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

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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 experimental treatment which has not been approved by any government regulatory bodies, including the United States Food and Drug Administration (FDA), and has not been determined by the FDA to be a safe or effective treatment for any disease or condition. This presentation is not designed or intended to promote the use of ZYN002 or any other Company product in order to impact prescribing.

- Nancy Tich, Anthony Thibodeau, and Stephen O'Quinn are employees of Zynerba Pharmaceuticals. Joseph Palumbo is a former employee of Zynerba Pharmaceuticals. Thomas Dobbins is a contractor for Zynerba Pharmaceuticals.

- The trial was funded by Zynerba Pharmaceuticals.

Background

- Fragile X syndrome (FXS) is the most common monogenic cause of autism spectrum disorder (ASD)[1]
- Disruption in the endocannabinoid system is one of the proposed mechanisms for the loss of synaptic plasticity and the deficits in emotional responsivity observed in FXS[2,3]
- Cannabidiol acts as a negative allosteric modulator at presynaptic CB_1 receptors, a $5HT_{1A}$ agonist, and a D_2 partial agonist[4-6]
- ZYN002 is a pharmaceutically produced cannabidiol transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS, ASD, and 22q11.2 deletion syndrome
- The Aberrant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObsRO) measure that has been validated in individuals with intellectual disabilities[7]
- An FXS-specific domain structure of the ABC-C (ABC-C_{FXS}), which is more representative of the FXS phenotype, has been established[8] and has been used to assess changes in behaviors in trials assessing ZYN002
- ZYN002 was superior to placebo in a pre-specified ad hoc analyses in patients with either ≥90% methylation or complete methylation (100%) of their *FMR1* gene in ZYN-CL-016 (CONNECT-FX), suggesting methylation may impact response to ZYN002
- ZYN2-CL-033, RECONNECT, is an ongoing Phase 3, randomized, double-blind, placebo-controlled confirmatory trial evaluating the efficacy and safety of ZYN002 over 16 weeks (NCT04977986)

1. Salcedo-Arellano MJ, et al. *Neurotherapeutics*. 2020;18(1):265-283.
2. Jung KM, et al. *Nat Commun*. 2012;3:1080.
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5. Russo EB, et al. *Neurochem Res*. 2005;30(8):1037-1043.
6. McGuire P, et al. *Am J Psychiatry*. 2018;175(3):225-231.
7. Marshburn EC, Aman MG. *J Autism Dev Disord*. 1992;22(3):357-373.
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Objectives

- To determine the long-term safety and efficacy of ZYN002 in patients with FXS
- To report interim analyses of data of an ongoing, open-label extension trial (OLE), **ZYN2-CL-017** (NCT03802799), through February 2, 2022

