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

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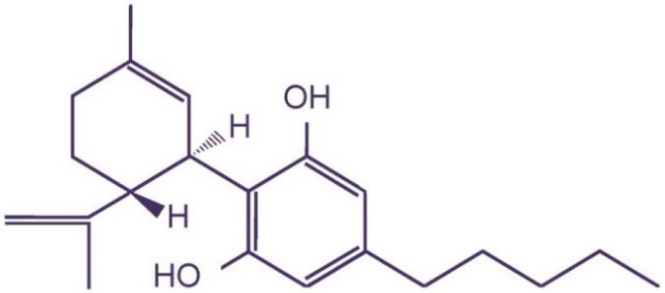
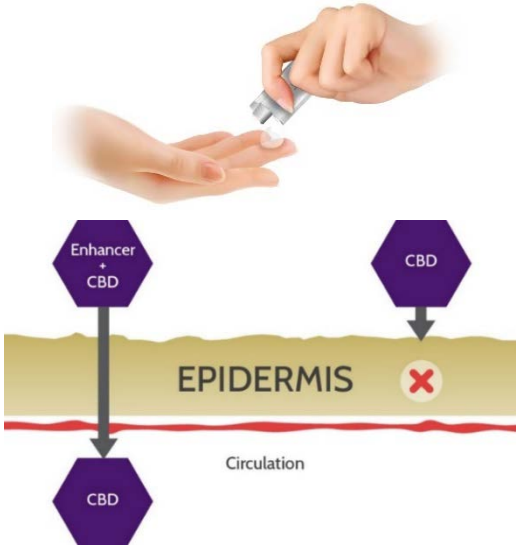
ZYN002: Cannabidiol (CBD) Gel

First and only patent-protected permeation-enhanced pharmaceutically-produced cannabidiol (CBD) gel formulated for transdermal delivery

CBD binds to multiple receptors and may mediate a number of pathways, including the endocannabinoid pathway



Patented formulation increases the delivery of CBD through the layers of the epidermis and into the circulatory system



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Fragile X Syndrome (FXS) and the Endocannabinoid System

- The Endocannabinoid system
  - Cannabinoid receptors (G protein-coupled receptors)
  - Endogenous cannabinoid receptor ligands

- Dysregulation of the endocannabinoid system appears central to the behavioral phenotype seen in FXS[1]

- CBD has been shown to increase levels of:
  - 2-Arachidonoylglycerol (2-AG)[2]
  - Anandamide (AEA)[3]

- Independent of the above associations, CBD has consistently been demonstrated as an anxiolytic[4]

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[1]Busquets-Garcia et al, 2013; [2]Di Marzo et al, 2008; [3]Elmes et al, 2015; [4]Blessing et al, 2015

Fragile X Syndrome Open-Label Phase 2 Objectives and Efficacy Measures

Objectives

- **Primary**: To evaluate the safety and tolerability of ZYN002 in children and adolescents with FXS
- **Secondary:** To evaluate the efficacy of ZYN002 in the treatment of symptoms of FXS

Efficacy Measures

- Anxiety, Depression, and Mood Scale (ADAMS)
- Aberrant Behavior Checklist (ABC-C_{FXS})
- Clinical Global Impression Scale – Improvement (CGI-I)
- Pediatric Anxiety Rating Scale – Revised (PARS-R)
- Pediatric Quality of Life Inventory (PedsQL)
- Visual Analogue Scales (VAS)
- Vineland Adaptive Behavior Scale – 3rd edition (VABS-III)

