286,008**	**$ (202,172,455)**	**$ 60,143,528**
Issuance of common stock, net of issuance costs	10,244,326	10,245	42,210,099	—	42,220,344
Issuance of restricted stock	1,018,822	1,019	(1,019)	—	—
Exercise of stock options	13,125	13	47,893	—	47,906
Stock-based compensation expense	—	—	1,264,837	—	1,264,837
Net loss	—	—	—	(7,961,628)	(7,961,628)
Balance at March 31, 2021	**41,251,537**	**41,252**	**305,807,818**	**(210,134,083)**	**95,714,987**
Stock-based compensation expense	—	—	1,934,349	—	1,934,349
Net loss	—	—	—	(9,950,079)	(9,950,079)
Balance at June 30, 2021	**41,251,537**	**41,252**	**307,742,167**	**(220,084,162)**	**87,699,257**
Issuance of restricted stock	30,000	30	(30)	—	—
Stock-based compensation expense	—	—	1,569,993	—	1,569,993
Net loss	—	—	—	(10,582,251)	(10,582,251)
Balance at September 30, 2021	**41,281,537**	**$ 41,282**	**$ 309,312,130**	**$ (230,666,413)**	**$ 78,686,999**

	Nine months ended September 30, 2020				
	Common stock		Additional paid-in capital	Accumulated deficit	Total stockholders' equity
	Shares	Amount			
Balance at December 31, 2019	**23,211,391**	**$ 23,211**	**$ 226,409,156**	**$ (150,835,624)**	**$ 75,596,743**
Issuance of common stock, net of issuance costs	356,000	356	1,581,694	—	1,582,050
Issuance of restricted stock	5,000	5	(5)	—	—
Stock-based compensation expense	—	—	1,323,352	—	1,323,352
Net loss	—	—	—	(12,337,829)	(12,337,829)
Balance at March 31, 2020	**23,572,391**	**23,572**	**229,314,197**	**(163,173,453)**	**66,164,316**
Issuance of common stock, net of issuance costs	5,682,784	5,683	27,240,793	—	27,246,476
Stock-based compensation expense	—	—	1,347,433	—	1,347,433
Net loss	—	—	—	(20,332,761)	(20,332,761)
Balance at June 30, 2020	**29,255,175**	**29,255**	**257,902,423**	**(183,506,214)**	**74,425,464**
Issuance of restricted stock	194,000	194	(194)	—	—
Stock-based compensation expense	—	—	1,262,625	—	1,262,625
Net loss	—	—	—	(9,048,531)	(9,048,531)
Balance at September 30, 2020	**29,449,175**	**$ 29,449**	**$ 259,164,854**	**$ (192,554,745)**	**$ 66,639,558**

See accompanying notes to unaudited consolidated financial statements.

ZYNERBA PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(UNAUDITED)

	Nine months ended September 30,	
	2021	2020
Cash flows from operating activities:		
Net loss	$ (28,493,958)	$ (41,719,121)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	185,245	147,253
Stock-based compensation	4,769,179	3,933,410
Changes in operating assets and liabilities:		
Incentive and tax receivables	(361,104)	6,396,274
Prepaid expenses and other assets	1,424,002	(1,727,805)
Right-of-use assets and liabilities	(7,858)	(333)
Accounts payable	113,634	(1,270,587)
Accrued expenses	(3,252,118)	(86,366)
Net cash used in operating activities	(25,622,978)	(34,327,275)
Cash flows from investing activities:		
Purchases of property and equipment	(47,570)	(383,223)
Net cash used in investing activities	(47,570)	(383,223)
Cash flows from financing activities:		
Proceeds from the issuance of common stock	43,193,660	29,766,385
Payment of financing fees and expenses	(1,085,707)	(807,924)
Proceeds from the exercise of stock options	47,906	—
Net cash provided by financing activities	42,155,859	28,958,461
Net increase in cash and cash equivalents	16,485,311	(5,752,037)
Cash and cash equivalents at beginning of period	59,157,187	70,063,242
Cash and cash equivalents at end of period	$ 75,642,498	$ 64,311,205
Supplemental disclosures of cash flow information:		
Financing costs included in accounts payable and accrued expenses at end of period	$ 42,500	$ —
Property and equipment acquired but unpaid at end of period	$ —	$ 13,418

See accompanying notes to unaudited consolidated financial statements

ZYNERBA PHARMACEUTICALS, NC.
NOTES TO UNAUDITED CONSOLIDATED FINANCIAL STATEMENTS

(1) Nature of Business and Liquidity

Zynerba Pharmaceuticals, Inc., together with its subsidiary, Zynerba Pharmaceuticals Pty Ltd (collectively, "Zynerba," the "Company," or "we"), is a clinical stage specialty pharmaceutical company focused on the development of pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders, including Fragile X syndrome, autism spectrum disorder, 22q11.2 deletion syndrome, and a heterogeneous group of rare and ultra-rare epilepsies known as developmental and epileptic encephalopathies.

The Company has incurred losses and negative cash flows from operations since inception and has an accumulated deficit of $230.7 million as of September 30, 2021. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant revenue from its product candidates currently in development. The Company's primary source of liquidity has been the issuance of equity securities.

On May 11, 2021, the Company entered into a Controlled Equity Offering^{SM} Sales Agreement (the "2021 Sales Agreement") with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., as sales agents (collectively, the "2021 Sales Agents"), pursuant to which the Company may sell, from time to time, up to $75.0 million of its common stock. As of November 15, 2021, there have been no sales of common stock under the 2021 Sales Agreement.

In August 2019, the Company entered into a Controlled Equity Offering^{SM} Sales Agreement (the "2019 Sales Agreement") with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., as sales agents (collectively, the "2019 Sales Agents"), pursuant to which the Company sold $75.0 million of its common stock. In the first quarter of 2021, the Company sold and issued 10,244,326 shares of common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $4.22 per share, resulting in gross proceeds of $43.2 million. Net proceeds after deducting commissions and offering expenses were $42.2 million. In 2020, the Company sold and issued 6,596,873 shares of common stock in the open market at a weighted-average selling price of $4.81 per share, for gross proceeds of $31.7 million and net proceeds, after deducting commissions and offering expenses, of $30.7 million. The last sale under the 2019 Sales Agreement was made on February 9, 2021. From August 2019 through February 9, 2021, the Company received cumulative gross proceeds of $75.0 million from shares sold in the open market under the 2019 Sales Agreement, which was terminated pursuant to its terms.

