

# ZYN002 Cannabidiol Transdermal Gel Efficacy and Safety: Recent Clinical Research Advances in the Treatment of Autism and Fragile X Syndrome

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# Disclaimers

- This presentation is intended to communicate scientific and medical information about data from clinical trials involving ZYN002. ZYN002 is an experimental treatment which has not been approved by any government regulatory bodies, including the United States Food and Drug Administration (FDA), and has not been determined by the FDA to be a safe or effective treatment for any disease or condition. This presentation is not designed or intended to promote the use of ZYN002 or any other Company product in order to impact prescribing.
- Stephen O'Quinn is an employee of Zynerba Pharmaceuticals, Inc.



# Background

- Autism spectrum disorder (ASD) and Fragile X syndrome (FXS) are complex neurodevelopmental disorders characterized by difficulties with behaviors, communication, and reciprocal social interaction<sup>1,2</sup>
- FXS is the most common monogenic cause of ASD<sup>3</sup>
- Current management options for ASD and FXS symptoms are restricted to cognitive behavioral therapy and a limited number of approved pharmacologic treatments for ASD and off-label prescribing for FXS, highlighting the substantial unmet need for novel therapies in this population<sup>2,4</sup>
- The endocannabinoid system is a key modulator of emotion and social behavior and is dysregulated in ASD<sup>5</sup> and FXS<sup>6</sup>
- Cannabidiol, the main non-euphoric component of the Cannabis plant, may provide therapeutic benefit in ASD and FXS through its effects on the endocannabinoid system
- ZYN002 is a pharmaceutically produced cannabidiol transdermal gel in clinical development for the treatment of behavioral symptoms associated with ASD and FXS

1. Masi A et al. *Neurosci Bull.* 2017;33(2):183-193. 2. Hagerman RJ et al. *Nat Rev Dis Primers.* 2017;3:17065. 3. Salcedo-Arellano, MJ, et al. *Neurotherapeutics.* 2020;18(1):265-283. 4. Sanchack KE, Thomas CA. *Am Fam Physician.* 2016;94(12):972-979. 5. Poleg S et al. *Prog Neuropsychopharmacol Biol Psychiatry.* 2019;89:90-96. 6. Tartaglia N et al. *Cannabis Cannabinoid Res.* 2019;4(1):3-9.



# Clinical Studies of ZYN002 in Patients With Autism Spectrum Disorder and/or Fragile X Syndrome

Trial	Population (N)	Design	Patients With ASD, n (%)	Patients With Moderate-Severe ASD <sup>a</sup> n (%)
BRIGHT (ZYN2-CL-030)	ASD (37)	Open-label, Phase 2	37 (100%)	34 (92%)
FAB-C (ZYN2-CL-009) <sup>1,b</sup>	FXS (20)	Open-label, Phase 2	N/A	N/A
CONNECT-FX (ZYN2-CL-016) <sup>b</sup>	FXS (212)	Randomized, controlled, Phase 3	180 (85%)	158 (75%)
RECONNECT (ZYN2-CL-033) <sup>b</sup> <i>Ongoing</i>	FXS (204)	Randomized, controlled, Phase 3	TBD	TBD

<sup>a</sup>Severity of ASD-related symptoms as defined by Autism Diagnostic Observation Schedule<sup>®</sup>-2 (ADOS<sup>®</sup>-2) comparison scores

<sup>b</sup>Patients who entered the extension of FAB-C, were screened for CONNECT-FX, as well as patients who enter RECONNECT, were/will be eligible to enroll in the open-label extension trial ZYN2-CL-017



Longer Term Tolerability and Efficacy of ZYN002 Cannabidiol  
Transdermal Gel in Children and Adolescents With Autism  
Spectrum Disorder (ASD): An Open-Label Phase 2 Trial  
(BRIGHT [ZYN2-CL-030])



# Methods

- The trial enrolled patients with an Aberrant Behavior Checklist-Community (ABC-C) Irritability score  $\geq 18$  and a Clinical Global Impression (CGI)–Severity score  $\geq 4$  (moderate or greater)
- Primary objective: To evaluate the safety and tolerability of ZYN002 for up to 38 weeks (14-week treatment period [Period 1] and a 24-week extension period [Period 2])
  - Safety assessments included adverse events (AEs), skin assessments, laboratory tests, and electrocardiograms (ECGs)
- The primary efficacy assessments included the ABC-C and CGI-Improvement
- Secondary objectives comprised evaluation of the efficacy of ZYN002 in the treatment of symptoms of ASD, including measuring parental/caregiver stress (APSI<sup>†</sup>), Parent Rated Anxiety Scale (PRAS), Autism Impact Measure (AIM), and qualitative caregiver-reported behavioral problems
- Patients received ZYN002 250 mg or 500 mg (weight-based dose) daily for up to 38 weeks, as add on to stable standard of care medications (including antipsychotic agents, when prescribed)
- Patients demonstrating  $\geq 35\%$  improvement in the ABC-C irritability subscale at week 14 were allowed to continue treatment for an additional 24 weeks