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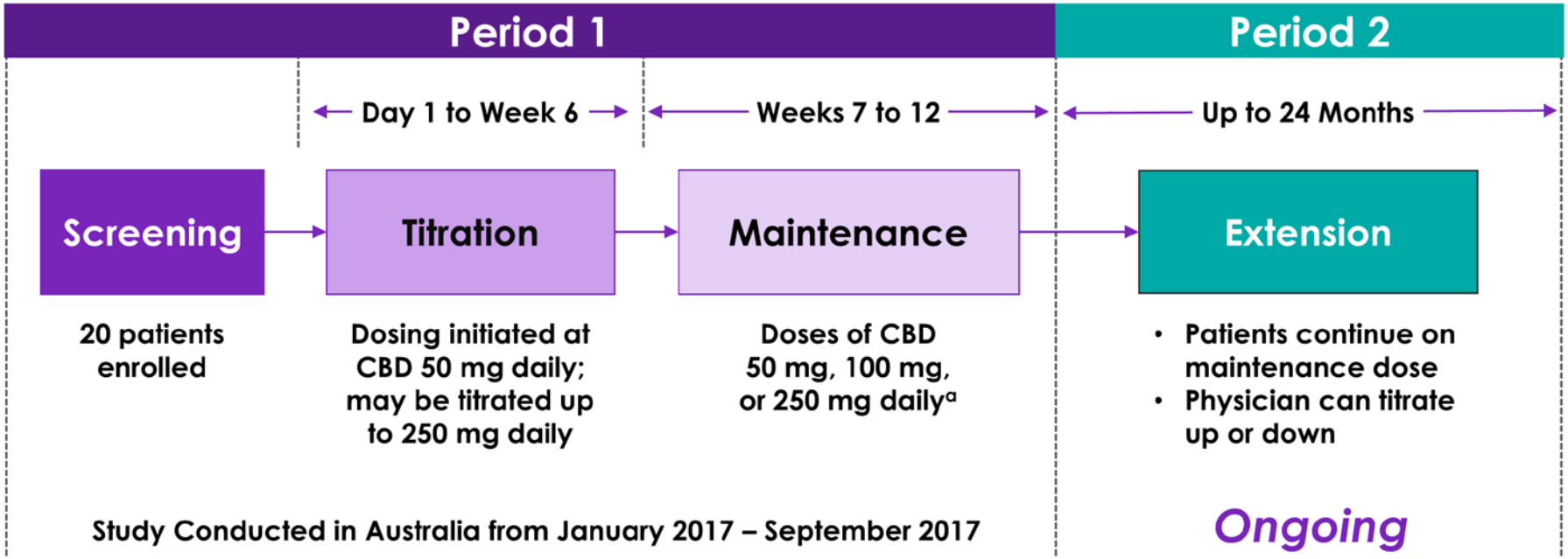
Fragile X Syndrome Open-Label Phase 2 Trial Design

Treatment of Fragile X Syndrome Anxiety and Behavioral Challenges with CBD (FAB-C)



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

FAB-C Key Inclusion/Exclusion Criteria

- Key Inclusion
  - Molecular documentation of full mutation of FMR1 gene
  - PARS-R score ≥ 11
  - CGI-S score ≥ 3

- Key Exclusion
  - Any progressive neurological disorder other than FXS
  - Use of more than one anti-psychotic and one anxiolytic medication
  - Exposure to cannabidiol (CBD) or delta-9-tetrahydrocannabinol (THC) in the four weeks prior to Screening

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FAB-C Demographics

Females, n (%)	5 (25)
Males, n (%)	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)

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FAB-C Week 12 Efficacy Data: ADAMS

Scale: ADAMS	Baseline (n=20)	Week 12 (n=18)	Week 12 % Improvement Group Mean	P-value vs Baseline
Total Score	**33.4**	**18.1**	**45.8**	**<0.0001**
General Anxiety	10.0	4.6	54.0	<0.0001
Social Avoidance	10.2	4.8	52.9	0.0002
Compulsive Behavior	2.8	1.4	50.0	0.0262
Manic/Hyperactive Behavior	9.4	6.1	35.1	0.0003
Depressed Mood	2.8	2.0	28.6	0.1417

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FAB-C Week 12 Efficacy Data: ABC-C_{FXS}

Scale: ABC-C_{FXS}	Baseline (n=20)	Week 12 (n=18)	Week 12 % Improvement Group Mean	P-value vs Baseline
Stereotypy	7.9	3.2	59.5	0.0006
Social Avoidance	5.1	2.3	54.9	0.0005
Socially Unresponsive/ Lethargic	8.7	4.1	52.9	0.0034
Inappropriate Speech	6.1	3.5	42.6	0.0018
Irritability	18.2	10.6	41.8	0.0096
Hyperactivity	14.5	9.8	32.4	0.0237

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FAB-C Week 12 Efficacy Data: CGI, PARS-R, PedsQL, VAS, and Vineland

Scales	Baseline (n=20)	Week 12 (n=18)	Week 12 % Improvement Group Mean	P-value vs Baseline
CGI Improvement (7-point scale)	n/a	2.5*	n/a	n/a
Pediatric Anxiety Rating Scale – Revised (5-item used for Clinical Trials)	15.6	10.6	32.1	0.0006
Pediatric Quality of Life Inventory: Total	57.3	67.7	18.2	0.0100
VAS Hyperactivity/Impulsivity	6.2	3.6	41.9	0.0002
VAS Tantrum/Mood Lability	5.0	3.2	36.0	0.0023
VAS Anxiety	6.2	3.8	38.7	0.0005
Vineland III: Overall Adaptive Behavior	48.3	48.9	1.2	0.0472

