

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

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## 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<sub>1A</sub> receptors, may have therapeutic potential

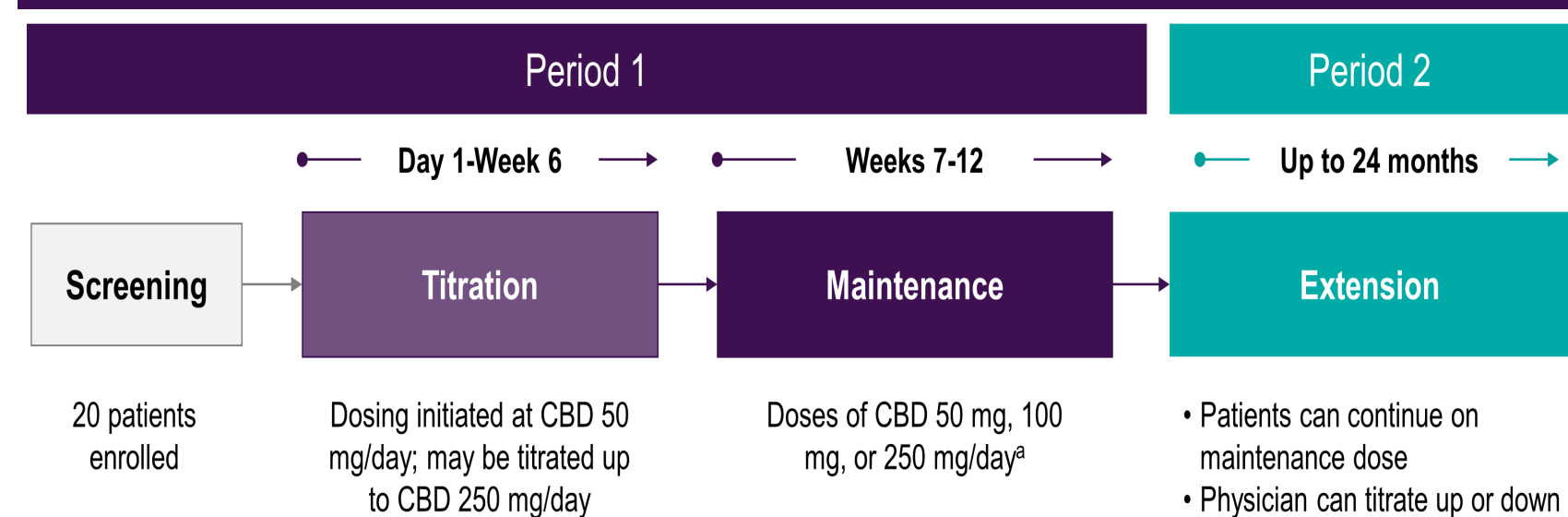
## OBJECTIVES

- 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



<sup>a</sup>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 one 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<sub>FXS</sub>) subscale scores: Social Avoidance, Irritability, Socially Unresponsive/Lethargic, Hyperactivity, Stereotypy, and Inappropriate Speech

## 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 <sup>2</sup>	17 (13-35)

### EFFICACY

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

Table 3. Efficacy at Week 12

Scale: ADAMS	Baseline (n=20)	Week 12 (n=18)	Week 12 Δ (% Improvement Group Mean)	P-value <sup>a</sup>
Total Score	33.4	18.1	-14.1 (45.8)	<0.0001
Social Avoidance	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