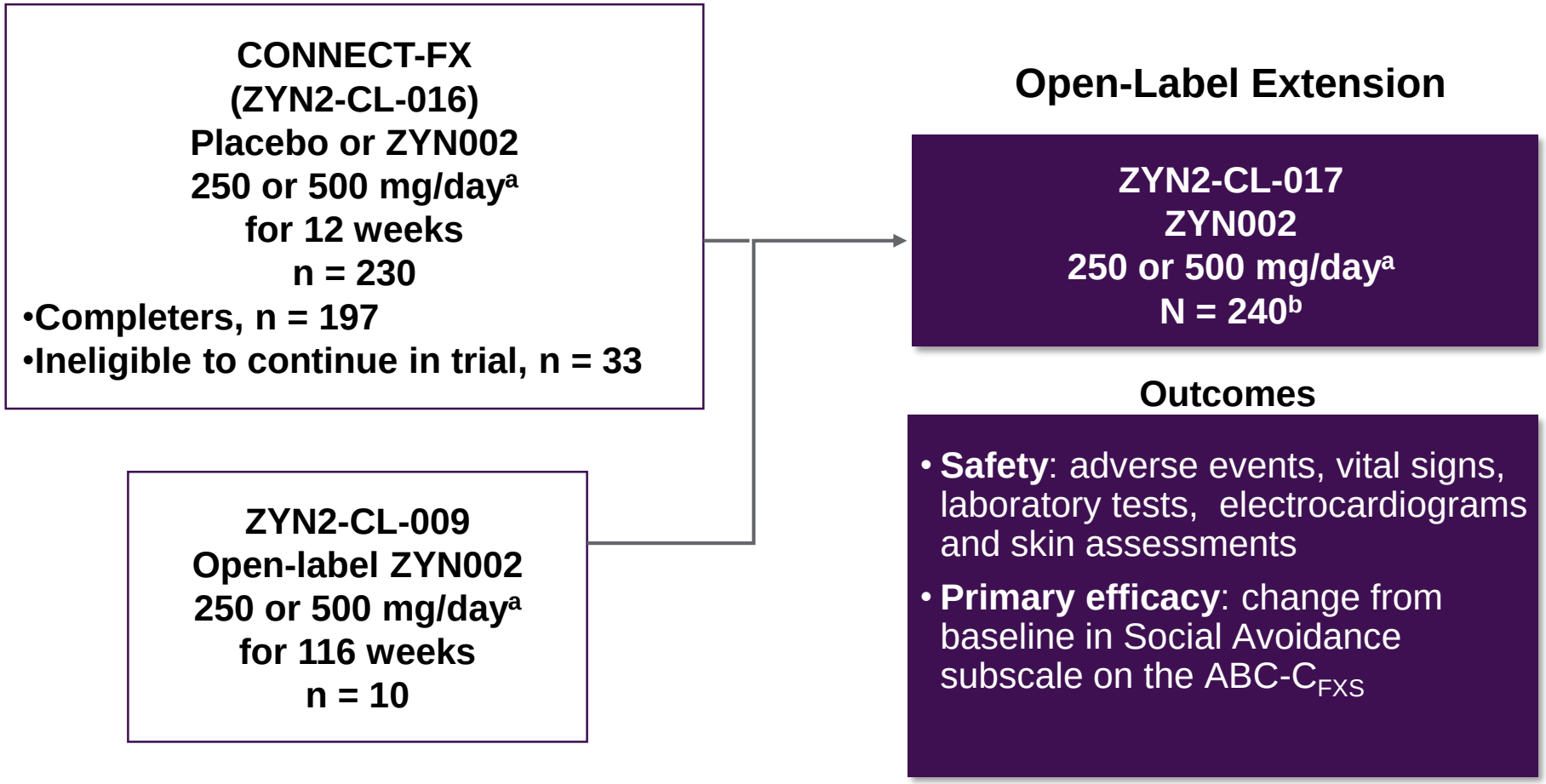
Methods

- Patients ages 3 through 17 years entered the trial from:
  - **ZYN2-CL-009**, 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 over 12 weeks (NCT03614663)
    - Patients randomized into CONNECT-FX were eligible for entry into ZYN2-CL-017, as were those who were screened for CONNECT-FX but ineligible to continue in the trial

Methods (continued)

- Safety data for all enrolled patients with up to 38 months of exposure are reported
- Safety assessments included adverse events, vital signs, laboratory tests, electrocardiograms and skin assessments at the site of application
  - Investigator skin irritation assessments were scored as:
    - 0=no erythema
    - 1=minimal erythema
    - 2= moderate erythema with sharply defined borders
    - 3=intense erythema with or without edema
    - 4=intense erythema with edema and blistering/erosion
- Efficacy findings through 15 months for patients with complete (100%) methylation of their *FMR1* gene who completed CONNECT-FX are reported
  - The primary efficacy measure was change from baseline in the Social Avoidance subscale of the ABC-C_{FXS} (ABC-C_{FXS})

ZYN2-CL-017 Trial Design and Path of Patient Entry



[a]Weight-based in 2 divided doses applied twice daily.
[b]Through February 2, 2022.