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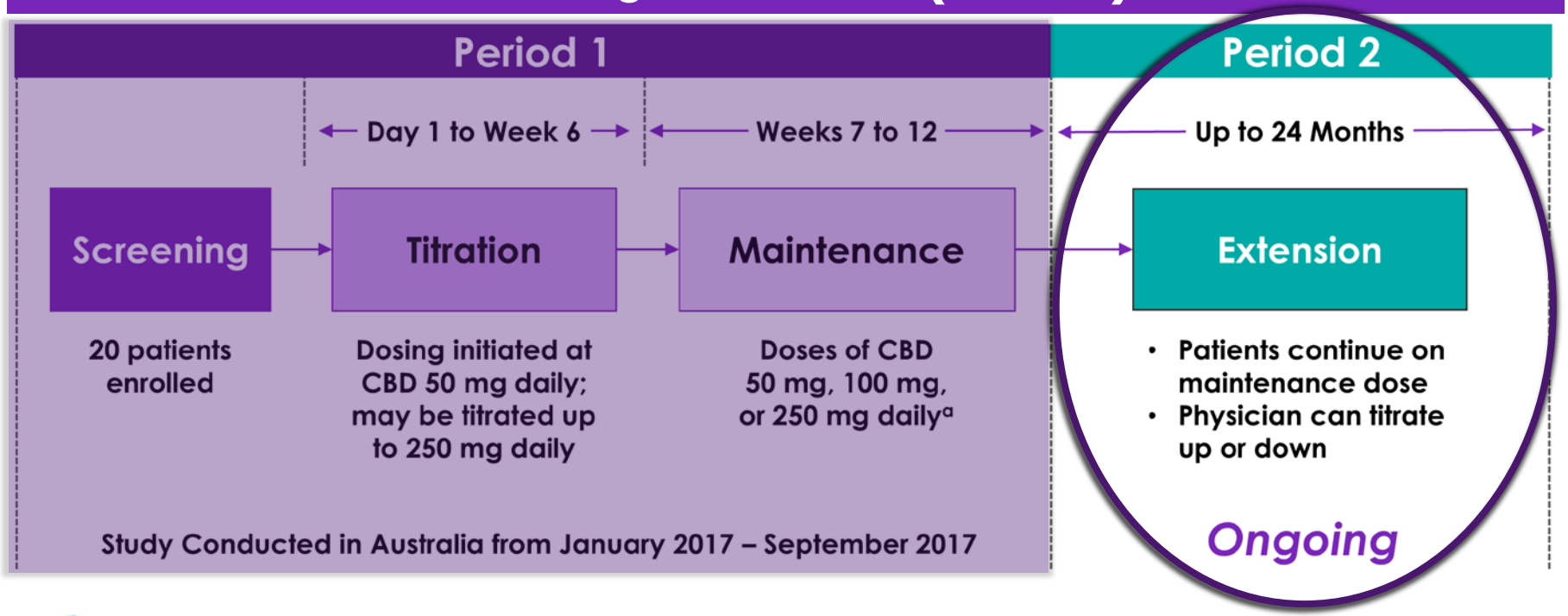
* n=17 at Week 12

Fragile X Syndrome Open-Label Phase 2 Trial Design

Treatment of Fragile X Syndrome Anxiety and Behavioral Challenges with CBD (FAB-C)



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

FAB-C Patient Disposition: Week 38 - Extension Phase

Patients Completing Week 12	18
Patients Continuing into the 24-month Extension	13
Patients at Week 38 (as of June 2018)	12