Management believes that the Company's cash and cash equivalents as of September 30, 2021 are sufficient to fund operations and capital requirements well into the first half of 2024. Substantial additional financings will be needed by the Company to fund its operations, and to complete clinical development of and to commercially develop its product candidates. The Company's ability to raise sufficient additional financing depends on many factors beyond its control, including the current and ongoing volatility in the capital markets as a result of the COVID-19 pandemic. There is no assurance that such financing will be available when needed or on acceptable terms.

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

(2) Summary of Significant Accounting Policies

a. Basis of Presentation

The accompanying unaudited interim consolidated financial statements of the Company have been prepared in accordance with U.S. generally accepted accounting principles ("GAAP") for interim financial information and with the instructions to Form 10-Q and Article 10 of Regulation S-X. The interim unaudited consolidated financial statements have been prepared on the same basis as the consolidated financial statements as of and for the year ended December 31, 2020 included in the Company's Annual Report on Form 10-K for the year ended December 31, 2020 ("2020 Annual

Report"), filed with the Securities and Exchange Commission (the "SEC"). In the opinion of management, the accompanying consolidated financial statements of the Company include all normal and recurring adjustments (which consist primarily of accruals, estimates and assumptions that impact the consolidated financial statements) considered necessary to present fairly the Company's financial position as of September 30, 2021, its results of operations for the three and nine months ended September 30, 2021 and 2020 and cash flows for the nine months ended September 30, 2021 and 2020. Operating results for any interim period are not necessarily indicative of results for any future interim period or for the entire year. The accompanying unaudited interim consolidated financial statements should be read in conjunction with the consolidated financial statements and related notes included in the Company's 2020 Annual Report.

b. Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities at the date of the financial statements and reported amounts of expenses during the reporting period. Actual results could differ from such estimates.

c. Incentive and Tax Receivables

The Company's subsidiary, Zynerba Pharmaceuticals Pty Ltd (the "Subsidiary"), is incorporated in Australia. The Subsidiary is eligible to participate in an Australian research and development tax incentive program. As part of this program, the Subsidiary is eligible to receive a cash refund from the Australian Taxation Office ("ATO") for a percentage of the research and development costs expended by the Subsidiary in Australia. The cash refund is available to eligible companies with an annual aggregate revenue of less than $20.0 million (Australian dollars) during the reimbursable period. The Company estimates the amount of cash refund it expects to receive related to the Australian research and development tax incentive program and records the incentives when it is probable (1) the Company will comply with relevant conditions of the program and (2) the incentive will be received.

Certain research and development expenses incurred with respect to the Company's lead product candidate Zygel outside of Australia may also be eligible for the Australian research and development tax incentive program. To receive a cash refund with respect to such expenses incurred outside of Australia, the expenses must have been for eligible research and development activities, as determined by AusIndustry, a division of the Australian Government's Department of Industry, Innovation and Science ("AusIndustry"), and the expenditures must have a scientific link to the Australian activities, be unable to be conducted in Australia and be less than the expenditures for activities conducted in Australia, as determined by the ATO. In December 2018, the Company submitted an Advance Overseas Finding ("AOF") application to AusIndustry for a determination that a portion of the Company's activities outside of Australia are eligible research and development activities, which was approved by AusIndustry in July 2019.

As a result of this finding, the Company believes it is eligible to receive a cash refund from the ATO for qualifying expenditures related to its research and development activities outside of Australia in 2018, 2019 and 2020. During the year ended December 31, 2019, the Company recorded $8.3 million as an incentive and tax receivable and recorded a corresponding credit to research and development expense for amounts expected to be received through the AOF for the period January 1, 2018 through September 30, 2019. As of September 30, 2021, incentive and tax receivables included $8.5 million related to the AOF. The increase of $0.2 million was due to unrealized foreign currency gains related to the remeasurement of the Subsidiary's assets and liabilities.

The Company evaluates its eligibility under tax incentive programs as of each balance sheet date based on the most current and relevant data available. If the Company is deemed to be ineligible or unable to receive the Australian research and development tax credit, or the Australian government significantly reduces or eliminates the tax credit, the actual cash refund the Company receives may materially differ from its estimates. In June 2020, the ATO informed the Company that it may not qualify for the AOF program based on their interpretation of certain eligibility requirements. Although the Company continues to believe that it complies with the relevant conditions of the AOF program that were in place when the Company received its original approval from AusIndustry, the Company determined it was no longer probable that the AOF claim would be received. As a result, during the three months ended June 30, 2020, the Company recorded a full reserve against the AOF receivable.

In addition, the Subsidiary incurs Goods and Services Tax ("GST") on services provided by Australian vendors. As an Australian entity, the Subsidiary is entitled to a refund of the GST paid. The Company's estimate of the amount of cash refund it expects to receive related to GST incurred is included in "Incentive and tax receivables" in the accompanying consolidated balance sheets. As of September 30, 2021, incentive and tax receivables included $0.3 million for refundable GST on expenses incurred with Australian vendors during the three months ended September 30, 2021.

Current incentive and tax receivables consisted of the following as of September 30, 2021 and December 31, 2020:

	September 30, 2021	December 31, 2020
Research and development incentive (non-AOF) for the period 1/1/18 - 12/31/18	$ 3,225,983	$ 3,425,791
Research and development incentive (non-AOF) for the period 1/1/19 - 12/31/19	3,005,880	3,192,056
Research and development incentive (non-AOF) for the period 1/1/20 - 12/31/20	2,002,949	2,127,005
Research and development incentive (AOF) for the period 1/1/18 - 12/31/19	8,518,450	9,046,058
Goods and services tax	300,795	297,734
Total incentive and tax receivables before reserve for AOF	17,054,057	18,088,644
Reserve for research and development incentive (AOF) for the period 1/1/18 - 12/31/19	(8,518,450)	(9,046,058)
Total incentive and tax receivables - current assets	$ 8,535,607	$ 9,042,586

As of September 30, 2021, the Company's estimate of the amount of cash refund it expects to receive for 2020, 2019 and 2018 eligible spending as part of this incentive program was $8.2 million and was recorded as a current asset. The Company's estimate of the amount of cash refund it expects to receive for 2021 eligible spending through September 30, 2021 was $0.9 million and was recorded as a non-current asset.

d. Research and Development

Research and development costs are expensed as incurred and are primarily comprised of external research and development expenses incurred under arrangements with third parties, such as contract research organizations, contract manufacturing organizations, consultants and employee-related expenses including salaries and benefits. At the end of each reporting period, the Company compares the payments made to each service provider to the estimated progress towards completion of the related project. Factors that the Company considers in preparing these estimates include the number of patients enrolled in studies, milestones achieved and other criteria related to the efforts of its vendors. These estimates will be subject to change as additional information becomes available. Depending on the timing of payments to vendors and estimated services provided, the Company will record net prepaid or accrued expenses related to these costs. Research and development expenses are recorded net of expected refunds of eligible research and development costs paid pursuant to the Australian research and development tax incentive program and GST incurred on services provided by Australian vendors.