Baseline Demographics

	ZYN002
n	240
Mean Age, years (range)[a]	9.7 (3 to 17)
Sex, n (%)	
Male	183 (76.3)
Female	57 (23.8)
Race, n (%)	
White	193 (76.3)
Asian	8 (3.3)
Black or African American	9 (3.5)
Native Hawaiian or Other Pacific Islander	1 (0.4)
Other	16 (6.7)
Multiple	13 (5.4)
Weight (kg)	
Median	35.1
Range (Min, Max)	14.6, 91.8
Baseline psychoactive medications[b]	54%

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

Safety Results

- ZYN002 was safe and well tolerated in the ZYN-CL-017 extension trial in patients with a median duration of exposure of 16 months (range 21 to 1080 days) since trial entry
  - 211 (88%) patients completed ≥6 months and 176 (73%) completed ≥12 months of treatment
  - Patients who entered from the ZYN2-CL-009 trial have a median total exposure of 62 months
- Treatment-emergent adverse events (TEAEs), whether related or unrelated to study drug, were reported by 62.9% of patients; most related to conditions commonly reported in children and adolescents
- Treatment-related AEs were reported in 12.9% of patients; the most common was application site pain (6.7%)
  - Application site pain was transient and reported as mild in 15 and moderate in 1 patient
