Zynerba Pharmaceuticals Announces Phase 3 RECONNECT Trial Design for Zygel™ in Fragile X Syndrome

May 5, 2021

- Confirmatory pivotal trial expected to be initiated in the third quarter of 2021 -

- Zynerba to hold conference call today, May 5, 2021 at 5:30 pm ET -

DEVON, Pa., May 05, 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 announced the Company has received guidance from the U.S. Food and Drug Administration (FDA) on a confirmatory Phase 3 trial of Zygel in patients with Fragile X syndrome (FXS). The trial, which will be called RECONNECT (A **R**andomiz**e**d, Double-Blind, Pla**c**ebo-C**on**trolled, Multiple-Ce**nte**r, Effi**c**acy and Safe**t**y Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Fragile X Syndrome), is designed to evaluate the efficacy and safety of Zygel in children and adolescents with FXS. The study 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 that assessed the efficacy and safety of Zygel as a treatment for the behavioral symptoms of FXS previously conducted by the Company. The Company believes that the results, if positive, from RECONNECT will be sufficient to support the submission of a New Drug Application for Zygel in patients with FXS.

"Following productive discussions and alignment with the FDA, we believe we have a clear path forward for Zygel in Fragile X syndrome. We are excited to advance Zygel into the RECONNECT trial, a pivotal, multi-national, confirmatory Phase 3 trial in patients with FXS in the third quarter of 2021," said Armando Anido, Chairman and Chief Executive Officer of Zynerba. "If the results are positive, Zygel could become the first FDA approved treatment option for the significant unmet medical need that affects patients with FXS and their families."

The RECONNECT trial will be an 18-week trial which will enroll approximately 200 children and adolescents of which approximately 160 patients will have complete (100%) methylation of their *FMR1* gene and approximately 40 patients will have partial methylation of their *FMR1* gene. The primary endpoint for the trial will be the change in the Aberrant Behavior Checklist-Community FXS Specific (ABC-C_{FXS}) Social Avoidance subscale in patients who have complete methylation of their *FMR1* gene. All patients, including the cohort of partially methylated patients, will be included in a key secondary endpoint analysis.

Complete Methylation Results from CONNECT-FX

The Company performed an analysis of the CONNECT-FX population within those patients having complete methylation of their *FMR1* gene (n = 137 of 212 in the intent to treat population) to evaluate the effect of Zygel versus placebo. One patient did not have a post-baseline efficacy measure and was therefore not included in the efficacy analysis.

Baseline demographics for patients with complete methylation of the *FMR1* gene are shown below. The group is similar to the previously reported full data set of patients and the cohort of patients with ≥90% methylation. The majority of patients were male and the children had a mean age of 9 to 10 years old.

	Placebo	Zygel	Total
n	65	72	137
Age (years)	9.7	9.5	9.6
Sex – Males			
n	43	47	90
%	66%	65%	66%
Weight – kg:			
Median	34.5	35.7	35.2
Range – Min, Max	16.8, 104.7	18.6, 87.0	16.8, 104.7
Baseline psychoactive medications, %	69%	56%	62%

The results in the cohort of patients with complete methylation of the *FMR1* gene across the primary and key secondary endpoints that will be used in the RECONNECT trial are summarized below.

	Placebo N=64		Zygel N=72				
	Baseline Mean	Week 12 Mean Change	Baseline Mean	Week 12 Mean Change	Treatment Difference**	Odds Ratio	Treatment P-Value
Primary Endpoint:							
ABC-C_{FXS} Social Avoidance Subscale	7.25	-1.84	6.88	-2.92	-1.08		0.027*
Secondary Endpoints:							

ABC-C_{FXS} Irritability Subscale	27.84	-3.98	28.89	-5.83	-1.85		0.220
CGI-I at Week 12 (Any Improvement)	–	36%	–	50%		1.75	0.128

*Statistically significant vs. placebo

**A negative treatment difference demonstrates that Zygel patients improved versus placebo

“The treatment difference versus placebo and p value on the primary endpoint of improvement in the ABC-C_{FXS} Social Avoidance subscale in patients with complete methylation are consistent with the previously reported findings in patients with at least 90% methylation, despite the fact that the study was not powered to evaluate either of these patient populations.” said Dr. Joseph Palumbo, Chief Medical Officer of Zynerba Pharmaceuticals, Inc. “We believe the CONNECT-FX trial was instrumental in advancing our understanding of the science of Fragile X Syndrome. We look forward to leveraging what we learned as we seek to confirm our findings in the RECONNECT trial.”

Conference call information

Zynerba management will host a live conference call and webcast today at 5:30 pm Eastern Time to discuss the design of the RECONNECT Trial. The call can be accessed by dialing (800) 708-4540 (U.S. and Canada) or (847) 619-6397 (international) and referencing conference ID 50161974. 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 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 US, 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. In neurotypical individuals, there are CGG repeats, but these repeats only occur between 5 and 40 times. As a result, FMRP is manufactured at levels that enable control over behaviors like social avoidance and anxiety. In people with full mutation of the Fragile X gene, the CGG segment is repeated more than 200 times and in most cases causes the *FMR1* gene to not function. However, the methylation of the *FMR1* gene also plays a role in determining functionality of the gene. For patients with complete (100%) methylation, the *FMR1* gene is silenced, therefore, no FMRP is produced, and the systems and processes that are expected to be affected 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, including the RECONNECT trial, 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; the Company’s planned RECONNECT trial may not be determined to be sufficient to support an NDA submission; 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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