



## Zynerba Pharmaceuticals Announces Top Line Results from Pivotal CONNECT-FX Trial of Zygel™ (CBD Gel) in Fragile X Syndrome

June 30, 2020

- Study Did Not Achieve Statistical Significance in Primary or Key Secondary Endpoints in Full Analysis Set -

- Achieved Statistical Significance on Primary Endpoint (p=0.020) in Pre-Planned Ad Hoc Analysis of Patients with Full Methylation of the FMR1 Gene Comprising 80% of the Study Population -

- Zynerba to host conference call and webcast today, June 30, 2020 at 8:30 am ET -

DEVON, Pa., June 30, 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 top line results from the 14-week pivotal CONNECT-FX (Clinical study of Cannabidiol (CBD) in Children and Adolescents with Fragile X) trial. The multi-national, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of Zygel™ CBD gel as a treatment in for behavioral symptoms of Fragile X syndrome (FXS) in 212 patients.

Zygel did not achieve statistical significance versus placebo in the primary endpoint of improvement in the Social Avoidance subscale of the Aberrant Behavior Checklist – Community FXS (ABC-C<sub>FXS</sub>). Zygel also did not demonstrate statistical significance versus placebo in the three key secondary endpoints, which were the change from baseline to the end of the treatment period in the Irritability subscale score of the ABC-C<sub>FXS</sub>, the Socially Unresponsive/Lethargic subscale score of the ABC-C<sub>FXS</sub> and Improvement in Clinical Global Impression (CGI-I).

A pre-planned ad hoc analysis of the most severely impacted patients in the trial, as defined by patients having at least 90% methylation (“full methylation”) of the impacted FMR1 gene, demonstrated that patients receiving Zygel achieved statistical significance in the primary endpoint of improvement at 12 weeks of treatment in the Social Avoidance subscale of the ABC-C<sub>FXS</sub> compared to placebo (p=0.020). This group comprised 80% of the patients enrolled in the CONNECT-FX study. The Company believes that full methylation occurs in approximately 60% of the overall FXS patient population. Based on this analysis, Zynerba intends to meet with the FDA regarding a regulatory path forward for Zygel.

“This study identified a key population of patients who appear to benefit from treatment of their behavioral symptoms of FXS with Zygel,” said Randi J. Hagerman, MD, an investigator in the clinical trial and Medical Director and Endowed Chair in Fragile X Research at UC Davis MIND Institute and Distinguished Professor at the Department of Pediatrics at UC Davis School of Medicine. “Zygel has the potential to be an important therapeutic option for the most severely impacted patients with Fragile X.”

“The results from CONNECT-FX identified a significant patient population who responded well to Zygel and may provide us with a pathway towards licensure,” said Armando Anido, Zynerba’s Chairman and Chief Executive Officer. “We intend to discuss the results of the study with the FDA as soon as possible. On behalf of the entire Zynerba team, I want to sincerely thank the patients, families and investigators who participated in this study as well as the National Fragile X Foundation, the FRAXA Research Foundation, and the Fragile X Association of Australia for their assistance in this study.”

### CONNECT-FX Patient Disposition

Two hundred and forty-five (245) patients with Fragile X syndrome, confirmed with the full mutation of the FMR1 gene, were enrolled at 21 clinical sites in the United States, Australia, and New Zealand. Unknown to the patients and their caregivers, all patients were given placebo during the first two weeks (called a “placebo run-in” which is often used in neuropsychiatric clinical trials), and as a result 33 patients were not randomized. The remaining 212 patients were included in the Intent-to-Treat (ITT) population (Zygel: n=110; placebo: n=102) and were randomized to receive either trial drug or placebo for an additional 12 weeks. One patient did not receive study medication so 211 patients are included in the safety analysis (Zygel: n=109; placebo: n=102.) One patient did not have a post-baseline efficacy measure, resulting in 210 patients in the full analysis set (Zygel: n=109; placebo: n=101).

### Baseline Demographics

Select baseline demographics for the ITT population are as follows:

	Placebo	Zygel	Total
n	102	110	212
Age (years)	9.8	9.6	9.7
Sex – Males			
n	78	81	159
%	76%	74%	75%
Weight – kg			
Median	34.3	36.8	35.7
Range – Min, Max	15.6, 104.7	14.6, 87	14.6, 104.7
>35 kg, %	48.0%	55.5%	51.9%

Baseline psychoactive medications, % 66% 57% 62%

### Primary and Key Secondary Endpoints - Full Analysis Set

The results of CONNECT-FX in the full analysis population for the primary and key secondary endpoints are summarized below.

Endpoint	Placebo N=101		Zygel N=109		Treatment Difference*	Odds Ratio	Treatment P-Value
	Baseline Mean	Week 12 Mean Change	Baseline Mean	Week 12 Mean Change			
ABC-C <sub>FXS</sub> Social Avoidance Subscale	7.24	-2.29	7.12	-2.68	-0.39		NS
ABC-C <sub>FXS</sub> Irritability Subscale	27.65	-4.14	28.49	-5.88	-1.74		NS
ABC-C <sub>FXS</sub> Socially Unresponsive / Lethargy Subscale	12.82	-3.14	13.42	-3.50	-0.36		NS
CGI-I at week 12 (Much and Very Much Improved)	-	15.9%	-	20.2%		1.33	NS