The following table summarizes research and development expenses for the three and nine months ended September 30, 2021 and 2020:

	Three months ended September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
Research and development expenses - before R&D incentive	$ 6,682,361	$ 6,177,830	$ 17,304,684	$ 23,526,911
Research and development incentive (non-AOF)	(341,190)	(371,882)	(902,555)	(1,596,024)
Research and development expenses (before impact of AOF)	6,341,171	5,805,948	16,402,129	21,930,887
Amounts reserved against AOF refund	—	—	—	8,107,695
Total research and development expenses	$ 6,341,171	$ 5,805,948	$ 16,402,129	$ 30,038,582

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO UNAUDITED CONSOLIDATED FINANCIAL STATEMENTS (Continued)

e. Net Loss Per Share

Basic net loss per share is determined using the weighted average number of shares of common stock outstanding during each period. Diluted net income per share includes the effect, if any, from the potential exercise or conversion of securities, such as restricted stock and stock options, which would result in the issuance of incremental shares of common stock. Basic and dilutive computations of net loss per share are the same in periods in which a net loss exists as the dilutive effects of restricted stock and stock options would be anti-dilutive.

The following potentially dilutive securities outstanding as of September 30, 2021 and 2020 have been excluded from the computation of diluted weighted average shares outstanding, as their effects on net loss per share for the periods presented would be anti-dilutive:

	September 30,	
	2021	2020
Stock options	5,300,538	4,710,201
Unvested restricted stock	1,053,822	205,800
	6,354,360	4,916,001

f. Recent Accounting Pronouncements

The Company does not expect the adoption of recently issued accounting pronouncements to have a significant impact on its results of operations, financial position or cash flow.

(3) Fair Value Measurements

The Company measures certain assets and liabilities at fair value in accordance with Accounting Standards Codification ("ASC") 820, *Fair Value Measurements and Disclosures*. ASC 820 defines fair value as the price that would be received to sell an asset or paid to transfer a liability (the exit price) in an orderly transaction between market participants at the measurement date. The guidance in ASC 820 outlines a valuation framework and creates a fair value hierarchy that serves to increase the consistency and comparability of fair value measurements and the related disclosures. In determining fair value, the Company maximizes the use of quoted prices and observable inputs. Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from independent sources. The fair value hierarchy is broken down into three levels based on the source of inputs as follows:

Level 1 — Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities.

Level 2 — Valuations based on observable inputs and quoted prices in active markets for similar assets and liabilities.

Level 3 — Valuations based on unobservable inputs and models that are supported by little or no market activity.

ZYNERBA PHARMACEUTICALS, INC.
NOTES TO UNAUDITED CONSOLIDATED FINANCIAL STATEMENTS (Continued)

In accordance with the fair value hierarchy described above, the following table sets forth the Company's financial assets measured at fair value on a recurring basis as of September 30, 2021 and December 31, 2020:

	Carrying amount as of September 30, 2021	Fair Value Measurement as of September 30, 2021		
		Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 75,304,732	$ 75,304,732	$ —	$ —
	$ 75,304,732	$ 75,304,732	$ —	$ —

	Carrying amount as of December 31, 2020	Fair Value Measurement as of December 31, 2020		
		Level 1	Level 2	Level 3
Cash equivalents (money market accounts)	$ 59,010,328	$ 59,010,328	$ —	$ —
	$ 59,010,328	$ 59,010,328	$ —	$ —

(4) Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following as of September 30, 2021 and December 31, 2020:

	September 30, 2021	December 31, 2020
Prepaid development expenses	$ 494,918	$ 866,498
Prepaid insurance	2,747,845	1,639,687
Insurance litigation settlement receivable	—	2,389,250
Other current assets	637,251	270,966
Total prepaid expenses and other current assets	$ 3,880,014	$ 5,166,401

(5) Property and Equipment

Property and equipment consisted of the following as of September 30, 2021 and December 31, 2020:

	Estimated useful life (in years)	September 30, 2021	December 31, 2020
Equipment	2-5	$ 740,543	$ 729,489
Computer equipment	3-5	30,319	30,319
Furniture and fixtures	3-5	311,356	311,355
Leasehold improvements	various	68,881	68,881
Construction in process		79,342	42,827
Total cost		1,230,441	1,182,871
Less accumulated depreciation		(782,713)	(597,468)
Property and equipment, net		$ 447,728	$ 585,403

Depreciation expense was $185,245 and $147,253 for the nine months ended September 30, 2021 and 2020, respectively.

(6) Accrued Expenses

Accrued expenses consisted of the following as of September 30, 2021 and December 31, 2020:

	September 30, 2021	December 31, 2020
Accrued compensation	$ 2,097,810	$ 1,928,865
Accrued research and development	5,489,055	4,999,881
Accrued litigation settlement expenses	126,745	4,000,000
Other	340,339	352,097
Total accrued expenses	$ 8,053,949	$ 11,280,843

(7) Common Stock

On May 11, 2021, the Company entered into the 2021 Sales Agreement with the 2021 Sales Agents, pursuant to which the Company may sell, from time to time, up to $75.0 million of its common stock. As of November 15, 2021, there have been no sales of common stock under the 2021 Sales Agreement.

In August 2019, the Company entered into the 2019 Sales Agreement with the 2019 Sales Agents pursuant to which the Company sold $75.0 million of its common stock. In the first quarter of 2021, the Company sold and issued 10,244,326 shares of common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $4.22 per share, resulting in gross proceeds of $43.2 million. Net proceeds after deducting commissions and offering expenses were $42.2 million. In 2020, the Company sold and issued 6,596,873 shares of common stock in the open market at a weighted-average selling price of $4.81 per share, for gross proceeds of $31.7 million and net proceeds, after deducting commissions and offering expenses, of $30.7 million. The last sale under the 2019 Sales Agreement was made on February 9, 2021. From August 2019 through February 9, 2021, the Company received cumulative gross proceeds of $75.0 million from shares sold in the open market under the 2019 Sales Agreement, which was terminated pursuant to its terms.