- No clinically significant changes were observed in vital signs or electrocardiograms
  - There was no evidence of ZYN002-related changes in liver function or any other laboratories
- Investigator Skin Assessments
  - Over 90% of patients had no erythema during any month of exposure
  - Only 2 patients were reported to have moderate erythema with sharply defined borders and no patients had intense erythema

ZYN002 OLE Trial Interim Safety Data – Adverse Events

Most related to conditions commonly reported in children and adolescents

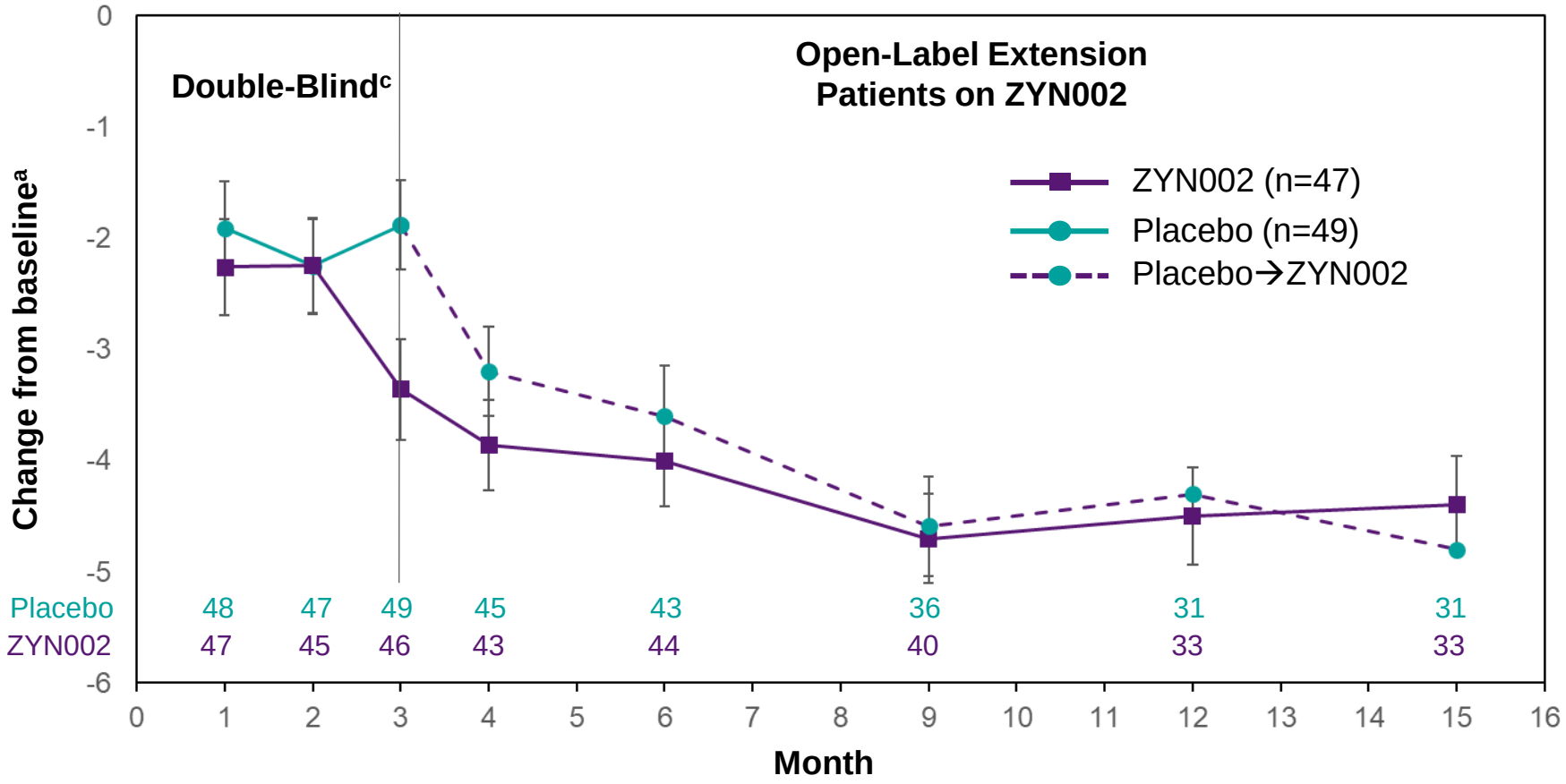
Adverse Event Type	Patients (n = 240) or Events, %
Treatment Emergent Adverse Events (TEAE)[a]	62.9%
Mild-to-moderate TEAEs	97.6% (events)
TEAEs (≥3% of patients) Upper respiratory infection	15.8%
Application-site pain	6.7%
Pyrexia	5.4%
Nasopharyngitis	5.0%
Vomiting	5.0%
Diarrhea	4.2%
Ear infection	4.2%
Anxiety	3.8%
Cough	3.3%
Influenza	3.3%
Discontinuations due to TEAEs	2.5% (6 patients)
Serious AEs (all non-treatment-related)	10 events in 7 patients
Treatment-Related TEAEs	12.9%
Most common treatment-related AE (≥3% of patients) Application-site pain (transient; mild in 15 and moderate in 1 patient)	6.7%

