Zynerba Pharmaceuticals Announces Publication in the Journal of Neurodevelopmental Disorders Describing the Role of the Endocannabinoid System and Cannabidiol Therapy in Fragile X Syndrome

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Comprehensive data review suggests a central role for the endocannabinoid system (ECS) in neuronal development, cognitive function and in the pathogenesis of Fragile X syndrome (FXS)

Cannabidiol may help restore the function of the ECS in FXS patients according to review of data

Consistent with the proposed mechanisms of action of cannabidiol in FXS, Zygel™ showed a significant reduction in behavioral symptoms, in patients with ≥90% methylation of the FMR1 gene, compared to those treated with placebo in the CONNECT-FX clinical study

DEVON, Pa., Jan. 11, 2023 (GLOBE NEWSWIRE) -- Zynerba Pharmaceuticals, Inc. (Nasdaq: ZYNE), the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for orphan neuropsychiatric disorders, today announces the publication of a paper entitled, "***Role of the Endocannabinoid System in Fragile X Syndrome: Potential Mechanisms for Benefit From Cannabidiol Treatment***," in the *Journal of Neurodevelopmental Disorders*. The review of evidence suggests a central role for the endocannabinoid system (ECS) in neuronal development and cognitive function and in the pathogenesis of Fragile X syndrome (FXS), and the potential role of cannabidiol as a treatment for FXS. The article can be accessed online at the *Journal of Neurodevelopmental Disorders* at https://rdcu.be/c25fu.

"This publication describes the potential of Zygel as a treatment for Fragile X syndrome based on the central role the endocannabinoid system plays in neuronal development and function," said Armando Anido, Chairman and Chief Executive Officer of Zynerba. "The proposed mechanisms of action of cannabidiol are supported by the results from our Phase 3 CONNECT-FX trial in patients with Fragile X syndrome with greater than or equal to 90% methylation of the *FMR1* gene, benefited from treatment with Zygel. These findings bolster our confidence in the design of the ongoing, confirmatory, pivotal Phase 3 RECONNECT trial."

FXS is caused by deficiency or absence of the *FMR1* protein, FMRP. The absence of FMRP disrupts ECS signaling, which has been implicated in FXS pathogenesis. The ECS helps maintain neuronal function and signaling and is thought to be disrupted in FXS. Cannabidiol may help restore the function of the ECS in FXS according to a review of data to date. Cannabidiol may also act as an agonist on serotonin $5HT_{1A}$ and other receptors which may contribute to beneficial effects in people with FXS. Consistent with these proposed mechanisms of action of cannabidiol in FXS, in the Phase 3 CONNECT-FX trial, Zygel was associated with improvements in measures of social avoidance, irritability and social interaction, particularly in patients showing ≥90% methylation of the *FMR1* gene. Results from the CONNECT-FX study of Zygel for the treatment of behavioral symptoms in children and adolescents with FXS can be accessed online at the *Journal of Neurodevelopmental Disorders* at https://rdcu.be/c0sKz.

About Zygel

Zygel is the first and only pharmaceutically-manufactured cannabidiol 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 cannabidiol may modulate the endocannabinoid system and improve certain behavioral symptoms associated with neuropsychiatric conditions. Zygel is an investigational drug product in development for the potential treatment of behavioral symptoms associated with Fragile X syndrome (FXS), 22q11.2 deletion syndrome (22q) and autism spectrum disorder (ASD). The Company has received orphan drug designation for cannabidiol, the active ingredient in Zygel, from the FDA and the European Commission in the treatment of FXS and the treatment of 22q. Additionally, Zygel has been designated a Fast Track development program for treatment of behavioral symptoms of FXS.

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 4,000 males and 1 in 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). 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 U.S., there are about 78,000 people suffering with FXS, approximately 60% of whom have complete methylation of the *FMR1* gene.

FXS is caused by a mutation in *FMR1*, a gene which modulates a number of systems, including important effects on the endocannabinoid system, and most critically, codes for a protein called FMRP. This protein helps regulate the production of other proteins and plays a role in the development of synapses, which are critical for relaying nerve impulses, and in regulating synaptic plasticity. The *FMR1* mutation manifests as multiple repeats of a DNA segment, known as the CGG triplet repeat. In most neurotypical people, the *FMR1* gene correctly codes for the FMRP protein. As a result, FMRP is produced at levels that enable control over behaviors like social avoidance and anxiety. In people with full mutation of the *FMR1* gene, the CGG segment is repeated more than 200 times, and in most cases causes the gene to not function. Methylation of the *FMR1* gene also plays a role in determining functionality of the gene. For patients with complete methylation, no FMRP is produced. With no FMRP, the systems and processes that are modulated by FMRP become dysregulated.

About Zynerba Pharmaceuticals, Inc.

Zynerba Pharmaceuticals is the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for orphan neuropsychiatric disorders. We are committed to improving the lives of patients and their families living with severe, chronic health conditions including Fragile X

syndrome and 22q11.2 deletion syndrome. 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. 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 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 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 U.S. Food and Drug Administration, the European Medicines Agency and other 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; the Company’s expectations regarding its ability to obtain and adequately maintain sufficient intellectual property protection for its product candidates; the extent to which health epidemics and other outbreaks of communicable diseases, including COVID-19, could disrupt our operations or adversely affect our business and financial conditions; and the extent to which inflation or global instability, including political instability, may disrupt our business operations or our financial condition. 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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