(8) Stock-Based Compensation

The Company maintains the Amended and Restated 2014 Omnibus Incentive Compensation Plan, as amended (the “2014 Plan”), which allows for the granting of incentive stock options, nonqualified stock options, stock appreciation rights, stock awards, stock units, performance units and other stock-based awards to employees, officers, non-employee directors, consultants, and advisors. In addition, the 2014 Plan provides selected executive employees with the opportunity to receive bonus awards that are considered qualified performance-based compensation. The 2014 Plan is subject to automatic annual increases in the number of shares authorized for issuance under the 2014 Plan on the first trading day of January each year equal to the lesser of 1.5 million shares or 10% of the number of shares of common stock outstanding on the last trading day of December of the preceding year. As of January 1, 2021, the number of shares of common stock that may be issued under the 2014 Plan was automatically increased by 1.5 million shares, increasing the total number of shares of common stock available for issuance under the 2014 Plan to 9,304,869 shares. As of September 30, 2021, 2,227,008 shares were available for future issuance under the 2014 Plan.

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

During the nine months ended September 30, 2021, the Company granted 506,911 time-based restricted stock awards to employees with two-year cliff vesting. In addition, during the nine months ended September 30, 2021, the Company

granted 506,911 performance-based restricted stock awards to employees. Vesting of the performance-based restricted stock awards is dependent on meeting certain performance conditions, which relate to the Company's research and development progress, which were established by the Company's board of directors. The Company's board of directors determines if the performance conditions have been met.

Stock-based compensation expense for these performance-based grants are recorded when management estimates that the vesting of these shares is probable based on the status of the Company's research and development programs and other relevant factors. During the nine months ended September 30, 2021, the performance-based conditions were deemed probable of achievement and the Company has recorded $1.2 million in stock-based compensation expense related to these performance-based grants. As of September 30, 2021, there was $0.6 million of unrecognized stock-based compensation expense related to these performance-based awards, which will be expensed over the estimated service period related to each performance condition.

During the third quarter of 2020, the Company granted 194,000 restricted stock awards that contain both performance-based and service-based conditions, of which 162,000 restricted stock awards remained outstanding as of December 31, 2020. These awards vest on the earlier of: (a) meeting the performance condition or (b) service provided for one-year from the grant date. Awards with both performance and service conditions are being expensed over the service period, with an acceleration of the remaining compensation expense if the performance-based criteria is met before the end of the service condition. During the three months ended September 30, 2021, the outstanding 162,000 restricted stock awards became fully vested.

For the nine months ended September 30, 2021 and 2020, the Company recorded stock-based compensation expense related to its stock option grants and restricted stock awards, as follows:

	Stock Option Grants		Restricted stock awards		Total	
	2021	2020	2021	2020	2021	2020
Research and development	$ 1,198,492	$ 1,548,971	$ 1,245,175	$ 41,314	$ 2,443,667	$ 1,590,285
General and administrative	1,307,844	2,331,520	1,017,668	11,605	2,325,512	2,343,125
	$ 2,506,336	$ 3,880,491	$ 2,262,843	$ 52,919	$ 4,769,179	$ 3,933,410

The following table summarizes the Company's stock option activity for the nine months ended September 30, 2021:

	Number of Shares	Weighted-Average Exercise Price	Weighted-Average Contractual Life (in Years)	Aggregate Intrinsic Value
Outstanding as of December 31, 2020	4,546,484	$ 9.76		
Granted	831,117	3.69		
Exercised	(13,125)	3.65		
Forfeited	(63,938)	15.84		
Outstanding as of September 30, 2021	5,300,538	8.75	6.51	$ 992,108
Exercisable as of September 30, 2021	3,641,575	10.58	5.56	$ 366,167
Vested and expected to vest as of September 30, 2021	5,300,538	$ 8.75		

The weighted-average grant date fair values of options granted during the nine months ended September 30, 2021 and 2020 were $2.84 and $3.58, respectively.

The fair values of stock options granted were calculated using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Nine months ended September 30,	
	2021	2020
Weighted-average risk-free interest rate	0.37%	1.27%
Expected term of options (in years)	6.21	6.18
Expected stock price volatility	95.60%	82.00%
Expected dividend yield	0%	0%

As of September 30, 2021, there was $4.8 million of unrecognized stock-based compensation expense related to stock options, which is expected to be recognized over a weighted-average period of 2.36 years. During the nine months ended September 30, 2021, the Company received $47,906 in cash from the exercise of employee stock options.

The following table summarizes the Company's restricted stock award activity under the 2014 Plan for the nine months ended September 30, 2021:

	Shares	Weighted Average Grant Date Fair Value	Aggregate Intrinsic Value
Unvested as of December 31, 2020	173,800	$ 3.64	
Granted	1,048,822	3.61	
Vested	(168,800)	3.60	
Unvested as of September 30, 2021	1,053,822	$ 3.62	$ 4,468,205
Vested and expected to vest as of September 30, 2021	1,048,822	$ 3.61	$ 4,447,005

As of September 30, 2021, there was $1.9 million of unrecognized stock-based compensation expense related to unvested restricted stock awards, which is expected to be recognized over a weighted-average period of 1.05 years. The Company expects that 1,048,822 of the unvested restricted stock awards will vest.

(9) Operating Lease Obligations

The Company adopted ASC 842 prospectively using the modified-retrospective method and elected the package of transition practical expedients that does not require reassessment of: (1) whether any existing or expired contracts are or contain leases, (2) lease classification and (3) initial direct costs. In addition, the Company has elected other available practical expedients to not separate lease and nonlease components, which consist principally of common area maintenance charges, and to exclude leases with an initial term of 12 months or less.

The Company leases its headquarters where it occupies 10,877 square feet of office space. On March 1, 2021, the Company extended its lease for three additional years until May 31, 2024. The Company's lease contains variable lease costs that do not depend on a rate or index and consist primarily of common area maintenance, taxes, and insurance charges. As the implicit rate was not readily determinable for the Company's lease, the Company used an estimated incremental borrowing rate, or discount rate, to determine the initial present value of the lease payments. The discount rate for the lease was calculated using a synthetic credit rating model.