[a]TEAE, whether related or unrelated to study drug.

Efficacy Results

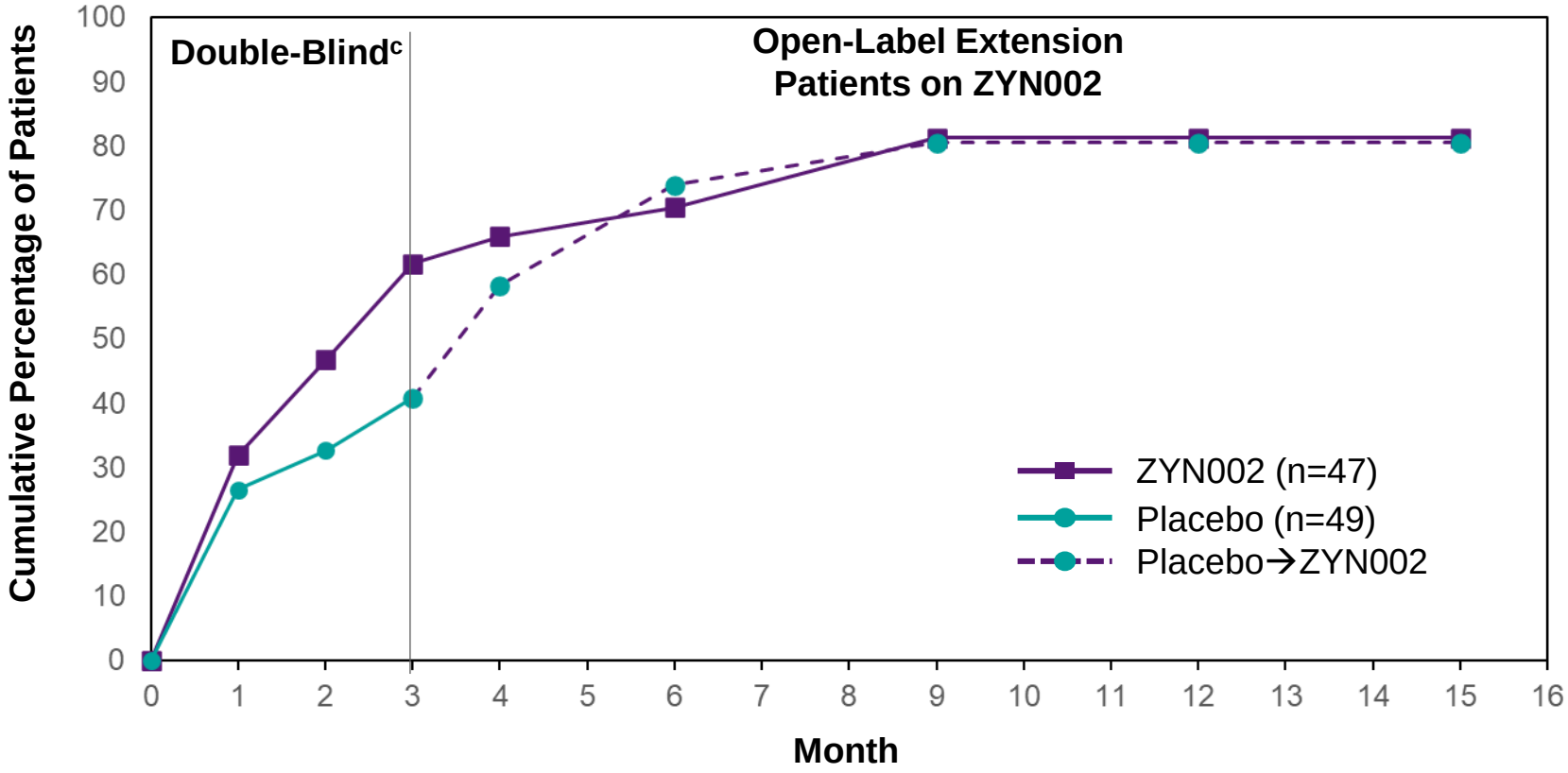
- Improvements were seen in ABC-C_{FXS} Social Avoidance in the full population, with the greatest improvements being seen in patients with complete methylation of their *FMR1* gene
- 156 patients (70.3%) for whom methylation status was determined had complete methylation of their *FMR1* gene
- Patients with complete methylation who completed CONNECT-FX, who also match the primary efficacy population in RECONNECT
  - Demonstrated sustained improvement in ABC-C_{FXS} Social Avoidance from baseline
  - Achieved and maintained clinically meaningful change (≥3-point improvement) in ABC-C_{FXS} Social Avoidance
  - Demonstrated similar improvements in ABC-C_{FXS} Irritability subscale scores

Sustained Improvement in ABC-C_{FXS} Social Avoidance in ZYN002 and Placebo Patients who Switched to Open-Label ZYN002: Patients With Complete Methylation of *FMR1*[a]



[a]Patients matching primary efficacy population in RECONNECT
[b]Least square mean ± SE; reduction equals improvement
[c]ZYN2-CL-016 (CONNECT-FX)

ZYN002-Treated Patients Achieved and Maintained Clinically Meaningful Change[a] in ABC-C_{FXS} Social Avoidance: Patients with Complete Methylation of *FMR1*[b]



[a]Meaningful change in Social Avoidance: ≥3-point improvement from baseline; maintained for ≥ 2 consecutive visits
[b]Patients matching primary efficacy population in RECONNECT
[c]ZYN2-CL-016 (CONNECT-FX)

Conclusions

- ZYN002 is safe and well tolerated during long-term administration
- ZYN002 led to improvements in ABC-C_{FXS} Social Avoidance in the full population, with the greatest improvements being seen 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

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