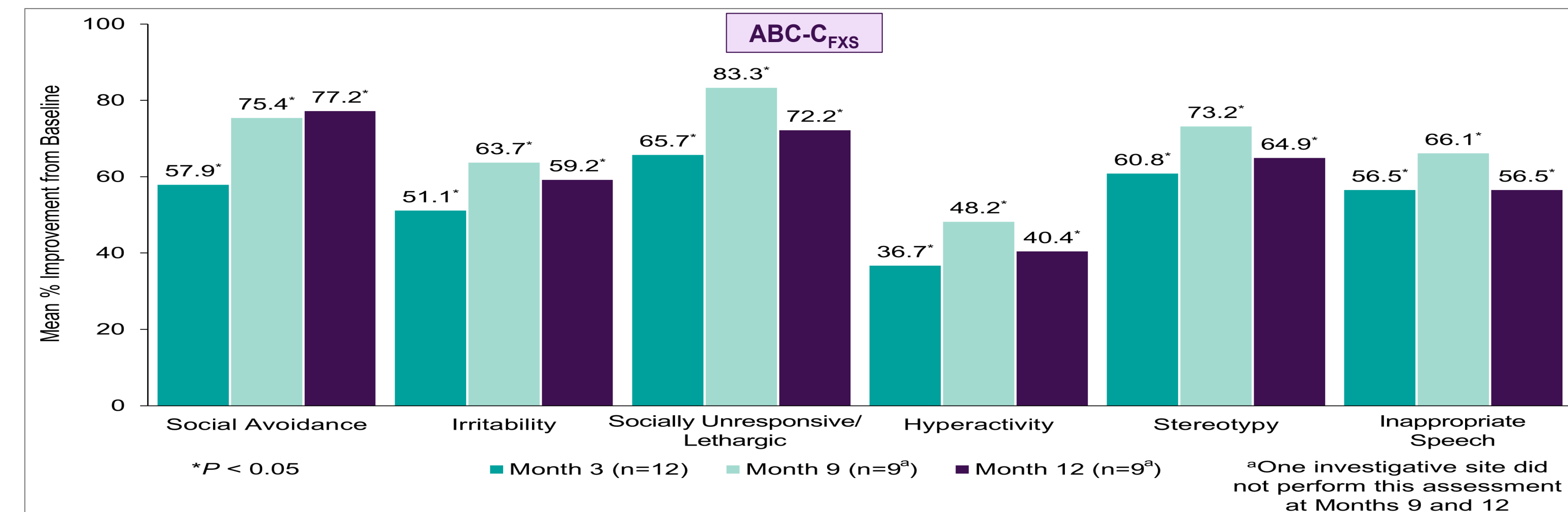
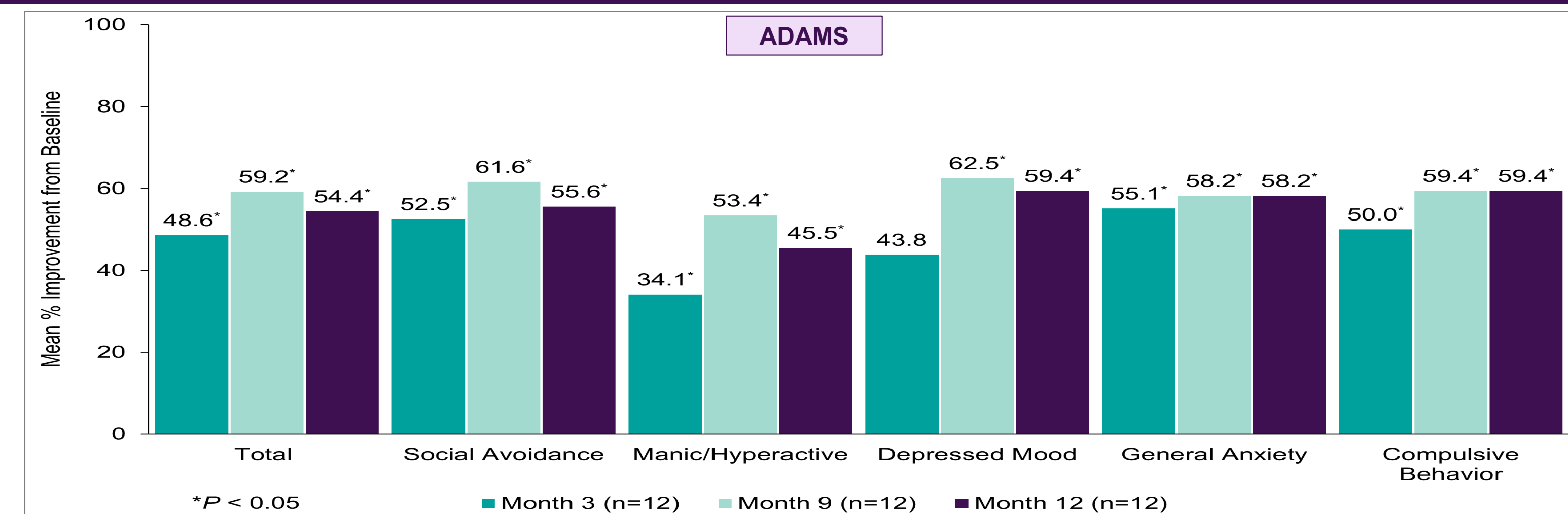
Scale: ABC-C <sub>FXS</sub>	Baseline (n=20)	Week 12 (n=18)	Week 12 Δ (% Improvement Group Mean)	P-value <sup>a</sup>
Social Avoidance	5.1	2.3	-2.8 (54.9)	0.0005
Irritability	18.2	10.6	-7.1 (41.8)	0.0096
Socially Unresponsive/Lethargic	8.7	4.1	-5.1 (52.9)	0.0034
Hyperactivity	14.5	9.8	-3.9 (32.4)	0.0237
Stereotypy	7.9	3.2	-4.9 (59.5)	0.0006
Inappropriate Speech	6.1	3.5	-2.4 (42.6)	0.0018

<sup>a</sup>Compared with baseline

## 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