# Zynerba Pharmaceuticals Presents Health State Utility Index Data on Severity of Fragile X Syndrome (FXS) and Diagnostic Challenges Faced by Caregivers

March 3, 2020

- Data Presented at the American Society for Experimental Neurotherapeutics (ASENT) 2020 Meeting -

- Health State Utility Index Data Estimate the Significant Health Burden of FXS, and Suggest the Potential Benefit of Treatment with Zygel™ -

- Caregiver's Perspective on Protracted Journey to Diagnosis, Current Standard of Care and Comorbid Conditions Described -

DEVON, Pa., March 3, 2020 – Zynerba Pharmaceuticals, Inc. (NASDAQ:ZYNE), the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders, is presenting two posters this week on the health burden and diagnostic challenges of Fragile X syndrome (FXS). These data are being presented at the American Society for Experimental Neurotherapeutics (ASENT) 2020 Meeting, which is being held in Bethesda, MD on March 2nd through March 5th, 2020.

The first poster presents health state utility indices that estimate the severity of pediatric disorders including FXS, and the potential benefit of Zygel (CBD transdermal gel; ZYN002) in children and adolescents with FXS. Joseph M. Palumbo, MD, FAPA, MACPsych, Chief Medical Officer of Zynerba, will also present these data during the ASENT Pipeline Data Blitz on March 4. The second poster speaks to the initial family experience in FXS, expanding upon the existing knowledge of patient presentation, diagnosis and understanding of FXS; the protracted journey to diagnosis; and the high prevalence of comorbid conditions. A copy of the posters are available on the Zynerba corporate website at http://zynerba.com/publications/.

***Post Hoc Analysis - An Open-Label Study of Transdermal Cannabidiol (ZYN002) for the Treatment of Fragile X Syndrome in Children and Adolescents: Estimating Health State Utility Scores***

- *Poster number: 29*
- *Poster presentation time: Tuesday, March 3 from 5:00 to 6:00 PM and Wednesday, March 4 from 5:00 to 7:00 PM.*
- *Oral presentation time: Wednesday, March 4 from 1:00 to 3:00 PM during the ASENT Pipeline Data Blitz session.*

FXS is a rare genetic condition characterized by a range of developmental, neuropsychiatric, and behavioral symptoms. The spectrum and severity of FXS symptoms result in a high clinical, humanistic, and economic burden on patients and caregivers, including important healthcare resource utilization and associated costs. Health state utility indices (HUI) are used in clinical and economic analyses of therapies with potential impact on health-related quality of life (HRQoL) and enable comparison of HRQoL across conditions. Health state utility is measured on a 0 to 1 scale in which 0 represents death and 1 represents complete health; the lower the score, the more significant the impact of the disease to HRQoL. The Aberrant Behavior Checklist - Community Utility Index (ABC-UI) - a utility index specific to FXS - was derived from the Aberrant Behavior Checklist - Community for FXS (ABC-CFXS) to measure the HRQoL benefit of treatments for FXS. The ABC-UI, created and subsequently published in the peer-reviewed journal Quality of Life Research, in 2015, established an algorithm that calculates utility index score based on ABC-CFXS items pertaining to the core symptom domains of FXS.

"The mean health state utility index score for FXS in this seminal analysis was calculated to be 0.57, estimating a significant disease-related impact on HRQoL in FXS which may be as robust as, or perhaps even more impactful, than that described in the published literature for other debilitating pediatric conditions in measures of HUI", said Dr. Palumbo. "We will work to confirm our initial observations in future analyses."

