

# 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)<sup>1</sup>
- 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 FXS<sup>2,3</sup> and cannabidiol, a non-psychoactive molecule, may have favorable effects on this system<sup>4</sup>
- ZYN002 (also known as Zylgel™) is a pharmaceutically produced cannabidiol (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 Aberrant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObsRO) measure that has been validated in individuals with intellectual disabilities<sup>5</sup>
- An FXS-specific version of the ABC-C (ABC-C<sub>FXS</sub>), which is more representative of FXS, has been established<sup>6</sup> 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 ≥90% methylation or complete methylation (100%) of their *FMR1* gene in ZYN2-CL-016 (CONNECT-FX) (NCT03614663)
- 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

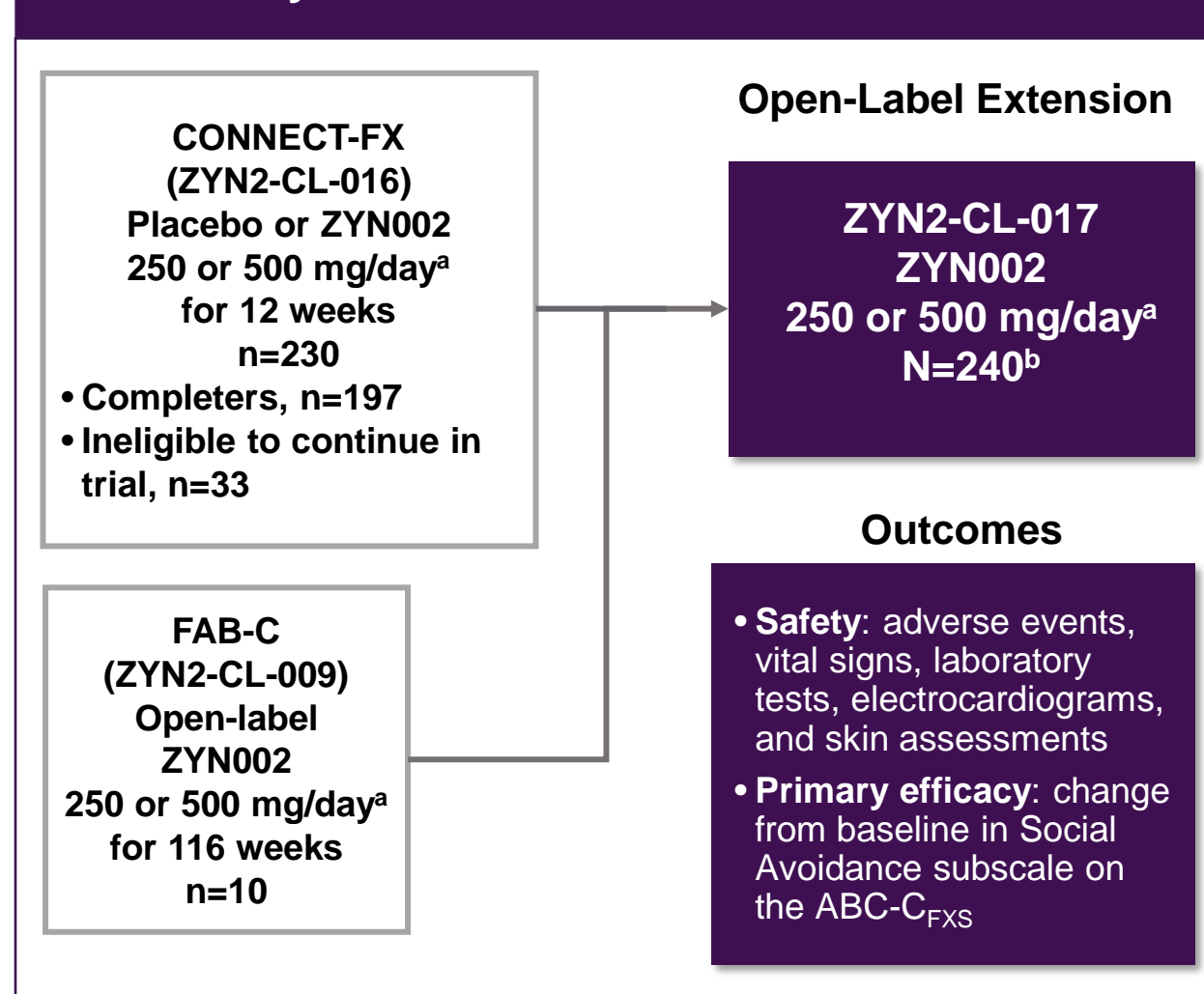
- To determine the long-term safety and efficacy of ZYN002 in patients with FXS
- Here, we report interim analyses of data from the ongoing OLE trial, ZYN2-CL-017 through January 23, 2023