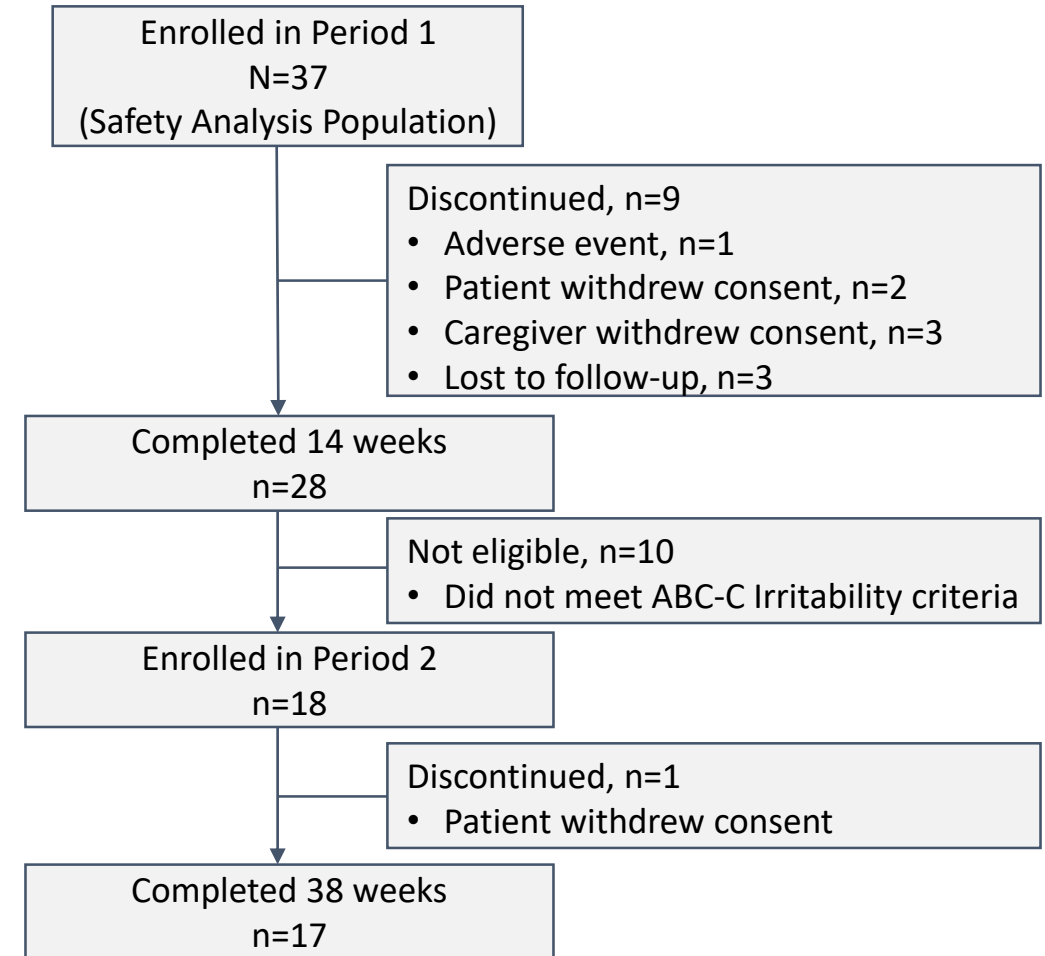
<sup>†</sup>APSI=Autism Parenting Stress Index.



# Baseline Demographics and Patient Disposition

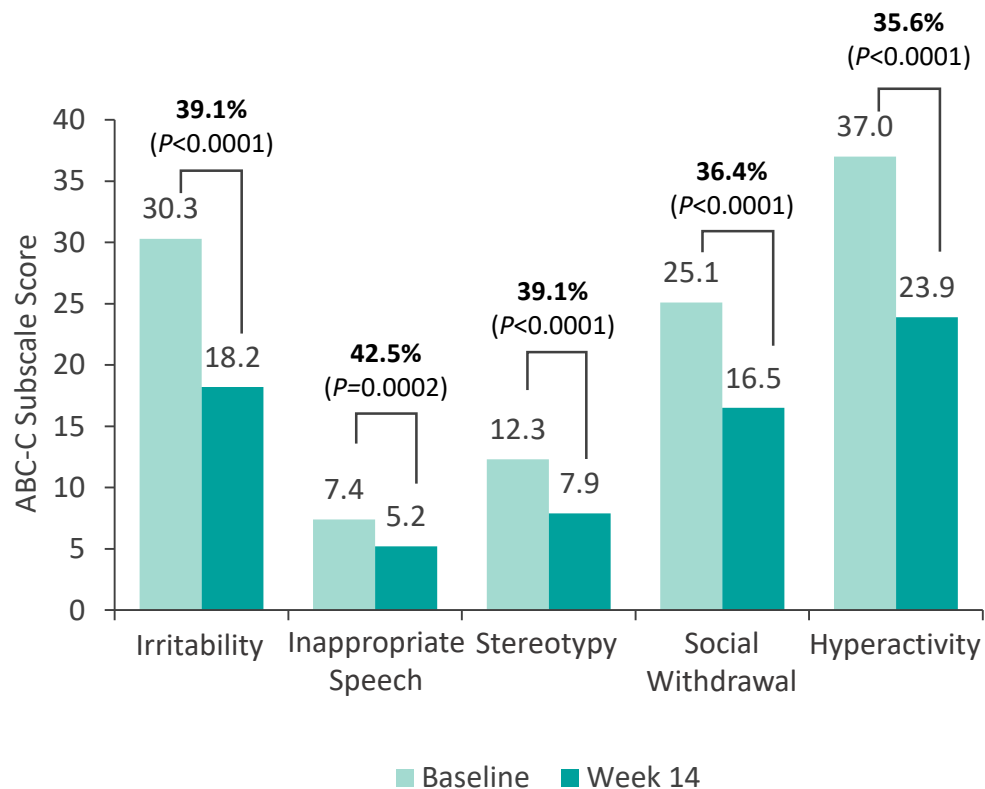
Demographics were similar for patients in Period 1 and Period 2

Characteristic	BRIGHT Participants Period 1 N=37	BRIGHT Participants Period 2 n=18
Age, mean years (range)	9.2 (3-16)	9.2 (3-16)
Sex, n (%)		
Male	34 (91.9)	16 (89)
Female	3 (8.1)	2 (11)
Race, %		
White	75.7	77.8
Indigenous Australian	5.4	0
Asian	8.1	5.6
Other	10.8	16.7

