Long-Term Safety and Sustained Efficacy of ZYN002 Cannabidiol Transdermal Gel in the Treatment of Behavioral Symptoms in Children and Adolescents with Fragile X Syndrome (ZYN2-CL-017)

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BACKGROUND
• Fragile X syndrome (FXS), a condition driven by a mutation of the FMR1 gene, is the most common single gene cause of autism spectrum disorder (ASD).
• Disruption in the endocannabinoid system as a result of the change in the FMR1 gene is one of the proposed mechanisms for the symptoms observed in FXS1,2 and cannabinoid, non-psychotropic molecule, may have favorable effects on this system.3
• ZYN002 (also known as Zygel®) is a pharmaceutically produced cannabinoid (not from a plant) that has been uniquely formulated as a gel for transdermal delivery (absorbed through the skin).
• ZYN002 is in clinical development for the treatment of behavioral symptoms associated with FXS and 22q11.2 deletion syndrome (22q).
• The Avertant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObRO) measure that has been validated in individuals with intellectual disabilities,4 and has been used to assess changes in behaviors in trials for ZYN002.
• ZYN002 was superior to placebo in pre-specified ad hoc analyses in patients with either complete methylation or complete methylation (100%) of their FMR1 gene in ZYN2-CL-016 (CONNECT-FX) (NCT03146183).
• ZYN2-CL-033, RECONNECT, is an ongoing Phase 3, randomized, double-blind, placebo-controlled, confirmatory trial evaluating the efficacy and safety of ZYN002 over 18 weeks (NCT04977986).
• ZYN2-CL-017 is an ongoing, open-label extension trial (OLE) (NCT03802799).

OBJECTIVES
• To determine the long-term safety and efficacy of ZYN002 in patients with FXS.
• To determine interim analyses of data from the ongoing OLE trial, ZYN2-CL-017 through January 23, 2023.

METHODS
• Patients ages 3 through 17 entered the trial (Figure 1).
• ZYN2-CL-009 (FAB-C), an open-label Phase 2 trial to explore the efficacy and safety of ZYN002.
• Patients who completed Part 1 of the trial demonstrated a response to therapy were eligible to enter Part 2 of the trial and received ZYN002 for 115 weeks prior to entering ZYN2-CL-017.
• ZYN2-CL-016 (CONNECT-FX), a randomized, double-blind, placebo-controlled confirmatory trial evaluating the efficacy and safety of ZYN002 (NCT03146183).
• Patients randomized into CONNECT-FX were eligible for entry into ZYN2-CL-017, as were those screened for CONNECT-FX but ineligible to continue in the trial.
• Safety data for all enrolled patients with up to 45 months of exposure are reported.

SAFETY RESULTS
• ZYN002 was safe and well tolerated in the ZYN2-CL-017 extension trial in patients with a median duration of exposure of 20 months (range 21 days to 45 months) since trial entry.
• Two hundred eleven (88%) patients completed 16 months (176 (73%)) completed ≥12 months, and 101 (48%) completed ≥24 months of treatment.
• Patients in the ZYN2-CL-009 trial had a median total exposure of 74 months.
• Treatment-emergent adverse events (TEAEs) were reported in 68.7% of patients (Table 2). Most TEAEs were related to conditions commonly reported in children/adolescents.
• Treatment-related AEs were reported in 13.3% of patients; the most common was application site pain (6.7%). Application site pain was short-lasting and reported as mild in 15 patients and moderate in 1 patient.
• Three patients had increases in ALT ≥ 3x ULN (2 of the 3 patients; the most common was application site pain (6.7%). Application site pain was short-lasting and reported as mild in 15 patients and moderate in 1 patient.
• Patients had suspected fatty liver disease and 1 patient was receiving valproic acid.
• No clinically significant changes in vital signs or electrocardiograms were observed.

SAFETY EFFICACY
• ZYN002 led to improvements in ABC-CFXS Social Avoidance in the full population, with the greatest improvements seen in patients with complete methylation of their FMR1 gene.
• Patients with complete methylation who matched the primary efficacy population achieved and maintained clinically meaningful change (≥3-point improvement) in ABC-CFXS Social Avoidance (ABC-CFXS SA) (Figure 2).

RESULTS
• Complete methylation of FMR1 gene who switched to open-label ZYN002 — Patients with Complete Methylation of FMR1 (Table 2).

REFERENCES

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Disclosures
• This presentation is intended to communicate scientific and medical information about data from clinical trials involving ZYN002. ZYN002 is an investigational treatment. This means that it is not approved for commercial distribution by government regulatory bodies, including the United States Food and Drug Administration (FDA). This presentation is not designed or intended to promote the use of ZYN002 or any other Company product in order to impact prescribing.
• NT, AT, TS, and SO are employees of Zynerba Pharmaceuticals.
• TD is a contractor for Zynerba Pharmaceuticals.

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