Transdermal Cannabidiol (CBD) Gel for the Treatment of Fragile X Syndrome (FXS)

Poster #P5-092

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ABSTRACT

Background
FXS is a genetic condition caused by a mutation in the Fragile X mental retardation 1 (*FMR1*) gene located on the X chromosome. Mutations in the *FMR1* gene silence the expression of the Fragile X mental retardation protein (FMRP), accounting for many of the neuropsychiatric symptoms of Fragile X. Parents/caregivers report the most impactful symptoms of FXS as anxiety, difficulties related to social interaction, avoidance and isolation, physical aggression, and anger/irritability. Dysregulation of the endocannabinoid system is central to clinical abnormalities seen in FXS. CBD may attenuate the loss of endogenous endocannabinoid signaling in FXS, bypassing the FMRP deficiency and resulting in an improvement in core FXS neuropsychiatric symptoms.

Methods
This 12-week open-label study evaluated the safety, tolerability and initial efficacy of ZYN002 (transdermal CBD gel) for the treatment of behavioral and emotional symptoms associated with child/adolescent FXS. Patients were titrated from an initial daily dose of 50 mg CBD up to a maximum of 250 mg CBD. Key endpoints included the Anxiety, Depression, and Mood Scale (ADAMS) and Aberrant Behavior Checklist (ABC-C_{FXS}). Following the 12-week open-label study, patients could roll into a 2-year open-label extension (OLE) study.

Results
Twenty patients (mean age = 10.4, SD = 3.9) were enrolled. Significant gains from baseline were observed across all outcome measures over the 12-week treatment period. Average improvement in overall anxiety and depression (ADAMS Total Score) reached 46% (p<0.0001), with particular benefit observed for the General Anxiety (54%; p<0.0001) and Social Avoidance (53%; p=0.0002) subscales. Improvements as high as 59% (Stereotypy; p=0.0006) were observed with the ABC-CFXS, with Social Avoidance (55%; p=0.0005), Social Unresponsiveness/Lethargy (53%; p=0.0034), and Irritability (42%; p=0.0096) subscales each also improving during the treatment period. Thirteen (72%) of the 18 patients who completed the initial 12-week study rolled into the OLE. While the OLE is ongoing, results demonstrate continued and sustained gains in the ADAMS Total Score (54%; p<0.0001) and ABC-CFXS Social Avoidance (77%; p=0.0013), Irritability (59%; p=0.0007), and Socially Unresponsiveness/Lethargy (72%; p=0.0035) subscales through Month 12, relative to baseline. ZYN002 was well tolerated. No serious adverse events or clinically meaningful trends in vital signs, ECG or clinical safety labs, including liver function tests, have been reported. The most common treatment-emergent adverse events have been mild-moderate gastroenteritis and upper respiratory infections, both unrelated to study drug.

Conclusion
Findings highlight the short and long-term positive impact of ZYN002 on emotional and behavioral symptoms experienced by children and adolescents with FXS. A randomized, double-blind, placebo-controlled trial to extend these findings to a larger child/adolescent FXS population is ongoing.

INTRODUCTION

- Cannabidiol (CBD) is the primary non-euphoric cannabinoid in cannabis
- Fragile X mental retardation 1 (FMR1) gene mutation in Fragile X Syndrome (FXS) causes dysregulation of the endocannabinoid (EC) system, resulting in significant social, behavioral, and cognitive deficits
- The most impactful behavioral, emotional, or social problems for patients with FXS and their families are: anxiety, difficulties related to social interaction, avoidance and isolation, physical aggression and anger/irritability
- Modulation of EC system with CBD, as well as effects on GABA and 5-HT_{1A} receptors, may have therapeutic potential