NS = Not statistically significant

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

### Pre-Planned Ad Hoc Analysis of Patients with Full Methylation of the FMR1 Gene

The Company performed a pre-planned ad hoc analysis of the ITT population (n= 212) to evaluate the effect of Zygel versus placebo according to severity of baseline disease as defined by patients having full methylation of the impacted FMR1 gene. Patients with genetically confirmed full mutation Fragile X and full methylation of their impacted FMR1 gene are generally the most severely impacted by the disorder. Within the CONNECT-FX trial, this was corroborated with patients in the analysis at baseline having higher anxiety, lower IQ, lower adaptive function, and more severe autism as compared to patients without a fully methylated FMR1 gene. One hundred and sixty nine (169) patients met the criterion of full methylation of the FMR1 gene. One patient was not treated and one did not have a post-baseline efficacy measure, resulting in 167 patients (Zygel: n=91; placebo: n=76).

Baseline demographics for patients with full methylation of the FMR1 gene are shown below.

	Placebo	Zygel	Total
n	77	92	169
Age (years)	9.6	9.2	9.4
Sex – Males			
n	54	65	119
%	70%	71%	70%
Weight – kg			
Median	33.9	35.7	35.0
Range – Min, Max	15.6, 104.7	14.6, 87.0	14.6, 104.7
>35 kg, %	45.5%	53.3%	49.7%
Baseline psychoactive medications, %	65%	54%	59%

### Primary and Key Secondary Endpoints - Patients with Full Methylation of the FMR1 Gene

The results of CONNECT-FX in the analysis set of patients with full methylation of the FMR1 gene across the primary and key secondary endpoints are summarized below.

Endpoint	Placebo N=76		Zygel N=91		Treatment Difference**	Odds Ratio	Treatment P-Value
	Baseline Mean	Week 12 Mean Change	Baseline Mean	Week 12 Mean Change			
ABC-C <sub>FXS</sub> Social Avoidance Subscale	7.18	-1.99	7.12	-2.99	-1.0		<b>0.020*</b>
ABC-C <sub>FXS</sub> Irritability Subscale	28.00	-4.13	29.36	-6.43	-2.30		0.091
ABC-C <sub>FXS</sub> Socially Unresponsive / Lethargy Subscale	13.17	-2.74	13.30	-3.91	-1.17		0.135
CGI-I at Week 12 (Any Improvement)	-	35.7%	-	51.1%		1.88	0.056

\*Statistically significant vs. placebo

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

The median improvement in the Social Avoidance subscale of the ABC-C<sub>FXS</sub> after twelve weeks of treatment was 40.0% for patients on Zygel and 21.1% for patients on placebo.

The interaction test of heterogeneity for the Social Avoidance subscale was statistically significant (p=0.002), which means that the difference in treatment effects between the subgroups was statistically significant.

## Safety Data

Zygel was very well tolerated in CONNECT- FX, and the safety profile was consistent with previously released data from other Zygel clinical trials. No safety signal was identified. Approximately half (54%) of the 211 patients included in the safety population experienced a treatment emergent adverse event (any event, whether unrelated or related to study drug), all of which were mild or moderate. The frequency of treatment emergent adverse events was similar across treatment groups (58% of patients on Zygel, 50% of patients on placebo). There were no serious or severe adverse events reported during the study. There were seven total psychiatric disorder TEAEs, five of which were in the placebo group.

Only 15 (7%) patients experienced a treatment-related adverse event (20 events total); 11 patients on Zygel experienced 14 treatment-related TEAEs, while four patients on placebo experienced six treatment-related TEAEs. The most common treatment-related TEAE was application site pain (Zygel: 6.4%; placebo: 1.0%).

Laboratory values for chemistry and hematology were comparable between the placebo and Zygel treatment groups, and there were no clinically relevant abnormalities in either group. Specifically, there were no clinically significant liver function tests.

## Upcoming Corporate Milestones

- **Fragile X syndrome:** Meet with the FDA to discuss CONNECT-FX results as soon as possible.
- **Developmental and epileptic encephalopathies (DEE):** The results of discussions with FDA on the positive Phase 2 BELIEVE results and the clinical path forward are expected in 3Q2020.
- **Autism spectrum disorder (ASD):** Zynerba intends to meet with FDA to discuss the positive Phase 2 BRIGHT trial results and clinical path forward in 2H2020.
- **22q11.2 deletion syndrome (22q):** As a result of COVID-19 travel restrictions in Australia, top line Phase 2 data from the INSPIRE trial are now expected in 4Q2020.

## Conference call information

Zynerba management will host a live conference call and webcast today at 8:30 am Eastern Time to discuss the results of this clinical trial. The call can be accessed by dialing (866) 573-0180 (U.S. and Canada) or (430) 775-1345 (international) and referencing conference ID 9953448. 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 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 full 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. At greater than 90% methylation, which is considered "full 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.

People with genetically confirmed full mutation Fragile X and full methylation of their FMR1 gene are generally the most severely impacted by the disorder.

## 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](http://www.zynerba.com) and follow us on Twitter at @ZynerbaPharma.

## Statistical Analysis Method

Inferential statistics for the primary endpoint are based on a linear mixed model for repeated measures (MMRM) including categorical effects for gender, region, treatment and week, treatment-by-week interaction, baseline score, and baseline score-by-week interaction. Inference for the primary endpoint in the subgroups defined by FMR1 status are also based on the primary model, and include the appropriate terms for subgroup interactions.

## 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 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](http://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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