As of March 1, 2021, the effective date of the lease modification, the Company remeasured the lease liability for the remaining portion of the lease and adjusted the lease liability to $755,085 and right-of-use assets to $752,391, which was recorded net of a deferred rent liability of $2,694. As of September 30, 2021, the Company's right-of-use asset, net of amortization, was $622,240.

Other operating lease information as of September 30, 2021:

Weighted-average remaining lease term - operating leases	2.7 years
Weighted-average discount rate - operating leases	2.76 %

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NOTES TO UNAUDITED CONSOLIDATED FINANCIAL STATEMENTS (Continued)

The following is a maturity analysis of the annual undiscounted cash flows of the operating lease liabilities as of September 30, 2021:

Year ending:	September 30, 2021
December 31, 2021	$ 60,105
December 31, 2022	240,420
December 31, 2023	240,421
December 31, 2024	100,175
Total minimum lease payments	641,121
Less: imputed lease interest	(22,249)
Total lease liabilities	$ 618,872

Lease expense for the nine months ended September 30, 2021 was comprised of the following:

	Nine months ended September 30,	
	2021	2020
Operating lease expense	$ 183,788	$ 192,628
Variable lease expense	46,190	44,023
Total lease expense	$ 229,978	$ 236,651

Cash payments related to operating leases were $191,646 and $192,961 for the nine months ended September 30, 2021 and 2020, respectively.

Item 2. ***Management's Discussion and Analysis of Financial Condition and Results of Operations***

You should read the following discussion and analysis of our financial condition and results of operations together with our unaudited interim consolidated financial statements and related notes appearing elsewhere in this Quarterly Report and the audited consolidated financial statements and notes thereto for the year ended December 31, 2020 and the related Management's Discussion and Analysis of Financial Condition and Results of Operations, both of which are contained in our 2020 Annual Report. The following discussion contains forward-looking statements that involve risks, uncertainties and assumptions. Our actual results and the timing of certain events could differ materially from those anticipated in these forward-looking statements as a result of many factors. We discuss factors that we believe could cause or contribute to these differences below and elsewhere in this Quarterly Report, including those set forth under "Cautionary Note Regarding Forward-looking Statements" and "Risk Factors" in this Quarterly Report and our 2020 Annual Report.

Overview

Company Overview

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

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. Following the positive meeting with the FDA on our development program in ASD, we are evaluating and prioritizing our development options for ASD, 22q and DEE and we expect to provide guidance on the path forward in each of these indications by the end of 2021. As of November 5, 2021, the Zygel safety database across all clinical studies conducted by us includes data from 910 volunteers and patients. Across these clinical studies, Zygel has been well-tolerated.

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 September 2021, we announced that we had initiated our 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) trial, a pivotal, multi-national, confirmatory Phase 3 trial of Zygel in patients with FXS. The trial is designed to confirm the positive results observed in a population of responders in our CONNECT-FX trial.

RECONNECT is an 18-week trial that is expected to enroll approximately 200 children and adolescents, aged three through 17 years, at approximately 25 clinical sites in the United States, Australia, the UK and Ireland. Approximately 160 of the patients enrolled will have complete (100%) methylation of their *FMR1* gene and approximately 40 patients will have partial methylation of their *FMR1* gene. Patients will be randomized 1:1 to either Zygel or placebo. Randomization will be stratified by gender, methylation status and weight.

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

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

Top-line results for the RECONNECT trial are expected in the second half of 2023. All patients who complete dosing in the RECONNECT trial will be eligible to enroll in our ongoing open-label extension 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. In the first half of 2021, we discussed data supporting the potential efficacy of Zygel in ASD, including the results of our Phase 2 BRIGHT trial, with the FDA to determine the regulatory path forward. The guidance from the FDA included agreement on utilizing the irritability subscale of the ABC-C as the primary endpoint to support an indication for the treatment of irritability in ASD. This is the same primary endpoint utilized in the previously completed BRIGHT open label Phase 2 trial.

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. We have added an additional U.S. clinical trial site to the INSPIRE trial to enable recruitment of patients in the United States. 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. In September 2021, these results were published in the *Journal of the American Medical Association (JAMA) Network Open* in an article entitled “Safety and tolerability of transdermal cannabidiol gel in children with developmental and epileptic encephalopathies: A nonrandomized controlled trial.” In December 2020, we reported twelve-month treatment data from the BELIEVE trial for patients who continued to participate during the six-month extension period. 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.

Operations

We continue to closely monitor the status 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 shipments, 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 have not been adversely impacted by COVID-19.

We have never been profitable and have incurred net losses since inception. Our net losses were $28.5 million and $41.7 million for the nine months ended September 30, 2021 and 2020, respectively. As of September 30, 2021, our accumulated deficit was $230.7 million. We expect to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, our product candidates. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability.

Financial Operations Overview

The following discussion sets forth certain components of our consolidated statements of operations as well as factors that impact those items.

Research and Development Expenses

Our research and development expenses relating to our product candidates consisted of the following:

- expenses associated with preclinical development and clinical trials;
- personnel-related expenses, such as salaries, benefits, travel and other related expenses, including stock-based compensation;
- payments to third-party CROs or CMOs, contractor laboratories and independent contractors; and
- depreciation, maintenance and other facility-related expenses.

We expense all research and development costs as incurred. Clinical development expenses for our product candidates are a significant component of our current research and development expenses. Generally, expenses associated with clinical trials will increase as our clinical trials progress. Product candidates in later stage clinical development generally have higher research and development expenses than those in earlier stages of development, primarily due to increased size and duration of the clinical trials. We track and record information regarding external research and development expenses for each grant, study or trial that we conduct. We use third-party CROs, CMOs, contractor laboratories and independent contractors in preclinical studies and clinical trials. We recognize the expenses associated with third parties performing these services for us in our preclinical studies and clinical trials based on the percentage of each study completed at the end of each reporting period.

Our Australian subsidiary, Zynerba Pharmaceuticals Pty Ltd, or the Subsidiary, is incorporated in Australia and is eligible to participate in an Australian research and development tax incentive program. As part of this program, the Subsidiary is eligible to receive a cash refund from the Australian Taxation Office, or ATO, for a percentage of the research and development costs expended by the Subsidiary in Australia. The cash refund is available to eligible companies with an annual aggregate revenue of less than $20.0 million (Australian dollars) during the reimbursable period. We estimate the amount of cash refund we expect to receive related to the Australian research and development tax incentive program and record the incentives when it is probable (1) we will comply with relevant conditions of the program and (2) the incentive will be received.

