



## Zynerba Pharmaceuticals Announces Positive Top Line Results in ZYN002 Open Label Phase 2 FAB-C Study in Children with Fragile X Syndrome

September 28, 2017

ZYN002 successfully met the primary endpoint and showed clinically meaningful improvements

Zynerba to host conference call and webcast today, September 28 at 8:30 am ET

DEVON, Pa., Sept. 28, 2017 (GLOBE NEWSWIRE) -- [Zynerba Pharmaceuticals](#), Inc. (NASDAQ:ZYNE), a clinical-stage specialty pharmaceutical company dedicated to developing and commercializing innovative pharmaceutically-produced transdermal cannabinoid treatments, today announced positive top line results from an open label exploratory Phase 2 FAB-C (Treatment of Fragile X Syndrome Anxiety and Behavioral Challenges with CBD) clinical trial evaluating ZYN002 cannabidiol (CBD) gel in pediatric and adolescent patients with Fragile X syndrome (FXS). The study successfully met its primary endpoint, achieving a 46% improvement ( $p < 0.0001$ ) in the total score of Anxiety, Depression, and Mood Scale (ADAMS) at week twelve compared to baseline. ZYN002 also achieved clinically meaningful improvements in all measures of the Aberrant Behavior Checklist for Fragile X (ABC-FXS), which address the key symptoms of FXS including social avoidance, temper tantrums, repetitive movements, and hyperactivity.

"The data from the FAB-C trial are very exciting and demonstrate that ZYN002 may have a profound effect on improving many of the most disabling symptoms of Fragile X, such as anxiety and difficult behaviors," said Steven Siegel, MD, PhD Professor and Chair, Psychiatry and Behavior Sciences, Keck School of Medicine of USC. "Fragile X is a challenging genetic autism spectrum disorder, with complex symptomatology that significantly impacts patients and their families. Many children with Fragile X and their families struggle with the lack of approved drugs to safely treat their symptoms. This study suggests that ZYN002 is ready for the next phase of development, and I believe that this drug holds great promise as a potential treatment for these very difficult-to-treat symptoms."

With these data, Zynerba anticipates that it will meet with the U.S. Food and Drug Administration (FDA) in the first half of 2018 with the goal of moving quickly into a pivotal Phase 2/3 program in pediatric and adolescent patients with FXS in 2018. The FDA has granted Zynerba Orphan Drug designation for the use of CBD as treatment of patients with FXS. Orphan Drug designation is granted to novel drugs that treat a rare disease or condition affecting fewer than 200,000 patients in the U.S., and provides benefits including a seven-year period of U.S. marketing exclusivity upon marketing approval for the designated indication and may provide a rapid path to market authorization.

"We are thrilled with the positive clinical results of ZYN002 in the FAB-C trial; it is a major step forward for the hundreds of thousands of patients worldwide with Fragile X who currently have no approved therapeutic options to treat their symptoms," said Armando Anido, Chairman and Chief Executive Officer of Zynerba. "The clinically meaningful improvements in Fragile X symptoms and the excellent tolerability seen in the FAB-C trial are compelling. These data will allow us to discuss the pathway to approval in a meeting with the FDA, which we expect to take place during the first half of 2018. I want to thank the patients, families, physicians, study coordinators, and the Zynerba team for their support of this important study."

"The symptoms of Fragile X can be overwhelming to a patient and caregiver, so I'm very enthusiastic about the responses to ZYN002 that we saw during this study," said Honey Heussler, FRACP, Associate Professor at Children's Health Queensland, Medical Director Child Development and lead investigator in the FAB-C study. "These data are extremely promising, particularly the improvements in anxiety, social avoidance, and irritability as measured by scales including ADAMS, ABC-FXS, and PARS-R. Tolerability is essential in these patients, so I'm very pleased to see that ZYN002 was well tolerated in Fragile X patients."