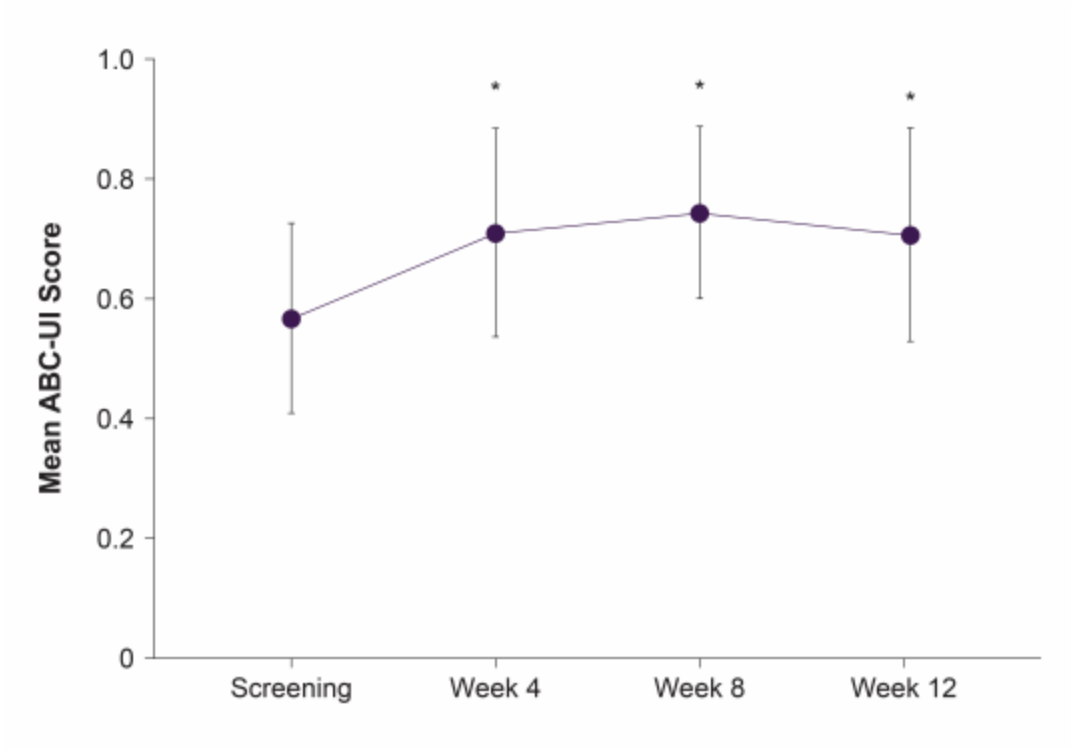
The objective of the analysis undertaken was to evaluate the potential benefit of Zygel on the ABC-UI in pediatric and adolescent patients with FXS through post hoc analysis of data from the Phase 2 open label FAB-C (Treatment of Fragile X Syndrome Anxiety and Behavioral Challenges with CBD) trial. Individual patient-level data from the FAB-C study were mapped to the ABC-UI algorithm to generate a utility index score for each patient.

"Fragile X syndrome is a debilitating diagnosis, and for the first time we have estimated the health state utility index scores of patients with FXS, in the context of the published HUI literature, helping to clarify the significance of this disorder," continued Dr. Palumbo. "Further, we observed statistically significant improvements in the health state utility index scores of patients treated with Zygel in the 12-week exploratory Phase 2 FAB-C trial compared to baseline, suggesting a potential broad spectrum of benefit of the drug in the important domains of the ABC-CFXS that were incorporated into the utility index."

**Improvement in ABC-UI Score with Zygel Treatment**

As shown in Figure 1 below, compared to their baseline scores, patients on Zygel experienced significant ($P < 0.01$) improvement in their mean ABC-UI beginning at week 4 and this improvement was maintained through weeks 8 and 12.

Figure 1. Mean ABC-UI Score at Each Timepoint during Treatment with Zygel (*P<0.01)




The authors of the poster concluded that:

- Treatment with Zygel significantly improved health state utility index scores in pediatric and adolescent patients with FXS, suggesting a potential broad spectrum of benefit of Zygel in the important domains of the ABC-CFXS that were incorporated into the utility index;
- The correlation of the ABC-UI scores with Clinical Global Impression of Severity (CGI-S) scores in these patients suggests that the ABC-UI appropriately reflects symptom severity in FXS; and
- The estimated health state utility index score of 0.57 in patients with FXS enrolled in FAB-C appear to describe a poor baseline level of HRQoL, despite standard of care, highlighting the considerable impact of FXS symptoms on patient HRQoL.

***Fragile X Syndrome Diagnosis and Patient Journey: The Caregiver's Perspective***

- *Poster number: 28*
- *Poster presentation time: Tuesday, March 3 from 5:00 to 6:00 PM and Wednesday, March 4 from 5:00 to 7:00 PM.*

"Children with Fragile X syndrome generally remain undiagnosed until approximately three years of age, and the path to diagnosis is complex," said Dr. Palumbo. "These children also have a high prevalence of comorbid conditions which complicates the diagnosis. Today's standard of care includes counseling and therapy and the use of traditional prescription medications that aren't specifically indicated for FXS. This information supports the importance of testing for the disorder early in the diagnostic journey and bringing novel treatments that specifically treat the behavioral symptoms of FXS through the FDA approval process for the benefit of patients and their families."