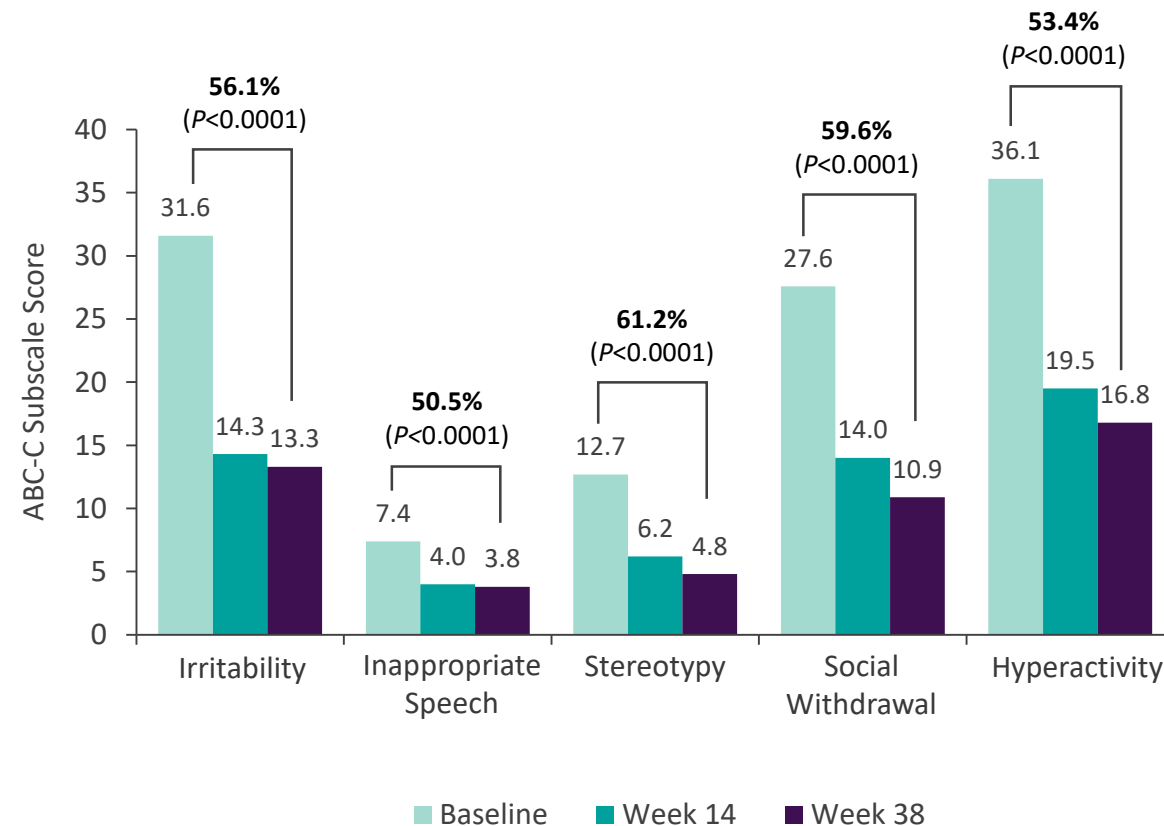


# Efficacy: Statistically Significant Improvements From Baseline in all ABC-C Subscale Scores\* Sustained Through Week 38

Mean Scores and Percent Improvement Period 1 (n=28 [n=26 for Inappropriate Speech])



Mean Scores and Percent Improvement Period 2 (n=18)



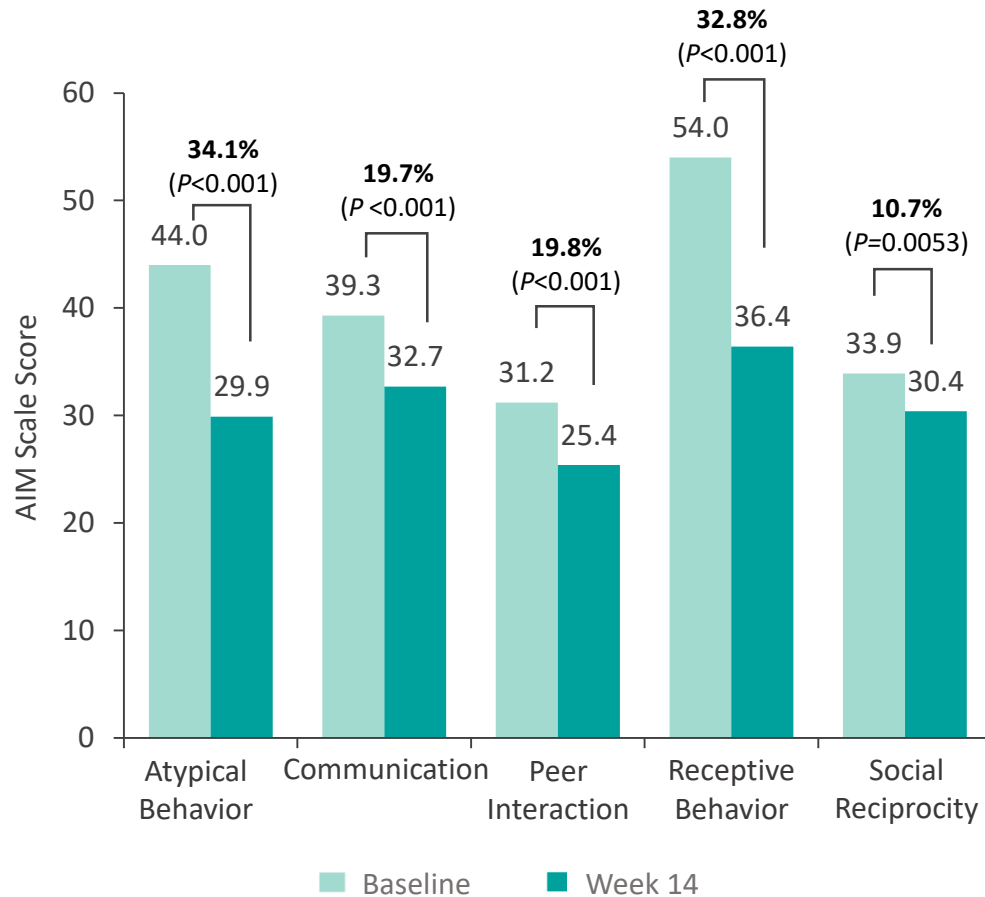
\*Lower values reflect improvement in each ABC-C subscale.



