Zynerba Pharmaceuticals Initiates RECONNECT, a Pivotal Phase 3 Trial of Zygel™ in Fragile X Syndrome

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Trial will evaluate the efficacy and safety of Zygel in children and adolescents with Fragile X Syndrome

Topline results expected in second half of 2023

DEVON, Pa., Sept. 13, 2021 (GLOBE NEWSWIRE) -- Zynerba Pharmaceuticals, Inc. (Nasdaq: ZYNE), the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders, today announces the initiation of a pivotal, multinational randomized, double-blind, placebo-controlled, multiple-center, efficacy and safety (RECONNECT) Phase 3 trial. The RECONNECT trial is designed to evaluate the efficacy and safety of Zygel (cannabidiol formulated in a transdermal gel) in children and adolescents with Fragile X syndrome (FXS). The trial is planned to confirm the positive results observed in a population of responders in the Company's CONNECT-FX trial, a randomized, double-blind, placebo-controlled trial which assessed the efficacy and safety of Zygel as a treatment for the behavioral symptoms of FXS. FXS is a genetic condition that causes intellectual disability, behavioral and learning challenges and is the most common known single-gene cause of autism spectrum disorder.

"The RECONNECT trial provides us with an opportunity to confirm the positive results observed in a population of responders in our CONNECT-FX trial and further demonstrate the effect of Zygel on behaviors associated with FXS," said Armando Anido, Chairman and Chief Executive Officer of Zynerba. "A significant unmet medical need continues to exist for therapeutics to treat patients with FXS. If successful, we believe the study could serve as the basis for Zygel approval in the U.S. for patients with FXS."

"Children with FXS exhibit a number of developmental and behavioral symptoms including anxiety, social avoidance, hyperactivity, and socially unresponsive behaviors that significantly impact the family and the child's capacity to interact with them, their peers, and care providers," said Caroline Buchanan, M.D., Greenwood Genetic Center, Greenville, S.C., and an investigator in the RECONNECT trial. "Potentially having an approved treatment option for these vulnerable patients would be a significant step forward for FXS patients and their families."

RECONNECT will be 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.
- 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.
- 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.
- 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).

Topline results for the RECONNECT trial are expected in the second half of 2023.

About Zynerba Pharmaceuticals, Inc.

Zynerba Pharmaceuticals is the leader in innovative 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.

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). 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 71,000 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.

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 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; the Company’s expectations regarding its ability to obtain and adequately maintain sufficient intellectual property protection for its product candidates; the timing and outcome of current and future legal proceedings; and 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. 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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