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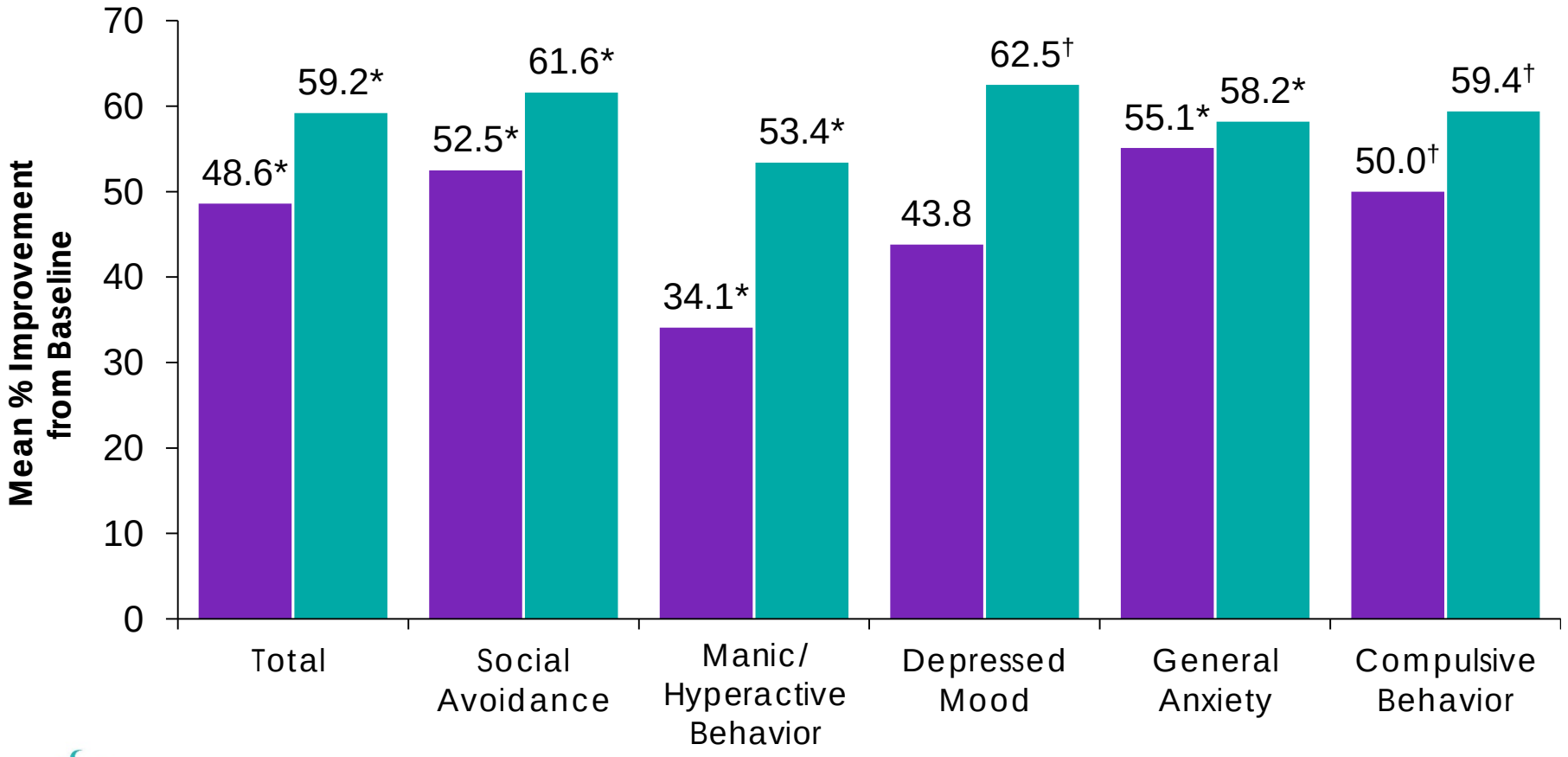
FAB-C Week 38 - Extension Phase Data: ADAMS Mean Percent Improvement From Baseline