## METHODS

- Patients ages 3 through 17 entered the trial from (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 and demonstrated a response to therapy were eligible to enter Part 2 of the trial and received ZYN002 for 116 weeks prior to entering ZYN2-CL-017
  - ZYN2-CL-016 (CONNECT-FX), a randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of ZYN002 (NCT03614663). 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 assessments included adverse events, vital signs (i.e., blood pressure), laboratory tests, electrocardiograms (heart rhythm), and skin assessments at the site of application
- Efficacy data through 24 months for patients with complete (100%) methylation of their *FMR1* gene who completed CONNECT-FX are reported
- The primary efficacy endpoint was change from baseline in the Social Avoidance (SA) subscale of the ABC-C<sub>FXS</sub>

Figure 1. ZYN2-CL-017 Trial Design and Path of Patient Entry



<sup>a</sup>Weight-based in 2 divided doses applied twice daily.  
<sup>b</sup>Through January 23, 2023.

## RESULTS

### BASELINE DEMOGRAPHICS

	ZYN002
n	240
Mean Age, years (range) <sup>a</sup>	9.7 (3-17)
Sex, n (%)	
Male	183 (76.3)
Female	57 (23.8)
Race, n (%)	
White	193 (80.4)
Asian	8 (3.3)
Black or African American	9 (3.8)
Native Hawaiian or Other Pacific Islander	1 (0.4)
Other	16 (6.7)
Multiple	13 (5.4)
Weight (kg)	
Median (Min, Max)	35.1 (14.6, 91.8)
Baseline psychoactive medications <sup>b</sup>	54%

<sup>a</sup>Age upon entry of original trial prior to entering the OLE.  
<sup>b</sup>Did not include diphenhydramine or melatonin if used for sleep.

## 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 ≥6 months, 176 (73%) completed ≥12 months, and 101 (48%) completed ≥24 months of treatment
  - Patients from the ZYN2-CL-009 trial had a median total exposure of 74 months
- Treatment-emergent adverse events (TEAEs) were reported in 66.7% 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 patients had suspected fatty liver disease and 1 patient was receiving valproic acid)
- No clinically significant changes were observed in vital signs or electrocardiograms.