Certain research and development expenses incurred with respect to Zygel outside of Australia may also be eligible for the Australian research and development tax incentive program. To receive a cash refund with respect to such expenses incurred outside of Australia, the expenses must have been for eligible research and development activities, as determined by AusIndustry, and the expenditures must have a scientific link to the Australian activities, be unable to be conducted in Australia and be less than the expenditures for activities conducted in Australia, as determined by the ATO. In December 2018, the Subsidiary submitted an AOF application to AusIndustry for a determination that its activities are eligible research and development activities, which was approved by AusIndustry in July 2019.

As a result of this finding, we believe the Subsidiary is eligible to receive a cash refund from the ATO for qualifying expenditures related to its research and development activities outside of Australia in 2018, 2019 and 2020. During the year ended December 31, 2019, we recorded $8.3 million as an incentive and tax receivable and recorded a corresponding credit to research and development expense for amounts expected to be received through the AOF for the period January 1, 2018 through September 30, 2019. As of September 30, 2021, incentive and tax receivables included $8.5 million related to the AOF. The increase of $0.2 million was due to unrealized foreign currency gains related to the remeasurement of the Subsidiary’s assets and liabilities.

We evaluate the Subsidiary’s eligibility under tax incentive programs as of each balance sheet date based on the most current and relevant data available. If the Subsidiary is deemed to be ineligible or unable to receive the Australian research and development tax credit, or the Australian government significantly reduces or eliminates the tax credit, the actual cash refund we receive may materially differ from our estimates. In June 2020, the ATO informed us that we may not qualify for the AOF program based on their interpretation of certain eligibility requirements. Although we continue to believe that we comply with the relevant conditions of the AOF program that were in place when we received our original approval from AusIndustry, we have determined it is no longer probable that the AOF claim will be received. As a result, during the three months ended June 30, 2020, we recorded a full reserve against the AOF receivable.

The following table summarizes research and development expenses for the three and nine months ended September 30, 2021 and 2020:

	Three months ended September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
Research and development expenses - before R&D incentive	$ 6,682,361	$ 6,177,830	$ 17,304,684	$ 23,526,911
Research and development incentive (non-AOF)	(341,190)	(371,882)	(902,555)	(1,596,024)
Research and development expenses (before impact of AOF)	6,341,171	5,805,948	16,402,129	21,930,887
Amounts reserved against AOF refund	—	—	—	8,107,695
Total research and development expenses	$ 6,341,171	$ 5,805,948	$ 16,402,129	$ 30,038,582

We expect research and development expenses to decrease for the year ending December 31, 2021 as compared to 2020, as we concluded our pivotal CONNECT-FX clinical trial and our BRIGHT clinical trial during 2020 and recently initiated our RECONNECT pivotal trial in FXS in September 2021. These expenditures are subject to numerous uncertainties regarding timing and cost to completion. Completion of our preclinical development and clinical trials may take several years or more and the length of time generally varies according to the type, complexity, novelty and intended use of a product candidate. The cost of clinical trials may vary significantly over the life of a project as a result of differences arising during clinical development, including, among others:

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

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

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our executive, finance, legal, human resource, investor relations and commercial functions. Our general and administrative expenses also include facility and related costs not included in research and development expenses, professional fees for legal services, including patent-related expenses, litigation settlement expenses, consulting, tax and accounting services, insurance, market research and general corporate expenses. We expect that our general and administrative expenses will increase for the next several years as we increase our headcount with the continued development and potential commercialization of our product candidates.

Interest Income

Interest income primarily consists of interest earned on balances maintained in our money market bank account.

Foreign Exchange (Loss) Gain

Foreign exchange (loss) gain relates to the effect of exchange rates on transactions incurred by the Subsidiary.

Critical Accounting Estimates

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

We define our critical accounting policies as those that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations as

well as the specific manner in which we apply those principles. Critical accounting estimates and the accounting policies critical to the process of making significant judgments and estimates in the preparation of our consolidated financial statements are discussed in our 2020 Annual Report under Part II, Item 7, “Critical Accounting Policies and Use of Estimates.” During the nine months ended September 30, 2021, there have been no material changes to the critical accounting estimates or critical accounting policies discussed in our 2020 Annual Report.

Results of Operations

Comparison of the Three Months Ended September 30, 2021 and 2020

Research and Development Expenses

Research and development expenses increased by $0.5 million, or 9%, to $6.3 million for the three months ended September 30, 2021 from $5.8 million for the three months ended September 30, 2020. The increase was primarily related to increases in manufacturing costs associated with our Zygel program, clinical trial expenses incurred for the initiation of our RECONNECT trial, stock-based compensation expenses and a reduction in the non-AOF Australian research and development incentive; partially offset by decreased clinical trial costs associated with our Zygel program following the conclusion of our CONNECT-FX and BRIGHT clinical trials.

General and Administrative Expenses

General and administrative expenses increased by $0.4 million, or 13%, to $3.9 million for the three months ended September 30, 2021 from $3.4 million for the three months ended September 30, 2020. The increase was primarily related to increases in directors’ and officers’ liability insurance and legal expenses.

Other Income (Expense)

During the three months ended September 30, 2021 and 2020, we recognized $5,038 and $10,781, respectively, in interest income. The decrease in interest income was related to lower average interest rates earned on our investments. During the three months ended September 30, 2021 and 2020, we recognized a foreign currency loss of $0.4 million and a foreign currency gain of $0.2 million, respectively. Foreign currency gains and losses are due primarily to the remeasurement of the Subsidiary’s assets and liabilities, which are denominated in the local currency to the Subsidiary’s functional currency, which is the U.S. dollar.

Comparison of the Nine Months Ended September 30, 2021 and 2020

Research and Development Expenses

	Nine months ended September 30,	
	2021	2020
Research and development expenses (before impact of AOF)	$ 16,402,129	$ 21,930,887
Amounts reserved against AOF refund	—	8,107,695
Total research and development expenses	$ 16,402,129	$ 30,038,582

Excluding the $8.1 million increase in research and development expenses for the amounts reserved against the AOF receivable during the nine months ended September 30, 2020, research and development expenses decreased by $5.5 million, or 25%, to $16.4 million for the nine months ended September 30, 2021 from $21.9 million for the nine months ended September 30, 2020. The decrease was primarily related to decreased clinical trial and manufacturing costs associated with our Zygel program following the conclusion of our CONNECT-FX and BRIGHT clinical trials; partially offset by expenses incurred for the initiation of our RECONNECT trial, an increase in stock-based compensation expenses and a reduction in the non-AOF Australian research and development incentive.