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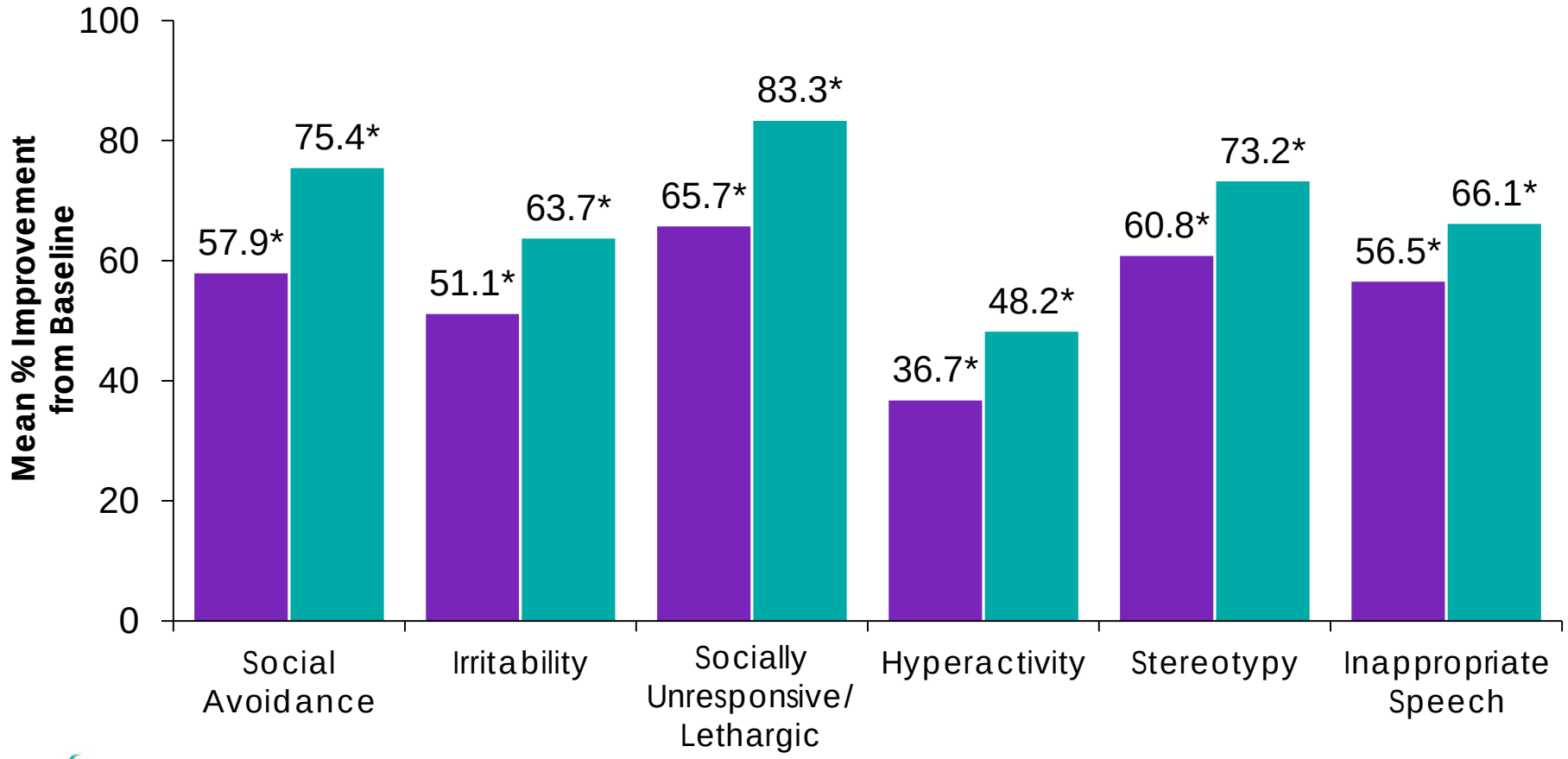
FAB-C Week 38 - Extension Phase Data: ABC-C_{FXS} Percent Improvement from Baseline



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FAB-C Treatment-Emergent Adverse Events

- Through Week 38, patients have reported 43 treatment-emergent adverse events (TEAEs)
  - TEAEs were mild or moderate
  - Most were unrelated to treatment with CBD
- Most common TEAEs (all considered not related and resolved during study period):
  - Gastroenteritis (14%)
  - Upper respiratory tract infection (12%)
- One patient, who continues in the trial, developed moderate application site rash – resolved

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FAB-C Safety Summary

- Well tolerated, consistent with previously reported clinical data[1]
- No SAEs
- No clinically meaningful trends in vital signs, ECG, or clinical safety laboratories, including liver function tests
- No THC was detected in the plasma

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[1] Safety database comprised of 570 volunteers and patients; single dose and up to 24 months of exposure

FAB-C Safety Summary

- Two sibling patients discontinued within the first 12 weeks of the study
  - One patient for worsening of pre-existing eczema (not considered treatment related)
  - One patient (sibling of the patient with eczema) discontinued due to administrative reasons
- Application site assessment scores showed little to no redness in most patients
  - One patient developed moderate application site rash, which resolved and did not recur
  - Patient remains in the study

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FAB-C Conclusions

- Efficacy
  - Improvement in behavioral symptoms across multiple measures
  - Improvement sustained through week 38 of the study
- Safety
  - Well tolerated
  - TEAEs
    - Mild or moderate
    - Most unrelated to treatment with CBD
  - No SAEs

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CONNECT-FX Study Initiated July 2018

Double-blind, placebo-controlled trial initiated

- Approximately 200 patients age 3-17 years
- Approximately 20 sites
  - USA
  - Australia
  - New Zealand

- Efficacy endpoints
  - ABC-C_{FXS}
  - CGI-Improvement, Severity

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