Table 2. ZYN002 OLE Trial Interim Safety Data – Adverse Events

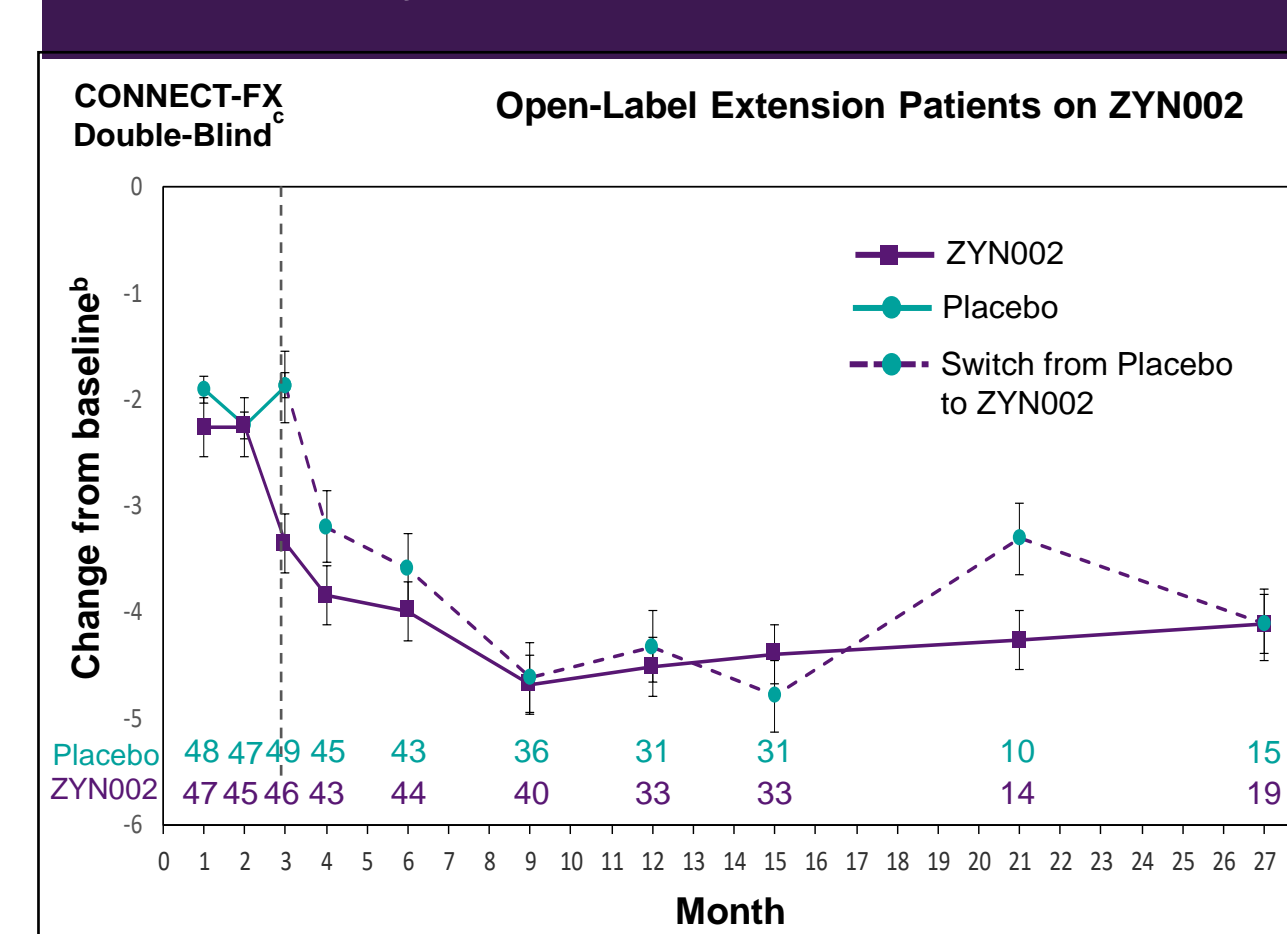
Adverse Event Type	Patients (n=240) or Events, %
<b>Treatment Emergent Adverse Events (TEAEs)<sup>a</sup></b>	66.7%
Mild-to-moderate TEAEs	97.8% (events)
<b>TEAEs (≥3% of patients)</b>	
Upper respiratory infection	17.9%
COVID-19	7.1%
Application-site pain	6.7%
Nasopharyngitis (common cold symptoms)	6.3%
Pyrexia (fever)	5.8%
Vomiting	5.4%
Diarrhea	5.0%
Ear infection	4.6%
Cough	4.2%
Influenza	4.2%
Anxiety	3.8%
Streptococcal pharyngitis	3.3%
<b>Discontinuations due to TEAEs</b>	2.9% (7 patients)
<b>Serious AEs (all non-treatment-related)</b>	11 events in 8 patients
<b>Treatment-Related AEs</b>	13.3%
<b>Most common treatment-related AE (≥3% of patients)</b>	
Application-site pain (short-lasting; mild in 15 and moderate in 1 patient)	6.7%

<sup>a</sup>TEAE, whether related or unrelated to study drug.