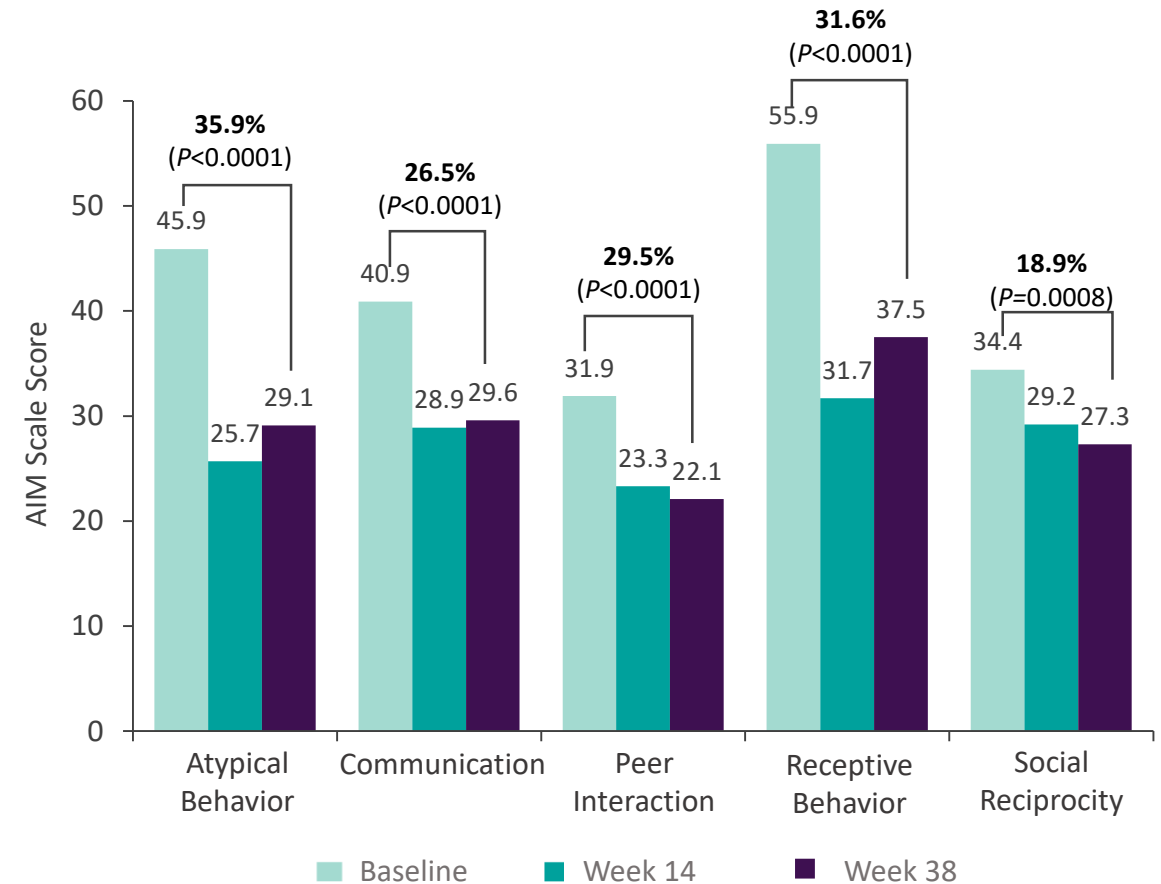


# Efficacy: Statistically Significant Improvements From Baseline in Autism Impact Measure Scores<sup>a</sup> Sustained Through 38 Weeks

Mean Scores and Percent Improvement Period 1 (n=28)



Mean Scores and Percent Improvement Period 2 (n=18)



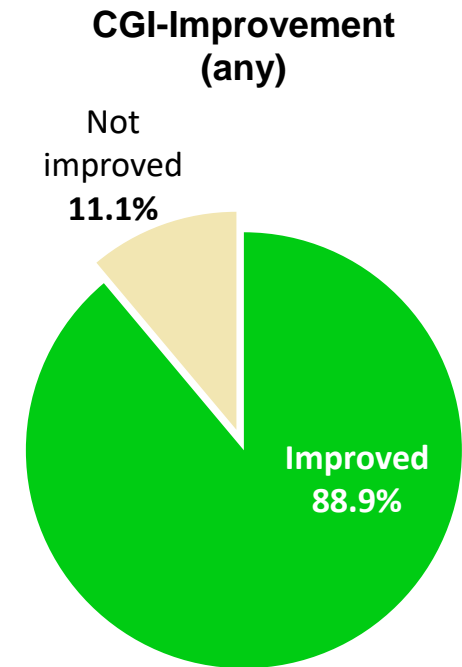
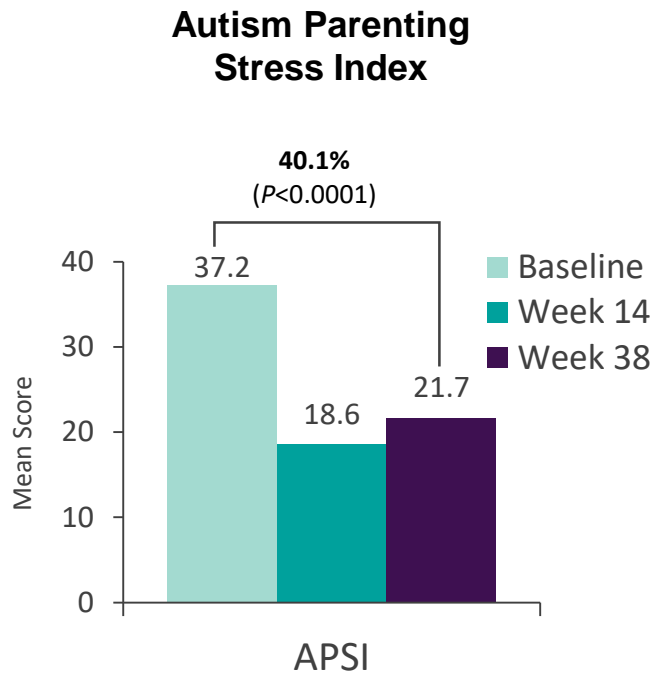
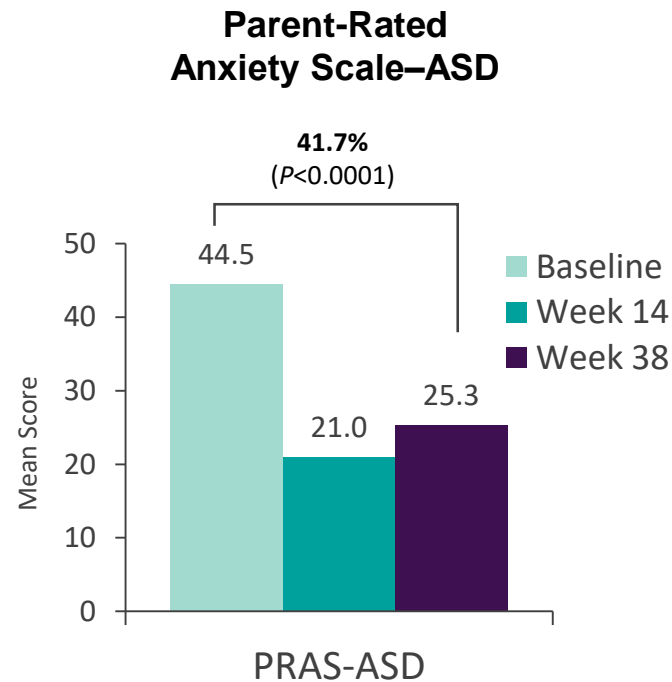
1. Mazurek MO, et al. *Autism Res.* 2020;13(11):1867-1879.



