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

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INTRODUCTION

- Cannabidiol (CBD) is the primary noneuphoric cannabinoid found in cannabis
- FMR1 mutation in FXS causes dysregulation of the endocannabinoid (EC) system, resulting in significant social, behavioral, and cognitive deficits
- Modulation of EC system with CBD may have therapeutic potential in ameliorating some of those symptoms

OBJECTIVE

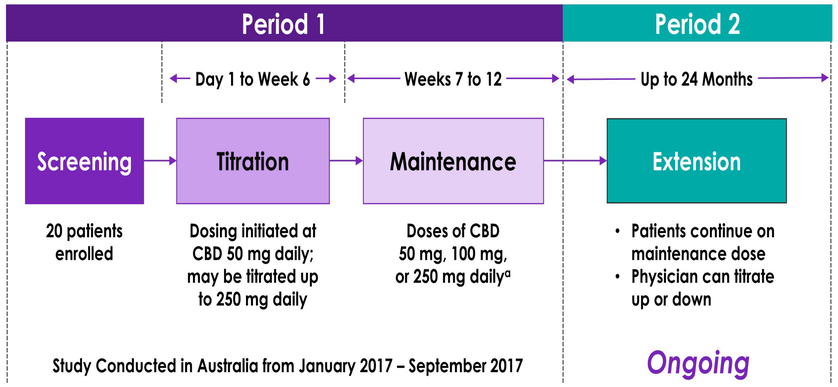
- Evaluate the safety and tolerability of ZYN002 (pharmaceutically produced transdermal CBD gel) in children and adolescents with FXS

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

METHODS *cont.*

Figure 1. Design of the FAB-C Study



[a]Daily dose, split BID in 4.2% gel

METHODS *cont.*

Patients

- Key Inclusion Criteria: Less than 18 year old, 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 one anti-psychotic and one anxiolytic medication; exposure to CBD or delta-9-tetrahydrocannabinol (THC) in the four 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

RESULTS

Patients

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

Table 1. Patient Disposition

Patients Enrolled	20
Patients Completing Week 12	18
Patients Continuing into the 24-month extension	13
Patients at Week 38	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)

Safety

- Through Week 38, patients have reported 43 treatment-emergent adverse events (TEAEs)
  - No SAEs
  - TEAEs were mild or moderate, and most were unrelated to treatment with CBD
  - Two patients discontinued during Period 1; one patient discontinued due to worsening eczema (not considered treatment related) and one patient (sibling of patient with eczema) discontinued for administrative reasons
- Most common TEAEs (all not related and resolved during study period):
  - Gastroenteritis (14%)
  - Upper respiratory tract infection (12%)
- One patient developed moderate application site rash; resolved and remained in the study
- No THC detected in the plasma

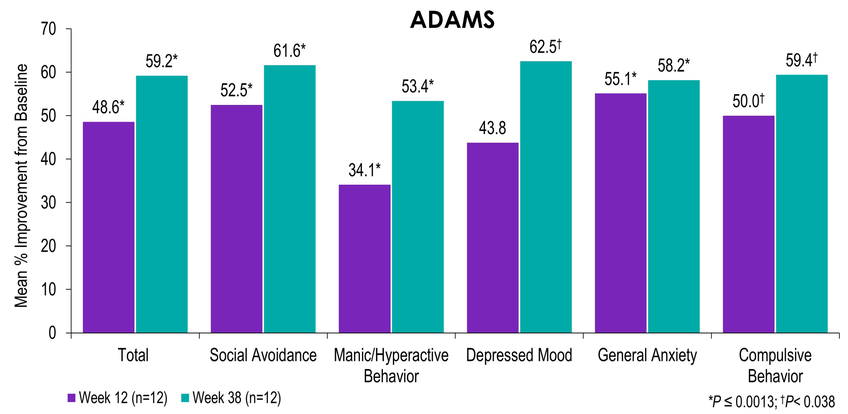
Efficacy

Table 3. Efficacy at Week 12

Scale: ADAMS	Baseline (n=20)	Week 12 (n=18)	Week 12 Δ (% Improvement Group Mean)	P-value vs baseline
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_{FXS}	Baseline (n=20)	Week 12 (n=18)	Week 12 Δ (% Improvement Group Mean)	P-value vs baseline
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

Figure 2. Efficacy at Weeks 12 and 38 Among Patients in the Extension



CONCLUSIONS

- ZYN002 was well tolerated, with no SAEs and most AEs mild and not treatment limiting
- There were no clinically meaningful trends in vital signs, ECG or clinical safety laboratories, including liver function tests
- Findings highlight improvement in behavioral symptoms across multiple measures, including ADAMS Total Score and ABC-C_{FXS} Social Avoidance, Irritability, and Social Unresponsiveness/Lethargy
- Improvement observed during the initial 12-week period was sustained through 38 weeks
- A pivotal, double-blind, placebo-controlled trial of approximately 200 patients aged 3-17 years has recently initiated in the US, Australia, and New Zealand

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