## EFFICACY RESULTS

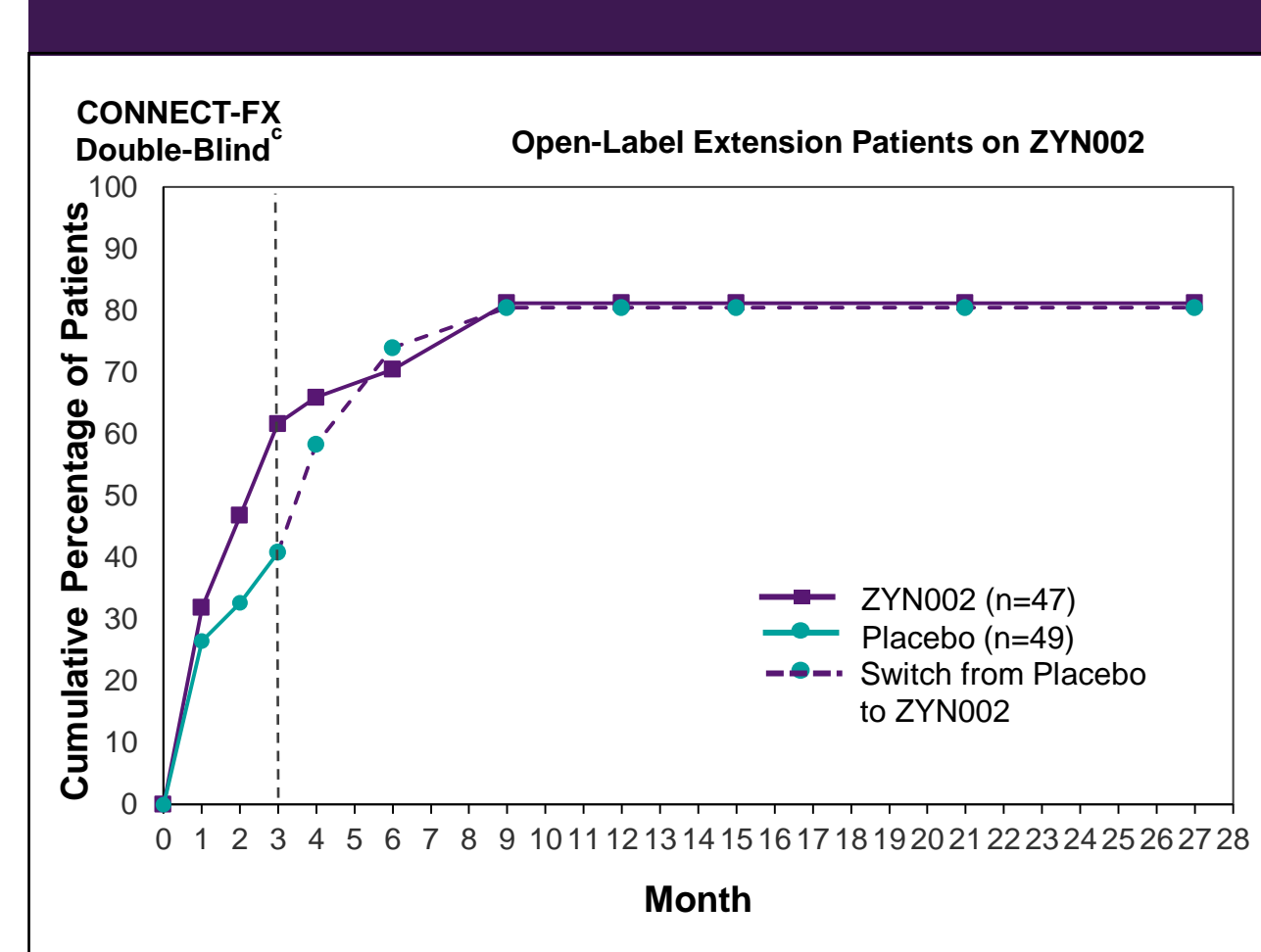
- Improvements were seen in ABC-C<sub>FXS</sub> SA in the full population, with the greatest improvements in patients with complete methylation of their *FMR1* gene
- Patients with complete methylation who completed CONNECT-FX, who also match the primary efficacy population in RECONNECT:
  - Demonstrated sustained improvement in ABC-C<sub>FXS</sub> SA from baseline (Figure 2)
  - Achieved and maintained clinically meaningful change (≥3-point improvement) in ABC-C<sub>FXS</sub> SA (Figure 3)

Figure 2. Sustained Improvement in ABC-C<sub>FXS</sub> Social Avoidance in ZYN002 and Placebo Patients Who Switched to Open-Label ZYN002 – Patients With Complete Methylation of *FMR1*<sup>a</sup>



<sup>a</sup>Patients matching primary efficacy population in RECONNECT.  
<sup>b</sup>Least square mean ± SE; reduction equals improvement.  
<sup>c</sup>ZYN2-CL-016 (CONNECT-FX).

Figure 3. ZYN002-Treated Patients Achieved and Maintained Clinically Meaningful Change<sup>a</sup> in ABC-C<sub>FXS</sub> Social Avoidance – Patients With Complete Methylation of *FMR1*<sup>b</sup>



<sup>a</sup>Clinically meaningful change in Social Avoidance: ≥3-point improvement from baseline.  
<sup>b</sup>Patients matching primary efficacy population in RECONNECT.  
<sup>c</sup>ZYN2-CL-016 (CONNECT-FX).

## CONCLUSIONS & ONGOING TRIAL

- ZYN002 was well tolerated during long-term administration
- ZYN002 led to improvements in ABC-C<sub>FXS</sub> Social Avoidance in the full population, with the greatest improvements in patients with complete methylation of their *FMR1* gene
- Patients with complete methylation who match the primary efficacy population in the ongoing confirmatory trial, RECONNECT, achieved and maintained clinically meaningful change in Social Avoidance, supporting design enhancements for RECONNECT
- The interim results from this open-label extension trial support the long-term safety and effectiveness of ZYN002 in children and adolescents with Fragile X syndrome, with the greatest improvements seen in those with complete methylation of their *FMR1* gene
- RECONNECT, being conducted in patients 3 through 22 years of age with complete (100%, the primary efficacy population) or partial (<100%) methylation of their *FMR1* gene is actively enrolling patients
- For more information on RECONNECT, visit [www.fragilexhelp.com](http://www.fragilexhelp.com) or scan the QR Code



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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 SOQ are employees of Zynerba Pharmaceuticals. TD is a contractor for Zynerba Pharmaceuticals.

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