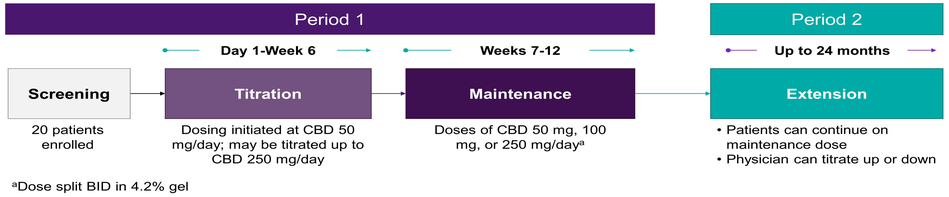
OBJECTIVES

- The objective of this study was to evaluate the long-term safety, tolerability, and efficacy of ZYN002, a permeation-enhanced, pharmaceutically-produced CBD gel formulated for transdermal delivery, for the treatment of FXS

METHODS

- FAB-C is a Phase 2 open-label study of ZYN002 administered for 12 weeks in children and adolescents with FXS, with a 24-month extension for completers of the first 12 weeks (Figure 1)
- Patients were initiated on a dose of 50 mg CBD daily with the option to titrate up to 250 mg CBD daily

Figure 1. FAB-C Study Design



[a]Dose split BID in 4.2% gel

PATIENTS

- Key Inclusion Criteria: < 18 years, molecular documentation of full mutation of FMR1 gene, Pediatric Anxiety Rating Scale – Revised (PARS-R) score of ≥ 11, Clinician Global Assessment of Severity ≥ 3
- Key Exclusion Criteria: Any progressive neurological disorder other than FXS; use of more than 1 anti-psychotic and 1 anxiolytic medication; exposure to CBD or delta-9-tetrahydrocannabinol (THC) in the 4 weeks prior to screening

ASSESSMENTS

- Primary Efficacy Variable: Anxiety, Depression, and Mood Scale (ADAMS) Total Score
- Key Secondary Variables
  - ADAMS subscale scores: Social Avoidance, Manic/Hyperactive Behavior, Depressed Mood, General Anxiety, and Compulsive Behavior
  - Aberrant Behavior Checklist (FXS Factor Structure; ABC-C_{FXS}) subscale scores: Social Avoidance, Irritability, Socially Unresponsive/Lethargic, Hyperactivity, Stereotypy, and Inappropriate Speech

This study was sponsored by Zynerba Pharmaceuticals.

RESULTS

PATIENTS

- 20 patients were enrolled, and 18 patients completed Period 1 and were analyzed for efficacy and safety at Week 12 (Table 1)
- 13 patients continued into the 24-month extension study

Table 1. Patient Disposition

Enrolled into FAB-C	20
Completed Period 1	18
Enrolled into Period 2	13
Patients Reaching Month 9	12
Patients Reaching Month 12	12
Patients Ongoing	12

- Most patients were male, with a median age of 9 years (Table 2)

Table 2. Baseline Demographics (n=20)

Females; Males, n (%)	5 (25); 15 (75)
Age (median [range]), years	9 (6-17)
Weight (median [range]), kg	33 (20-93)
BMI (median [range]), kg/m^2	17 (13-35)

EFFICACY

- At Week 12 in Period 1, 2 patients were on 100 mg ZYN002 daily and 16 patients were on 250 mg ZYN002 daily