### Study Design

Twenty patients (3:1 males) aged 6 to 17 years of age (mean = 10.7) with Fragile X as confirmed by molecular documentation of FMR1 full mutation were enrolled in the open label FAB-C study. ZYN002 was added on to other medications being administered. The first six weeks of the study were designed to titrate dosing in patients. Dosing was initiated at 50 mg daily and could be increased to 250 mg daily. Weeks 7 through 12 of the study was a maintenance period where patients were treated at the dose established at week six. At the completion of the study, patients could enter an open label extension study for up to 12 months.

### Top-line data: Primary endpoint

The primary endpoint for the trial was the change in the total score of the Anxiety, Depression, and Mood Scale (ADAMS) from baseline to week 12. The ADAMS is a 28-item scale designed to assess general anxiety, social avoidance, compulsive behavior, manic/hyperactive behavior, and depressed mood. It has been validated in patients with FXS.

Results for the primary endpoint are summarized as follows:

	Baseline	Week 12	Change in Score	% improvement	p Value
ADAMS: Total Score	33.4	18.1	-14.1	45.81 %	<0.0001

The subscales of ADAMS are as follows:

Baseline	Week 12	Change in Score	% Improvement	p Value
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ADAMS: General Anxiety Subscale	10.0	4.6	-4.8	54.00	%	<0.0001
ADAMS: Social Avoidance Subscale	10.2	4.8	-5.1	52.94	%	0.0002
ADAMS: Compulsive Behavior Subscale	2.8	1.4	-1.2	50.00	%	0.0262
ADAMS: Manic / Hyperactive Behavior Subscale	9.4	6.1	-2.7	35.11	%	0.0003
ADAMS: Depressed Mood Subscale	2.8	2.0	-0.9	28.57	%	0.1417

#### Top-line data: Secondary endpoints

The Company evaluated multiple secondary endpoints including the Aberrant Behavior Checklist – FXS Specific (ABC-FXS), a Clinical Global Impression of Improvement (CGI-I), the Pediatric Anxiety Rating Scale (PARS-R), Visual Analog Scales for Anxiety, Hyperactivity and Tantrum/Mood Liability, the Vineland Adaptive Behavior III, a Quality of Sleep measurement and the Pediatric Quality of Life (PedsQL™). The results of the secondary endpoints reinforce the results demonstrated in the ADAMS.

Results from the ABC-FXS are summarized as follows:

	Baseline	Week 12	Change in Score	% improvement	p Value
ABC: Irritability - "Has Temper Tantrums"	18.2	10.6	-7.1	41.76 %	0.0096
ABC: Hyperactivity - "Disrupts Group Activities"	14.5	9.7	-4.1	33.10 %	0.0194
ABC: Socially Unresponsive/Lethargic - "Does Not Pay Attention"	8.7	4.1	-5.1	52.87 %	0.0034
ABC: Social Avoidance - "Seeks Isolation"	5.1	2.3	-2.8	54.90 %	0.0005
ABC: Stereotypy - "Repetitive Movements"	7.9	3.2	-4.9	59.49 %	0.0006
ABC: Inappropriate Speech - "Repeats Words or Phrases"	6.1	3.5	-2.4	42.62 %	0.0018

#### Safety data

ZYN002 was shown to be very well tolerated, and the safety profile was consistent with previously released data from clinical trials. Two patients discontinued due to worsening of pre-existing eczema. Four other patients experienced an adverse event. No adverse events were considered severe. No patient experienced drug-related GI events during the 12-week treatment period, and no THC was detected in the plasma. Thirteen of the 18 patients who completed the study have enrolled in the open label extension.

#### Conference call information

Zynerba management will host a live conference call and webcast today at 8:30 am Eastern Time to discuss the results of this clinical trial. The call can be accessed by dialing (866) 573-0180 (U.S. and Canada) or (430) 775-1345 (international) and referencing conference ID 90858811. To access the live webcast or the replay, visit the investor page of the Company's website at <http://ir.zynerba.com/>. The webcast will be recorded and available on the Company's website for 30 days.

