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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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 (henceforth the 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) (NCT03614663), 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)

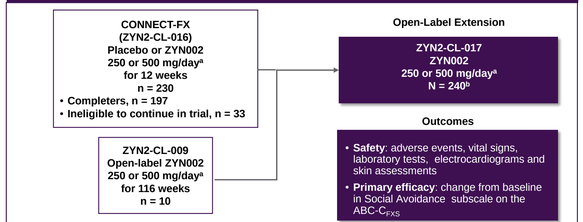
OBJECTIVES

- To determine the long-term safety and efficacy of ZYN002 in patients with FXS
- Here, we 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 1 completed and 1 ongoing trial: (**Figure 1**):
  - 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 ZYN-CL-017, as were those who were screened for CONNECT-FX but ineligible to continue in the trial
- 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; and 4=intense erythema with edema and blistering/erosion
- Efficacy data through 15 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_{FXS}

Figure 1. 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.

RESULTS

BASELINE DEMOGRAPHICS

- Baseline characteristics are shown in **Table 1**

Table 1. 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%) ≥12 months of treatment
  - Patients from the ZYN2-CL-009 trial have a median total exposure of 62 months
- Treatment-emergent adverse events (TEAEs) were reported in 62.9% of patients **(Table 2)**
- 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

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

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%

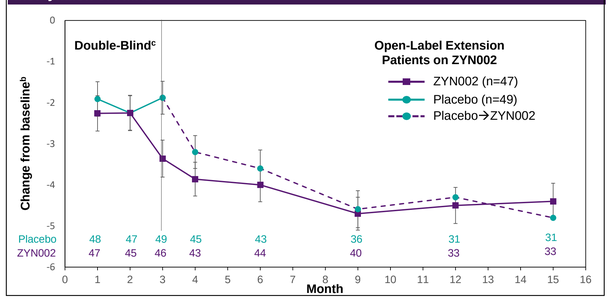
[a]TEAE, whether related or unrelated to study drug.

- Most TEAEs were related to conditions commonly reported in children/adolescents

EFFICACY RESULTS

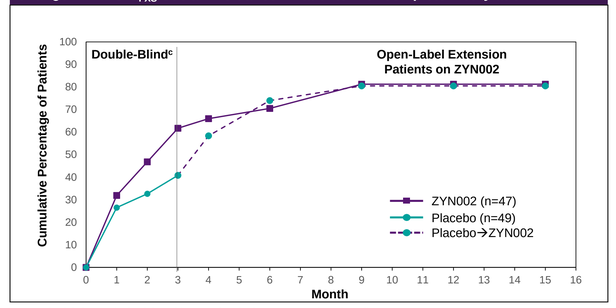
- Improvements were seen in ABC-C_{FXS} SA in the full population, with the greatest improvements being seen in patients with complete methylation of their *FMR1* gene
- 156 patients (70.3%) for whom methylation status was determined had complete methylation of their *FMR1* gene
- Patients with complete methylation who completed CONNECT-FX, who also match the primary efficacy population in RECONNECT
  - Demonstrated sustained improvement in ABC-C_{FXS} SA from baseline (**Figure 2)**
  - Achieved and maintained clinically meaningful change (≥3-point improvement) in ABC-C_{FXS} SA (**Figure 3)**
  - Demonstrated similar improvements in ABC-C_{FXS} Irritability subscale scores (data not shown)

Figure 2. 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. [c]ZYN2-CL-016 (CONNECT-FX)
[b]Least square mean ± SE; reduction equals improvement.

Figure 3. ZYN002-Treat 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.
[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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