General and Administrative Expenses

General and administrative expenses decreased by $0.3 million, or 3%, to $11.5 million for the nine months ended September 30, 2021 from $11.8 million for the nine months ended September 30, 2020. The decrease was primarily related to decreases in pre-commercialization expense for Zygel and decreased employee-related costs partially offset by

an increase in directors' and officers' liability insurance and an increase in proxy solicitation costs related to our annual stockholders' meeting.

Other Income (Expense)

During the nine months ended September 30, 2021 and 2020, we recognized $16,614 and $0.2 million, respectively, in interest income. The decrease in interest income was related to lower average interest rates earned on our investments. During the nine months ended September 30, 2021 and 2020, we recognized foreign currency losses of $0.6 million and $0.1 million, respectively. Foreign currency gains and losses are due primarily to the remeasurement of the Subsidiary's assets and liabilities, which are denominated in the local currency to the Subsidiary's functional currency, which is the U.S. dollar.

Liquidity and Capital Resources

Since our inception in 2007, we have devoted most of our cash resources to research and development and general and administrative activities. We have financed our operations primarily with the proceeds from the issuance and sale of equity securities (most notably our initial public offering, our follow-on public offerings and sales under our "at-the-market" offering) and convertible promissory notes, state and federal grants and research services.

To date, we have not generated any revenue from the sale of products, and we do not anticipate generating any revenue from the sales of products for the foreseeable future. We have incurred losses and generated negative cash flows from operations since inception. As of September 30, 2021, our principal sources of liquidity were our cash and cash equivalents of $75.6 million. Our working capital was $77.2 million as of September 30, 2021.

Management believes that cash and cash equivalents as of September 30, 2021 are sufficient to fund operations and capital requirements well into the first half of 2024. The economic effects of the COVID-19 pandemic remain fluid and management will continue to closely monitor the situation to ensure our cash and cash equivalents will help us manage the impact of the COVID-19 pandemic on our business and related liquidity needs. Substantial additional financings will be needed to fund our operations and to complete clinical development of and to commercially develop our product candidates. There is no assurance that such financing will be available when needed or on acceptable terms. Our ability to access the capital markets or otherwise raise such capital may be adversely impacted by potential worsening global economic conditions and the recent disruptions to, and volatility in, financial markets in the United States and worldwide resulting from the ongoing COVID-19 pandemic.

Equity Financings

On May 11, 2021, we entered into a Controlled Equity Offering^{SM} Sales Agreement, or the 2021 Sales Agreement, with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., as sales agents, pursuant to which we may sell, from time to time, up to $75.0 million of our common stock. As of November 15, 2021, there have been no sales of common stock under the 2021 Sales Agreement.

In August 2019, we entered into a Controlled Equity Offering^{SM} Sales Agreement, or the 2019 Sales Agreement, with Cantor Fitzgerald & Co., Canaccord Genuity, LLC, H.C. Wainwright & Co. LLC and Ladenburg Thalmann & Co. Inc., as sales agents, pursuant to which we sold $75.0 million of our common stock. In the first quarter of 2021, we have sold and issued 10,244,326 shares of our common stock under the 2019 Sales Agreement in the open market at a weighted average selling price of $4.22 per share, resulting in gross proceeds of $43.2 million. Net proceeds after deducting commissions and offering expenses were $42.2 million. In the first quarter of 2020, we sold and issued 356,000 shares of our common stock in the open market at a weighted-average selling price of $5.10 per share, for gross proceeds of $1.8 million and net proceeds, after deducting commissions and offering expenses, of $1.6 million. In 2020, we sold and issued 6,596,873 shares of our common stock in the open market at a weighted-average selling price of $4.81 per share, for gross proceeds of $31.7 million and net proceeds, after deducting commissions and offering expenses, of $30.7 million. The last sale under the 2019 Sales Agreement was made on February 9, 2021. From August 2019 through February 9, 2021, we received cumulative gross proceeds of $75.0 million from shares sold in the open market under the 2019 Sales Agreement, which was terminated pursuant to its terms.

Debt

We had no debt outstanding as of September 30, 2021 or December 31, 2020.

Future Capital Requirements

During the nine months ended September 30, 2021, net cash used in operating activities was $25.6 million, and our accumulated deficit as of September 30, 2021 was $230.7 million. Our expectations regarding future cash requirements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make in the future. To the extent that we enter into any of those types of transactions, we may need to raise substantial additional capital.

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

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

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

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

If we raise additional funds by issuing equity securities, including through our 2021 Sales Agreement, our stockholders will experience dilution.

Cash Flows

The following table summarizes our cash flows from operating, investing and financing activities for the nine months ended September 30, 2021 and 2020.

	Nine Months Ended September 30,	
	2021	2020
Statement of Cash Flows Data:		
Total net cash (used in) provided by:		
Operating activities	$ (25,622,978)	$ (34,327,275)
Investing activities	(47,570)	(383,223)
Financing activities	42,155,859	28,958,461
Net increase in cash and cash equivalents	$ 16,485,311	$ (5,752,037)

Operating Activities

For the nine months ended September 30, 2021, cash used in operating activities was $25.6 million compared to $34.3 million for the nine months ended September 30, 2020. The decrease from the comparable 2020 period was primarily the result of decreased research and development expenses related to clinical trial costs of our Zygel program and a decrease in general and administrative expenses. Our cash flows used in operations may differ substantially from our net loss due to non-cash charges and changes in balance sheet accounts.

Excluding any cash that may be received from the July 2019 AOF application, we expect cash used in operating activities to decrease for the year ending December 31, 2021 as compared to 2020, as we concluded our pivotal CONNECT-FX clinical trial and our BRIGHT clinical trial during 2020 and recently initiated our RECONNECT pivotal trial in FXS in September 2021.

Investing Activities

For the nine months ended September 30, 2021 and 2020, cash used in investing activities represented the cost of expenditures made for manufacturing equipment.

