Zynerba Pharmaceuticals Announces the Completion of Enrollment in the Pivotal CONNECT-FX Trial of Zygel™ in Fragile X Syndrome

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Topline Results are expected late in the Second Quarter of 2020

DEVON, Pa., Feb. 26, 2020 (GLOBE NEWSWIRE) -- Zynerba Pharmaceuticals, Inc. (NASDAQ:ZYNE), the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders, today announced that the Company has completed enrollment in its 14-week pivotal CONNECT-FX (**C**linical study **o**f Ca**nn**abidiol (CBD) in Childr**e**n and Adoles**c**en**t**s with **F**ragile **X**) trial. The trial is evaluating the efficacy and safety of Zygel™ CBD Gel as a treatment for behavioral symptoms of Fragile X syndrome (FXS) in 210 children ages three through 17 with full mutation FXS. Topline results are expected late in the second quarter of 2020.

“We are excited about the potential for Zygel, if approved by the FDA, to be the first drug ever indicated to treat the behavioral symptoms of Fragile X, and completion of enrollment in this trial is an important step toward that goal,” said Armando Anido, Chairman and Chief Executive Officer of Zynerba. “I want to thank everyone who participated in this achievement, particularly the patients in the study, their families, the clinicians involved in CONNECT-FX and their staff. We look forward to announcing the topline results of this trial late in the second quarter of this year.”

The multi-national, randomized, double-blind, placebo-controlled, 14-week CONNECT-FX trial is assessing the efficacy and safety of Zygel for the treatment of children and adolescents with FXS. Two hundred and ten (210) patients with Fragile X syndrome, confirmed with the full mutation of the FMR1 gene, have been randomized at 21 clinical sites in the United States, Australia, and New Zealand. The trial protocol targeted enrollment of at least 204 patients. Patients have been randomized 1:1 to either trial drug or placebo. The primary endpoint is the change from baseline to the end of the treatment period in the Aberrant Behavior Checklist-Community FXS Specific (ABC-C_{FXS}) Social Avoidance subscale. Key secondary endpoints are the change from baseline to the end of the treatment period in the ABC-C_{FXS} Irritability subscale score and the ABC-C_{FXS} Socially Unresponsive/Lethargic subscale score, and improvement in Clinical Global Impression (CGI-I) anchored to behavioral symptoms of FXS evaluated at the end of the treatment period. Consistent with recent guidance from the FDA on capturing the voice of the patient in drug development, additional qualitative data on the clinical relevance of various FXS behaviors to caregivers and patients is also being collected.

Baseline Characteristics of Patients Randomized into CONNECT-FX
As intended and prospectively designed, the trial has successfully enrolled a more severely affected population than the population that was enrolled in the previously completed Phase 2 FAB-C trial, as measured by baseline behavioral symptoms, enabling the study to potentially demonstrate the anticipated full range of efficacy of Zygel in several behavioral domains. The ABC-C_{FXS} mean baseline scores for the patients randomized in the CONNECT-FX trial in comparison to the FAB-C trial are as follows (higher baseline scores denote more severe behaviors):

- Social Avoidance subscale (primary endpoint): 7.2 in CONNECT-FX vs 5.1 in FAB-C;
- Irritability subscale (key secondary endpoint): 28.1 in CONNECT-FX vs 18.2 in FAB-C;
- Socially Unresponsive/Lethargic subscale (key secondary endpoint): 13.2 in CONNECT-FX vs 8.7 in FAB-C;
- Hyperactivity subscale: 18.4 in CONNECT-FX vs 14.5 in FAB-C;
- Stereotypy subscale: 9.4 in CONNECT-FX vs 7.9 in FAB-C; and
- Inappropriate Speech subscale: 6.9 in CONNECT-FX vs 6.1 in FAB-C.

During screening, the caregivers of patients in the trial were informed that their participating child may have the opportunity to receive Zygel in an open label extension trial following the child’s compliant completion of CONNECT-FX, regardless of their child’s perceived response or actual blinded drug assignment in CONNECT-FX. To date, 97% of the 158 patients who have completed CONNECT-FX have enrolled in the open label extension trial.

One hundred and fifty seven (157), or 75%, of the enrolled patients are male and the mean age at randomization in the study is 9.8 years.

The Company expects to announce topline results of this study late in the second quarter of 2020. If the results are positive, the Company expects to meet with the U.S. Food and Drug Administration (FDA) to determine acceptability of the data as a basis to submit its New Drug Application (NDA) for Zygel in FXS in the second half of 2020, with potential approval by mid-year 2021.

About Fragile X Syndrome (FXS)
Fragile X syndrome is a rare genetic developmental disability that is the leading known cause of both inherited intellectual disability and autism spectrum disorder, affecting 1 in 3,600 to 4,000 males and 1 in 4,000 to 6,000 females. It is the most common inherited intellectual disability in males and a significant cause of intellectual disability in females, and the leading genetic cause of autism spectrum disorder (ASD). FXS is caused by a mutation in the Fragile X Mental Retardation gene (FMR1) 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 and behavioral symptoms, such as social avoidance and irritability. In the US, there are about 71,000 patients suffering with FXS.

About Zygel™
Zygel (CBD gel) is the first and only pharmaceutically-manufactured CBD formulated as a patent-protected permeation-enhanced clear gel, designed to provide controlled drug delivery into the bloodstream transdermally (i.e. through the skin). Recent studies suggest that Fragile X Syndrome (FXS) and other neuropsychiatric conditions may be associated with a disruption in the endocannabinoid (EC) system. Clinical and anecdotal data suggest

that CBD may modulate the EC system and improve certain core social and behavioral autism-related symptoms, including social avoidance and anxiety.

About Zynerba Pharmaceuticals, Inc.
Zynerba Pharmaceuticals is 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, autism spectrum disorder, 22q11.2 deletion syndrome, and a heterogeneous group of rare and ultra-rare epilepsies known as developmental and epileptic encephalopathies. Learn more at www.zynerba.com and follow us 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 Zygel from the U.S. Food and Drug Administration (FDA) or foreign regulatory authorities; even if Zygel is approved, the Company may not be able to obtain the label claims that it is seeking from the FDA. 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 Company’s cash and cash equivalents may not be sufficient to support its operating plan for as long as anticipated; the Company’s ability to obtain additional funding to support its clinical development programs; the results, cost and timing of the Company’s clinical development programs, including any delays to such clinical trials relating to enrollment or site initiation; clinical results for the Company’s product candidates may not be replicated or continue to occur in additional trials and may not otherwise support further development in a specified indication or at all; actions or advice of the FDA and foreign regulatory agencies may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional clinical trials; the Company’s ability to obtain and maintain regulatory approval for its product candidates, and the labeling under any such approval; the Company’s reliance on third parties to assist in conducting pre-clinical and clinical trials for its product candidates; delays, interruptions or failures in the manufacture and supply of the Company’s product candidates 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. 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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