<sup>a</sup>The AIM score has been shown to be sensitive to change as a measure of core ASD symptoms.<sup>1</sup>

# Efficacy: Statistically Significant Improvements From Baseline in PRAS-ASD, APSI, and CGI-I Sustained Through Week 38

## Mean Scores and Percent Improvement Through Week 38



n=18

ASD=Autism Spectrum Disorder; CGI=Clinical Global Impression.



# BRIGHT: Summary of Overall Safety/Tolerability

- ZYN002 was generally well tolerated, and the safety profile was consistent with data from previous ZYN002 clinical trials
- During the 38-week trial, slightly more than half (54.1%) of patients experienced any adverse event (AE), whether unrelated or related to study drug
- All AEs were mild (80%) or moderate (20%) and transient
- 7 patients (19%) experienced a total of 10 AEs that were deemed to be treatment-related
- Of the 10 treatment-related AEs reported, 7 were application site-related (application site reaction, pruritus, and dryness) and 1 each of sleep disorder, increased appetite, and pollakiuria (frequent urination)
- There were no severe or serious AEs reported during the trial
- There were no clinically significant changes in vital signs, laboratories, or electrocardiogram (ECG) parameters



## BRIGHT: Summary of Results

- Through 38 weeks of treatment, BRIGHT provides initial evidence suggesting a positive benefit-risk profile for ZYN002 when administered, in addition to stable standard of care, to children and adolescents with moderate-to-severe ASD
- ZYN002 showed improvement in all ASD efficacy measures (ABC-C, AIM, PRAS-ASD, CGI-I)
- Further controlled trials are warranted in this difficult-to-treat population

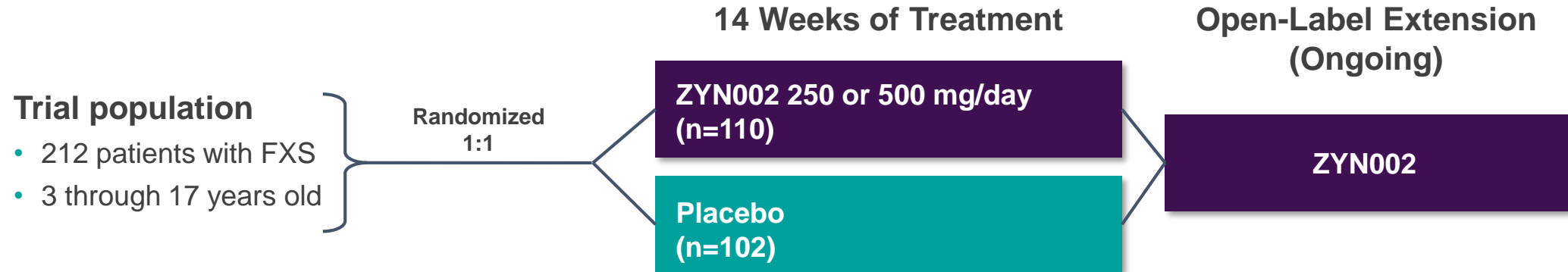


ZYN002 in Fragile X Syndrome:  
Key Data and Learnings From CONNECT-FX,  
Interim Data From Open-Label Extension, ZYN2-CL-017,  
and the Design of RECONNECT



# CONNECT-FX: Clinical Study Of CaNNabidiol in ChildrEn and AdolesCenTs With Fragile X

- CONNECT-FX was a randomized, double-blind, multinational, 14-week pivotal trial to evaluate the efficacy and safety of ZYN002 in children/adolescents aged 3 through 17 years with a full *FMR1* gene mutation