Financing Activities

Cash provided by financing activities for the nine months ended September 30, 2021 consisted primarily of $42.2 million in net proceeds from sales of our shares of common stock under the 2019 Sales Agreement. Cash provided by financing activities for the nine months ended September 30, 2020 consisted of $29.0 million in net proceeds from sales of our shares of common stock under the 2019 Sales Agreement.

Off-Balance Sheet Arrangements

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

Recent Accounting Pronouncements

For descriptions of recently issued accounting pronouncements, see “Note 2 –Recent Accounting Pronouncements” of our Notes to Unaudited Consolidated Financial Statements included above in Part I of this Quarterly Report.

Item 3. ***Quantitative and Qualitative Disclosures About Market Risk***

We are exposed to various market risks, which may result in potential losses arising from adverse changes in market rates, such as interest rates and foreign exchange rates. We do not enter into derivatives or other financial instruments for trading or speculative purposes nor do we engage in any hedging activities. As of September 30, 2021, we had cash and cash equivalents of $75.6 million, consisting primarily of cash and money market account balances. Because of the short-term maturities of our cash and cash equivalents, we do not believe that an immediate 10% increase in interest rates would have any significant impact on the realized value of our investments. Accordingly, we do not believe we are exposed to material market risk with respect to our cash and cash equivalents.

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

Item 4. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of September 30, 2021. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the rules and forms, promulgated by the Securities and Exchange Commission. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as of September 30, 2021, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting during the three months ended September 30, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II—OTHER INFORMATION

Item 1. Legal Proceedings.

Shareholder Class Action

Reference is made to the Company’s disclosure regarding a putative class action complaint against the Company and certain of its current officers in the United States District Court for the Eastern District of Pennsylvania, or the Shareholder Class Action, contained in the Company’s 2020 Annual Report and in its Quarterly Reports on Form 10-Q for the periods ending March 31, 2021 and June 30, 2021, filed with the SEC on May 12, 2021 and August 9, 2021, respectively. On September 16, 2021, following a settlement hearing, the court issued a final order and judgment, or the Final Approval Order, pursuant to which the court fully and finally approved the settlement of claims and dismissed the Shareholder Class Action with prejudice. Under its terms, the Final Approval Order may not be deemed to be evidence or an admission of liability, fault, breach of duty or wrongdoing on the part of the Company.

The Company and the individual defendants have denied, and continue to deny, that they have committed any violations of law or breaches of duty as alleged in the Shareholder Class Action and make no admission of liability or any form of wrongdoing.

Derivative Action

Reference is made to the Company's disclosure regarding a consolidated shareholder derivative action, captioned In Re Zynerba Pharmaceuticals, Inc. Derivative Litigation, or the Derivative Action, in the United States District Court for the District of Delaware contained in the Company's 2020 Annual Report and in its Quarterly Reports on Form 10-Q for the periods ending March 31, 2021 and June 30, 2021, filed with the SEC on May 12, 2021 and August 9, 2021, respectively. On July 15, 2021, following a settlement hearing, the Court issued a final order and judgment, or the Final Order, pursuant to which the court fully and finally approved the settlement set forth in the stipulation of settlement agreed to by the parties and dismissed the Derivative Action with prejudice. In accordance with the terms of the stipulation of settlement, the Company has undertaken to institute specified governance enhancements. Under their terms, the Final Order and the stipulation of settlement may not be deemed to be evidence or an admission of liability, fault, breach of duty or wrongdoing on the part of the Company. Attorneys' fees and service awards, granted in the Final Order to plaintiffs' counsel and their clients, respectively, were paid by the Company's insurance carrier under the terms of their insurance policy.

The Company and the individual defendants have denied, and continue to deny, that they committed any violations of law or breaches of duty as alleged in the Derivative Action and make no admission of liability or any form of wrongdoing.

Item 1A. Risk Factors.

You should carefully consider the risk factors described in our 2020 Annual Report under the caption "Item 1A. "Risk Factors." There have been no material changes in our risk factors included in our 2020 Annual Report. The risks described in our 2020 Annual Report are not the only risks facing our company. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially adversely affect our business, financial condition or future results.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds.

Recent Sales of Unregistered Securities

None.

Purchase of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Quarterly Report.

Item 3. Defaults Upon Senior Securities.

None.

Item 4. Mine Safety Disclosures.

Not applicable.

Item 5. Other Information.

Not applicable.

Item 6. Exhibits.

The following exhibits are being filed herewith:

EXHIBIT INDEX

Exhibit No.	Exhibit
31.1	Certification of Chief Executive Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (filed herewith).
31.2	Certification of Chief Financial Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002 (filed herewith).
32.1	Certification of Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
32.2	Certification of Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
101 INS	Inline XBRL Document (filed herewith).
101 SCH	Inline XBRL Taxonomy Extension Schema (filed herewith).
101 CAL	Inline XBRL Taxonomy Extension Schema Calculation Linkbase (filed herewith).
101 DEF	Inline XBRL Taxonomy Extension Schema Definition Linkbase (filed herewith).
101 LAB	Inline XBRL Taxonomy Extension Schema Label Linkbase (filed herewith).
101 PRE	Inline XBRL Taxonomy Extension Schema Presentation Linkbase (filed herewith).
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in exhibit 101)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

ZYNERBA PHARMACEUTICALS, INC.

Date: November 15, 2021

By: /s/ ARMANDO ANIDO
Armando Anido
Chief Executive Officer
(Principal Executive Officer)

Date: November 15, 2021

By: /s/ JAMES E. FICKENSCHER
James E. Fickenscher
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 31.1

CERTIFICATION

I, Armando Anido, certify that:

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

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

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

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

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

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

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

Dated: November 15, 2021

Exhibit 31.2

CERTIFICATION

I, James E. Fickenscher, certify that:

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

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

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

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

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

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

By: /s/ James E. Fickenscher
Name: James E. Fickenscher
Title: Chief Financial Officer

Dated: November 15, 2021

Exhibit 32.1

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

In connection with the quarterly report of Zynerba Pharmaceuticals, Inc. (the "Company") on Form 10-Q for the fiscal quarter ended September 30, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Armando Anido, Chairman and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

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

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

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

Dated: November 15, 2021

Exhibit 32.2

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

In connection with the quarterly report of Zynerba Pharmaceuticals, Inc. (the "Company") on Form 10-Q for the fiscal quarter ended September 30, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, James E. Fickenscher, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

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

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

/s/ James E. Fickenscher
James E. Fickenscher
Chief Financial Officer

Dated: November 15, 2021