Core FXS clinical symptoms include social avoidance/withdrawal, anxiety, irritability, deficits in learning and cognition, and sleep difficulties. These symptoms are frequently compounded by comorbid conditions, including autism and attention-deficit/hyperactivity disorder. Parents often first recognize the initial symptoms and developmental delays, leading to subsequent clinical diagnosis of FXS utilizing genetic testing for mutations in the FMR1 gene. Early diagnosis of FXS is important to facilitate treatment and coordinate the multidisciplinary supportive care and educational interventions required to manage the symptoms of FXS. Unfortunately, diagnosis of FXS is often delayed. A 2008 study reported a delay of 24 to 26 months between initial symptoms and diagnosis, and mean age at diagnosis has remained delayed over time (32 months in 2018 vs 38 months in 2008).

Zynerba utilized a 30-minute, anonymized, quantitative online survey, conducted in the United States from May 3 to June 12, 2019, to characterize the patient journey in FXS surrounding diagnosis and clinical experiences. Thirty-five (35) predominantly female (80%) primary caregivers of children with FXS completed the survey. The children of these caregivers were 3 to 17 years of age, had a full FMR1 mutation, and exhibited socially avoidant behaviors.

**Path to Diagnosis**

The mean age of children with FXS at the time of diagnosis was 36 months. When asked to rate the top 3 factors prompting caregivers to schedule an initial visit with a physician, the most common were:

1. Cognitive/intellectual developmental delays;

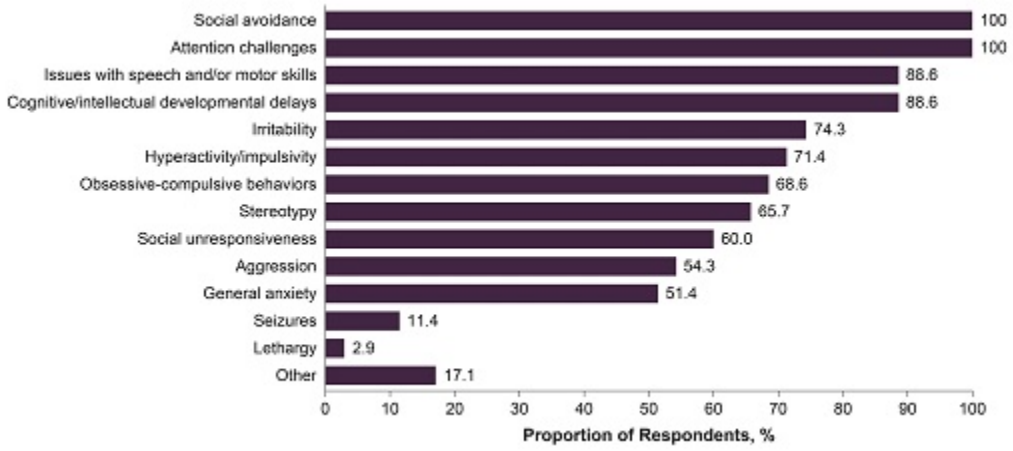
2. Issues with speech and/or motor skills; and
3. Social avoidance/social unresponsiveness.

Most caregivers scheduled an initial visit with a physician within 6 months of noticing symptoms (82.9%). The first physician seen was usually a primary care physician (family doctor or general pediatrician, 71.4%), but formal diagnosis of FXS was most often made by a specialist (80.0%), most frequently geneticists and neurologists/pediatric neurologists.

**Current Experience with FXS**

As shown in Figure 2 below, the most frequently experienced current symptoms of FXS were social avoidance and attention challenges. Most caregivers (85.7%) rated the severity of FXS at the time of the survey as severe (45.7%) or moderate (40.0%).

Figure 2. Current FXS Symptoms




Children of the surveyed caregivers were receiving a mean 1.94 treatments. Seventy-seven (77%) of children were currently receiving counseling/therapy; 46% were receiving traditional prescription treatment; and 31.4% were receiving nonprescription treatment/supplements. The most commonly received prescription medications were antidepressants/selective serotonin reuptake inhibitors (SSRIs) and stimulants. In addition, 77% of the children were reported to have comorbid conditions, the most common being autism spectrum disorder (66%), attention-deficit/hyperactivity disorder (26%), and sleep disorders (20%).

The authors concluded that:

- The results of this survey expanded upon existing knowledge of the initial presentation/diagnosis and experience of FXS, finding an average age of 3 years at initial diagnosis, a high prevalence of comorbid conditions, and standard of care consisting primarily of counseling/therapy and traditional prescription medications; and
- While caregivers of children with FXS often notice a variety of initial symptoms early and seek help from a health care professional, it is not until subsequent physician visits, often involving a specialist, that a formal diagnosis is made.

**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 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 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

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