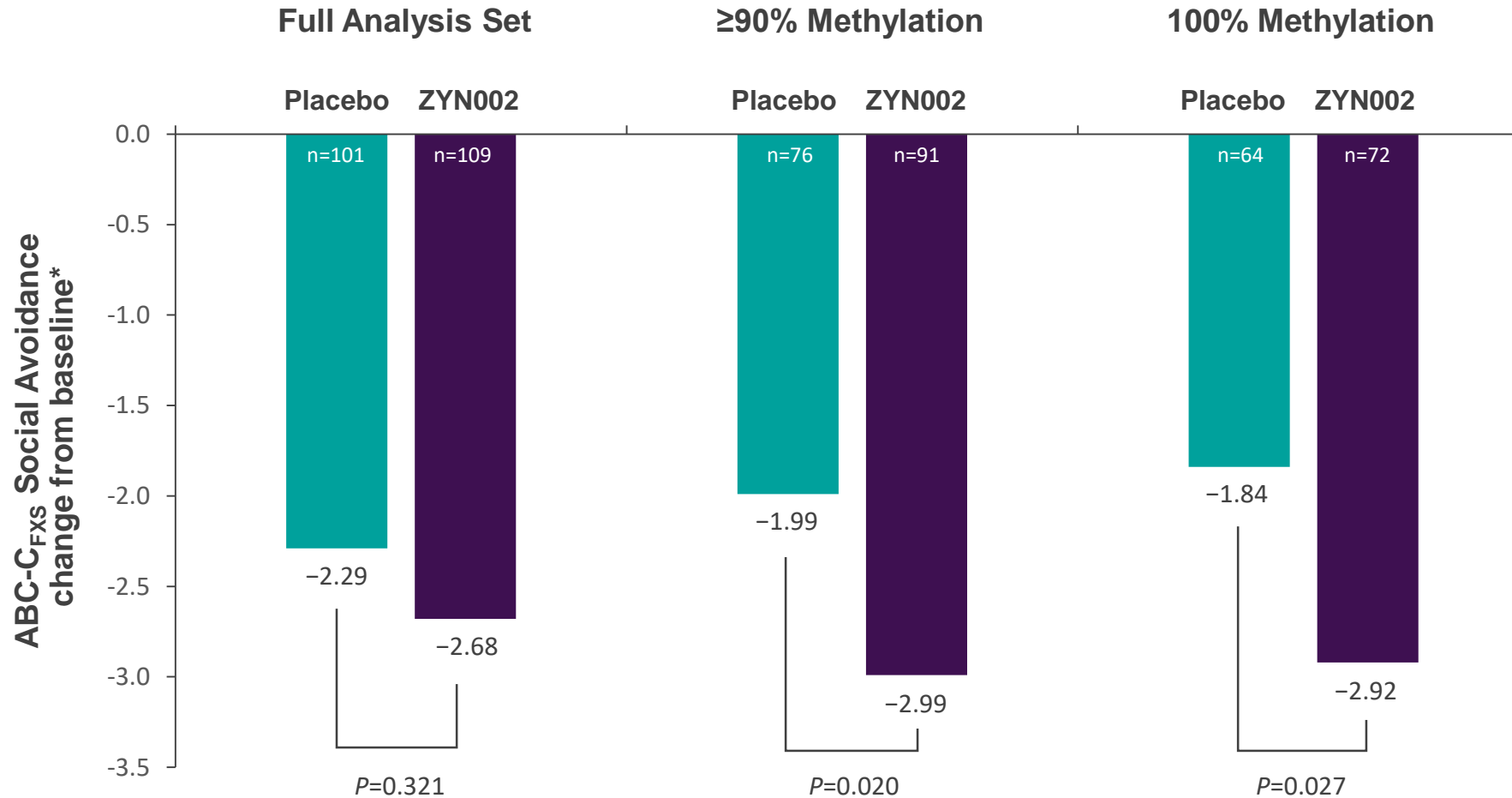


- ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set
- Building on current scientific evidence, a pre-planned ad hoc analysis of patients having at least 90% methylation of the impacted *FMR1* gene<sup>a</sup> was performed
- The results suggested that ZYN002 may have benefit in patients with  $\geq 90\%$  methylation of the *FMR1* gene
- ZYN002 was very well tolerated. All adverse events (AEs) were mild or moderate in severity and no serious AEs were reported
- Most common treatment-related AE was application site pain (ZYN002: 6.4%; placebo: 1.0%)
- Laboratory values and ECG parameters were comparable between the placebo and ZYN002 treatment groups and there were no clinically significant changes in liver function tests or other laboratories

<sup>a</sup>*FMR1* methylation status was determined by using Southern blot analysis.



# In Patients With $\geq 90\%$ Methylation or Complete Methylation (100%) of *FMR1*, Statistical Significance Was Achieved on Social Avoidance at Week 12 (ABC-C<sub>FXS</sub>)

