Zynerba Pharmaceuticals Announces Publication of Data from Phase 3 CONNECT-FX Study of Zygel™ in the Journal of Neurodevelopmental Disorders

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Study finds patients with Fragile X who have a highly methylated FMR1 gene that were treated with Zygel showed a significant reduction in behavioral symptoms compared to those treated with placebo

Topline results from follow-on RECONNECT confirmatory pivotal Phase 3 trial of Zygel in patients with a completely methylated FMR1 gene expected in second half 2023

DEVON, Pa., Nov. 28, 2022 (GLOBE NEWSWIRE) -- Zynerba Pharmaceuticals, Inc. (Nasdaq: ZYNE), the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for orphan neuropsychiatric disorders, today announced that the results from the Phase 3 CONNECT-FX study of Zygel for the treatment of behavioral symptoms in children and adolescents with Fragile X syndrome (FXS) were published in the *Journal of Neurodevelopmental Disorders.*

The paper titled, "***A Randomized, Controlled Trial of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents with Fragile X Syndrome (CONNECT-FX)***," details how Zygel was well tolerated in patients with FXS and demonstrated efficacy with a favorable benefit risk profile in patients with ≥90% methylation of the *FMR1* gene, in whom gene silencing is most likely, and the impact of FXS is typically most severe. The article can be accessed online at the *Journal of Neurodevelopmental Disorders* at https://rdcu.be/c0sKz.

"Children with Fragile X syndrome are dramatically impacted by debilitating behavioral and emotional challenges, including anxiety, social avoidance, irritability, inattention and aggression," said Elizabeth Berry-Kravis, M.D., Ph.D., Professor, Department of Pediatrics and Neurological Sciences, Rush University Medical Center. "The results from CONNECT-FX offer hope for children with FXS and their caregivers as additional treatment options are needed for children who continue to struggle with this condition."

CONNECT-FX was a randomized, double-blind, multinational, 14-week study to evaluate the efficacy and safety of Zygel in children and adolescents aged 3 to 17 years. A total of 212 patients were randomized to 12 weeks of Zygel (250 mg or 500 mg daily [weight-based]) or placebo, as add-on to standard of care. The trial was conducted at 21 investigational centers in the U.S., Australia and New Zealand. The primary endpoint assessed change in social avoidance (SA) measured by the Aberrant Behavior Checklist–Community Edition FXS (ABC-C_{FXS}) SA subscale in the full cohort of patients with full mutation FXS, regardless of the *FMR1* gene methylation status. Ad hoc analyses assessed efficacy in patients with ≥90% and 100% methylation of the promoter region of the *FMR1* gene, in whom *FMR1* gene silencing is most likely.

Although statistical significance for the primary endpoint was not achieved in the full cohort, significant improvement was demonstrated in patients with ≥90% methylation of *FMR1* (nominal *p=0.020*), representing 80% of the overall study population. This group also achieved statistically significant improvements in Caregiver Global Impression-Change in SA and Isolation, Irritable and Disruptive Behaviors, and Social Interactions (nominal p-values: *p=0.038, p=0.028, and p=0.002,* respectively). Similar results were seen in patients with 100% methylation of *FMR1*, representing 65% of the study population. Zygel was generally well tolerated. All treatment-emergent adverse events (TEAEs) were mild or moderate. The most common treatment-related TEAE was application site pain (Zygel: 6.4%; placebo: 1.0%).

"CONNECT-FX provided evidence that a biologically identifiable and clinically responsive population of patients with FXS, who are defined by both full mutation and greater than or equal to 90% methylation of the *FMR1* gene, benefited from treatment with Zygel," said Armando Anido, Chairman and Chief Executive Officer of Zynerba. "Given these findings, our follow-on pivotal Phase 3 trial, RECONNECT, is underway to confirm the results observed in this population. We believe having patients with complete methylation of their *FMR1* gene as the primary analysis population improves our chance of success and we look forward to topline results from RECONNECT in the second half of 2023 and believe the results, if positive, will be sufficient to support the submission of a New Drug Application in the U.S. and Marketing Authorization Application in the EU for Zygel in patients with FXS."

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, 22q11.2 deletion syndrome and autism spectrum disorder. 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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