#### About Fragile X syndrome

Fragile X syndrome is an autism spectrum disorder affecting 1 in 4,000 males and 1 in 8,000 females. It is the most common inherited intellectual disability in males and a significant cause of intellectual disability in females. It is caused by a mutation in the Fragile X Mental Retardation gene located on the X chromosome and leads to dysregulation of the endocannabinoid pathway including the reduction in endogenous cannabinoids (2-AG and anandamide). The disorder negatively affects synaptic function, plasticity and neuronal connections, and results in a spectrum of intellectual disabilities, social anxiety and memory problems. In the US, there are about 71,000 patients suffering with FXS.

#### About Our Technology

Cannabinoids are a class of chemical compounds found in the Cannabis plant. The two primary cannabinoids contained in *Cannabis* are cannabidiol, or CBD, and Δ9-tetrahydrocannabinol, or THC. Clinical and preclinical data support the potential for CBD in treating epilepsy, arthritis and Fragile X Syndrome, and THC has positive effects on treating pain. Zynerba is developing therapeutic medicines that utilize innovative transdermal technologies that, if successful, may allow for sustained and controlled delivery of therapeutic levels of CBD and THC. Transdermal delivery of cannabinoids may have benefits over oral dosing because it allows the drug to be absorbed through the skin directly into the bloodstream. This avoids first-pass liver metabolism, potentially enabling lower dosage levels of active pharmaceutical ingredients with a higher bioavailability and improved safety profile. Transdermal delivery also avoids the gastrointestinal tract, lessening the opportunity for GI related adverse events and the potential degradation of CBD by gastric acid into THC, which may be associated with unwanted psychoactive effects. Using an established chemical pharmaceutical process for manufacturing, Zynerba replicates the CBD and THC found in the *Cannabis* plant. We believe that this will allow us to meet stringent global regulatory agencies' standards while ensuring that we can efficiently supply the amount of product required to meet the demand of the large markets that we are targeting.

## About ZYN002

Zynerba's ZYN002 CBD gel is the first and only pharmaceutically-produced CBD formulated as a patent-protected permeation-enhanced gel and is being studied in children with Fragile X Syndrome, osteoarthritis and in adult epilepsy patients with focal seizures. ZYN002 is a clear, permeation-enhanced gel that is designed to provide controlled drug delivery transdermally with once- or twice-daily dosing.

## About Zynerba Pharmaceuticals, Inc.

Zynerba Pharmaceuticals (NASDAQ:ZYNE) is dedicated to improving the lives of people with severe health conditions where there is a high unmet medical need by developing and commercializing pharmaceutically-produced transdermal cannabinoid medicines designed to meet the rigorous efficacy and safety standards established by global regulatory agencies. Through the discovery and development of these life-changing medicines, Zynerba seeks to improve the lives of patients battling severe, chronic health conditions including epilepsy, Fragile X syndrome, osteoarthritis, fibromyalgia and peripheral neuropathic pain. Learn more at [www.zynerba.com](http://www.zynerba.com) and follow the Company on Twitter at @ZynerbaPharma.

## Cautionary Note on Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from the Company's current expectations. For example, there can be no guarantee that the Company will obtain approval for ZYN002 or ZYN001 from the U.S. Food and Drug Administration (FDA) or foreign regulatory authorities; even if ZYN002 or ZYN001 are approved, the Company may not be able to obtain the label claims that it is seeking from the FDA. In addition, the Company's cash and cash equivalents may not be sufficient to support its operating plan for as long as anticipated. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: the success, cost and timing of the Company's product development activities, studies and clinical trials; the success of competing products that are or become available; the Company's ability to commercialize its product candidates; the size and growth potential of the markets for the Company's product candidates, and the Company's ability to service those markets; the Company's ability to develop sales and marketing capabilities, whether alone or with potential future collaborators; the rate and degree of market acceptance of the Company's product candidates; and the Company's expectations regarding its ability to obtain and adequately maintain sufficient intellectual property protection for its product candidates. This list is not exhaustive and these and other risks are described in the Company's periodic reports, including the annual report on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K, filed with or furnished to the Securities and Exchange Commission and available at [www.sec.gov](http://www.sec.gov). Any forward-looking statements that the Company makes in this press release speak only as of the date of this press release. The Company assumes no obligation to update forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

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