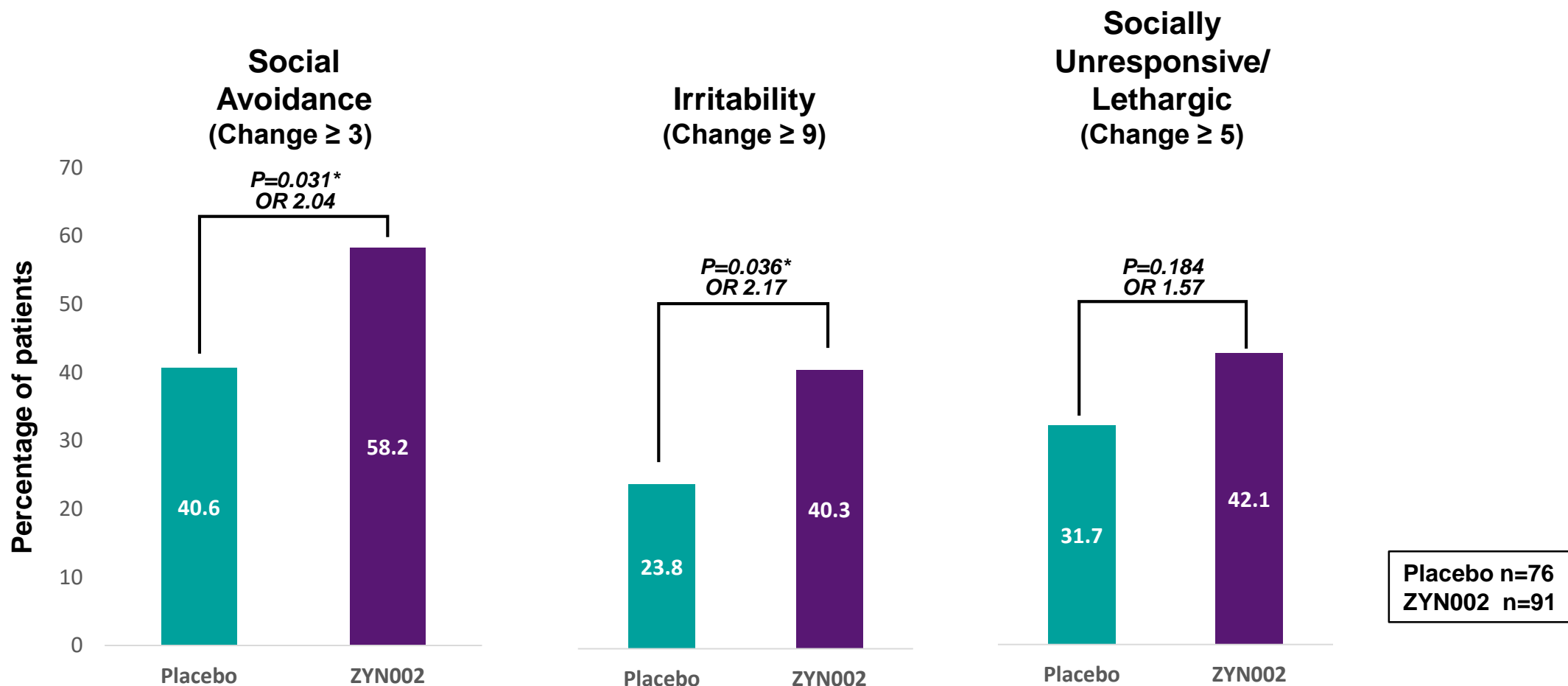


\*Negative numbers represent an improvement.



# Greater Percentages of Patients Achieved Meaningful Change in ABC-C<sub>FXS</sub> Social Avoidance and Irritability With ZYN002 vs Placebo

Meaningful within-subject change in  $\geq 90\%$  methylation group



OR= odds ratio  
\*Statistically significant. LS Means





# CONNECT-FX: Lessons Learned

1. Treatment response for ZYN002 was greatest in patients with  $\geq 90\%$  methylation of the *FMR1* gene
2. Psychometric assessments<sup>1</sup> determined that the ABC-C<sub>FXS</sub> was fit for purpose in FXS and meaningful within-patient change was determined in CONNECT-FX for the Social Avoidance, Irritability, and Socially Unresponsive/Lethargic subscales<sup>2</sup>
3. Caregiver Global Impression of Severity/Change (CaGI-S/C) was responsive to change, with greatest change on the Social Interactions
4. An FXS-specific Clinical Global Impression of Severity/Improvement (CGI-S/I) assessment was developed based upon outcomes in response to FDA guidance to use a disease-specific CGI
5. Virtual visits were successfully incorporated as a result of COVID-19 restrictions

1. Merikle E, et al. *Value in Health*. 2021. 23:S241-242

2. Merikle E, et al. *Value in Health*. 2021. 24:S197



# Open-Label Extension Trial (ZYN2-CL-017) Interim Safety Data

## ZYN002 Well Tolerated Over a Median of 21 Months

### CONNECT-FX (ZYN2-CL-016), n=230

- Completers, n=197
- Screen failures, n=12
- Ineligible for randomization, n=21

### ZYN2-CL-009<sup>a</sup>, n=10

### ZYN2-CL-017, N=240

- Interim analysis of data through May 21, 2021
- Median length of treatment: 21 months
- Adverse events- see table
- No clinically significant changes in vital signs, electrocardiograms or laboratories (including liver function)

Adverse Event Type	% of Patients (n=240) or Events
<b>Treatment Emergent Adverse Events (TEAEs)<sup>b</sup></b>	62.2%
Mild-to-moderate TEAEs	97.7% of events
Most common TEAEs (≥3% of patients)	
Upper respiratory infection	15.4%
Application site pain	6.6%
Pyrexia	4.6%
Diarrhea	4.1%
Vomiting	4.1%
Ear infection	4.1%
Nasopharyngitis	3.7%
Cough	3.3%
Discontinuations due to a TEAE	7 (2.9%)
<b>Serious AEs (all non-treatment-related)</b>	7 events in 6 patients
<b>Treatment-related AEs</b>	13.3%
Most common related AE (≥3% of patients)	
Application site pain	6.6%

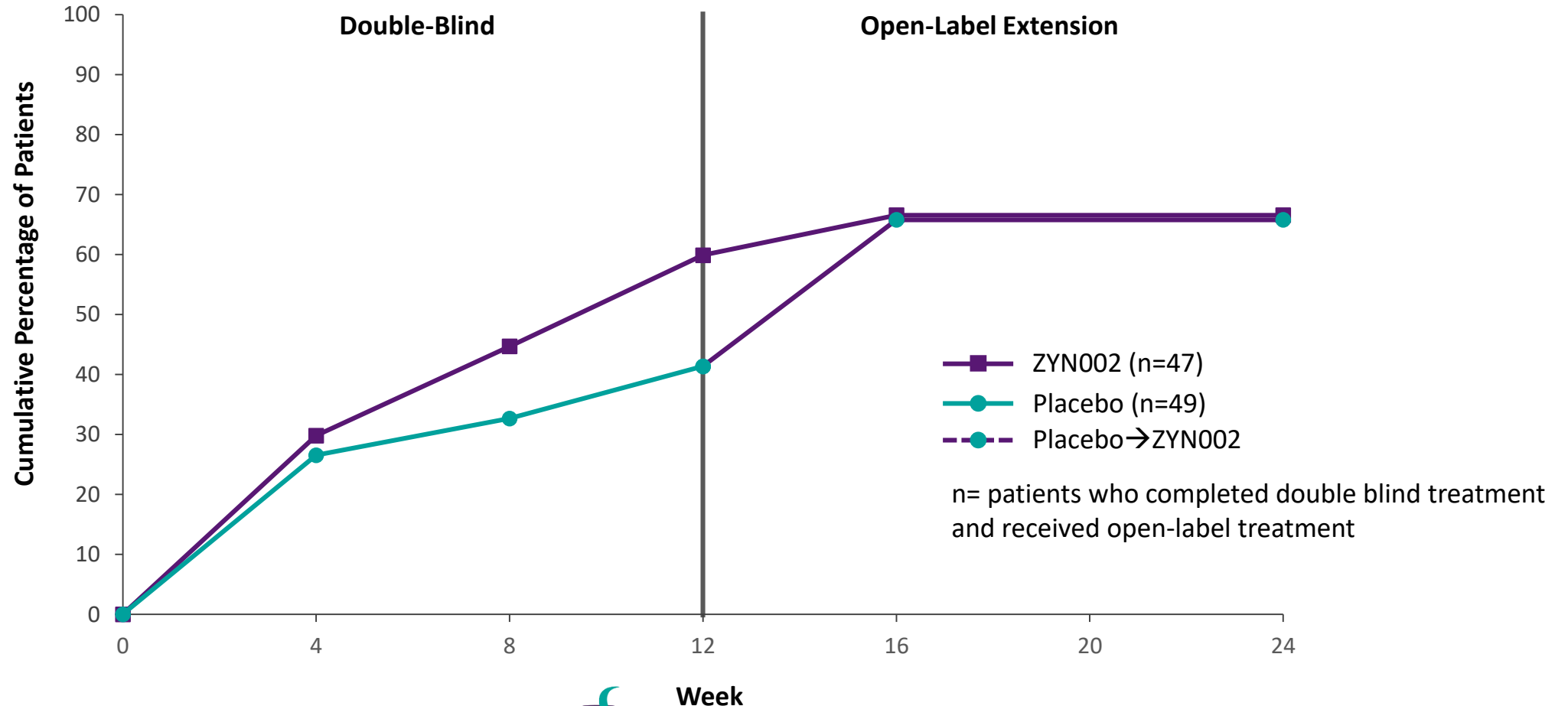
<sup>b</sup>TEAE=any adverse event, whether related or unrelated to study drug.