Table 3. Efficacy at Week 12

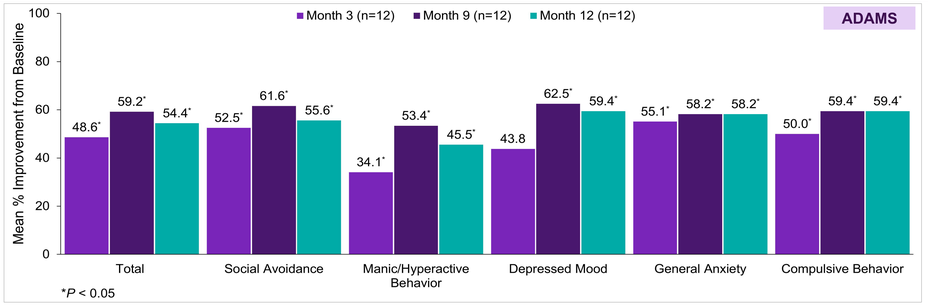
Scale: ADAMS	Baseline (n=20)	Week 12 (n=18)	Week 12 Δ (% Improvement Group Mean)	P-value[a]
Total Score	33.4	18.1	-14.1 (45.8)	<0.0001
Social Avoidance[b]	10.2	4.8	-5.1 (52.9)	0.0002
Manic/Hyperactive Behavior	9.4	6.1	-2.7 (35.1)	0.0003
Depressed Mood	2.8	2.0	-0.9 (28.6)	0.1417
General Anxiety	10.0	4.6	-4.8 (54.0)	<0.0001
Compulsive Behavior	2.8	1.4	-1.2 (50.0)	0.0262
Scale: ABC-C_{FXS}	**Baseline (n=20)**	**Week 12 (n=18)**	**Week 12 Δ (% Improvement Group Mean)**	**P-value[a]**
Social Avoidance[b]	5.1	2.3	-2.8 (54.9)	0.0005
Irritability	18.2	10.6	-7.1 (41.8)	0.0096
Socially Unresponsive/ Lethargic[c]	8.7	4.1	-5.1 (52.9)	0.0034
Hyperactivity	14.5	9.8	-3.9 (32.4)	0.0237
Stereotypy	7.9	3.2	-4.9 (59.5)	0.0006
Inappropriate Speech	6.1	3.5	-2.4 (42.6)	0.0018

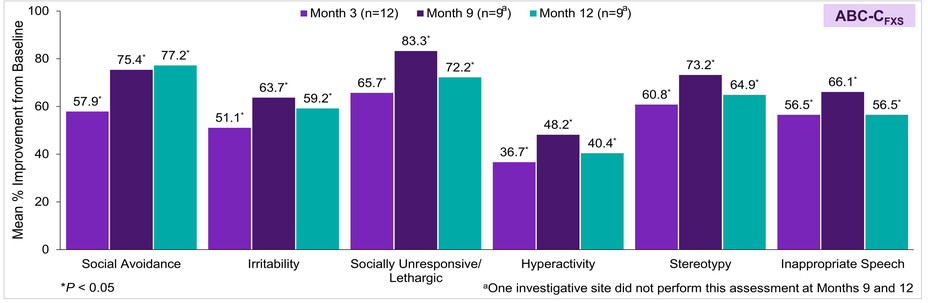
[a]Compared with baseline
[b]Prefers isolation from others, prefers solitary activities, avoids new social activities
[c]Lack of attention/interaction, inactive/lack of movement, can resist physical contact

RESULTS *cont.*

- At Month 12, 1 patient was on 100 mg ZYN002 and 11 patients were on 250 mg ZYN002

Figure 2. Efficacy at Months 3, 9, and 12 Among Patients Who Continued in Period 2





SAFETY

- ZYN002 was well tolerated
- Through Month 12, patients reported 43 treatment-emergent adverse events (TEAEs) that were mild or moderate
  - The most common TEAEs were gastroenteritis (14%) and upper respiratory tract infection (12%)
  - One patient developed skin rash and 1 patient developed dry skin; both resolved and the patients remained in the study
  - No serious AEs were reported
- In Period 1, there were 2 discontinuations, 1 patient for worsening eczema (not treatment-related) and 1 patient for administrative reasons; in Period 2, there was 1 discontinuation for administrative reasons
- There have been no clinically meaningful trends in vital signs, ECGs, or clinical safety labs, including liver function tests
- No THC has been detected in plasma

CONCLUSIONS

- **These open-label findings highlight both the short- and long-term positive impact of ZYN002 on emotional and behavioral symptoms experienced by children and adolescents with FXS**
- **A randomized, double blind, placebo-controlled trial to extend these findings to a larger population of children and adolescents with FXS is ongoing in Australia, New Zealand, and the US**

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