<sup>a</sup>Original open-label trial



# Patients Achieved and Maintained Meaningful Change in ABC-C<sub>FXS</sub> Social Avoidance With ZYN002 and Placebo Patients Switched to Open-Label ZYN002 Demonstrated a Similar Response

100% methylation group meeting entry criteria for RECONNECT and  $\geq 2$  consecutive visits with meaningful change\*



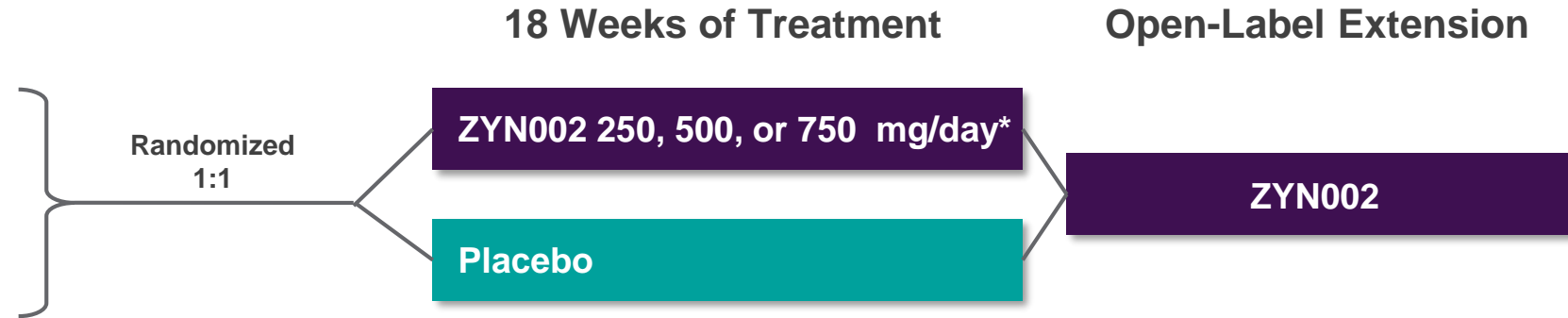
\*Meaningful Change in Social Avoidance:  
 $\geq 3$ -point improvement from baseline



# RECONNECT Trial Design

## Trial population

- ~200 patients with FXS
  - ~160 with complete methylation (100%) of *FMR1* gene
- 3 through 17 years old



\*Weight-based dosing:  $\leq 30$  kg = 250 mg/day;  $> 30$  kg = 500 mg/day;  $> 50$  kg = 750 mg/day

## Endpoints

### Primary end point

- Change from baseline in the ABC-C<sub>FXS</sub> Social Avoidance subscale at week 18 in patients with complete methylation (100%) of the *FMR1* gene

### Key secondary end points

#### Complete methylation (100%) population

- Change from baseline in ABC-C<sub>FXS</sub> Irritability subscale
- Improvement in CaGI-C Social Interactions
- Improvement in FXS-specific CGI-I

#### Total population

- Change from baseline in ABC-C<sub>FXS</sub> Social Avoidance in the full population (complete and partial [ $< 100\%$ ] methylation)



# Conclusions

## CONNECT-FX and the Open-Label Extension Trial (ZYN2-CL-017)

- Patients with complete/near complete methylation are believed to be most likely to have silencing of the *FMR1* gene and may be a different biologic population than the patients without silencing<sup>1,2</sup>
- ZYN002 was superior to placebo in multiple analyses in the groups of patients with either  $\geq 90\%$  methylation or complete methylation (100%) of their *FMR1* gene, which represented the majority of patients in the trial
- ZYN002 continues to be well-tolerated, without any reports of clinically significant changes vital signs, ECGs or laboratories (no changes in liver function)
- Patients with complete methylation continuing from CONNECT-FX into the OLE, who would also meet entry criteria for RECONNECT, achieved and maintained meaningful change in Social Avoidance

## RECONNECT

- The design of RECONNECT was optimized from learnings from CONNECT-FX and will provide key data to determine the effectiveness of ZYN002 in FXS, while reducing burden of participation in a clinical trial for families with children and adolescents with FXS
- Results from RECONNECT, if successful, could serve as the basis for ZYN002 approval for use in patients with FXS

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1. Hagerman RJ, et al. *Nat Rev Dis Primers*. 2017;3:17065.

2. Schneider, A, et al. *Transl Psychiatry*. 2020;10(1):205.

