

# Cannabidiol in Fragile X Syndrome (FXS): Proposed Mechanism of Action Translates Into Meaningful Clinical Benefits (CONNECT-FX [ZYN2-CL-016])

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## BACKGROUND

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- Fragile X syndrome (FXS) is a rare genetic disorder, which is a common cause of intellectual disability<sup>1</sup>
- Disruption in the endocannabinoid system is one of the proposed mechanisms for the loss of synaptic plasticity and the deficits in emotional responsivity observed in FXS<sup>2,3</sup>
- Cannabidiol acts as a negative allosteric modulator at presynaptic CB<sub>1</sub> receptors, a 5HT<sub>1A</sub> agonist, and a D<sub>2</sub> partial agonist<sup>4-6</sup>
- FXS causes intellectual disability, making symptom recognition and self-report problematic<sup>1</sup>
- Therapeutic response must rely on objective description of change
- The Aberrant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObsRO) measure that has been validated in individuals with intellectual disabilities<sup>7</sup>
- An FXS-specific domain structure of the ABC-C (henceforth the ABC-C<sub>FXS</sub>), which is more representative of the FXS phenotype, has been established<sup>8</sup>
- The ABC-C<sub>FXS</sub> was utilized to measure the primary and key secondary endpoints in ZYN2-CL-016 (CONNECT-FX), a randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of ZYN002, a transdermal synthetic cannabidiol gel, for the treatment of behavioral symptoms associated with FXS in children and adolescent patients (NCT03614663)
- The FDA Clinical Outcomes Assessment Group recommends determining clinical meaningfulness from the caregiver perspective using a mixed methods (qualitative and quantitative) approach<sup>9</sup>
- Thresholds for meaningful within-patient change were established using anchor-based methods with treatment benefit informed by interviews with caregivers of children with FXS

## OBJECTIVES

- To derive responder thresholds (RTs) representing individual patient-level change indicative of meaningful treatment benefit for the ABC-C<sub>FXS</sub> Social Avoidance (SA), Irritability, and Socially Unresponsive/Lethargic (SUL) subscales

## METHODS

- Anchor-based methods supplemented with visual plots were used to estimate RTs for change from Baseline to Week 12 in the ABC-C<sub>FXS</sub> SA, Irritability, and SUL subscales
  - SA: primary endpoint, score range 0 to 12
  - Irritability: key secondary endpoint, score range 0 to 54
  - SUL: key secondary endpoint, score range 0 to 39
  - Higher subscale scores represented higher severity of aberrant behavior

- Primary anchors were domain-specific (DS) behavioral problems and overall behavior (OB) of the Caregiver Global Impression of Severity (CaGI-S). Problems experienced by a child were rated on a 4-point scale (0=no problems to 3=severe problems). CaGI-S change was categorized on a 5-point scale (-2=much better to +2=much worse)
- Caregiver Global Impression of Change (CaGI-C) DS and OB were supportive anchors. Changes in problems experienced by a child were rated on a 7-point scale (-3=much worse to +3=much better)
- Identification of the point change on the CaGI-S/C representing meaningful change was informed by semi-structured cognitive interviews with 25 caregivers of children with FXS

## RESULTS

### CONNECT-FX Efficacy Results

- In the CONNECT-FX trial, in patients with ≥90% methylation of the *FMR1* gene, ZYN002 was associated with a statistically significantly greater mean change from baseline in Social Avoidance vs placebo (please see SOBP poster by Berry-Kravis E, et al, entitled "A Pivotal Study of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Fragile X Syndrome (CONNECT-FX [ZYN2-CL-016])")

### Anchor-Based Analyses

- Caregivers of children with FXS reported that even small improvements in their child's behavior would be meaningful
- Majority of caregivers (n=17; 68%) indicated that a 1-category change on the CaGI-S would be meaningful or important
- In the analyses (n=193), the mean (SD) changes for the ABC-C<sub>FXS</sub> subscales in patients with a 1-category improvement on the CaGI-S DS and OB items were (Table 1)
  - 3.0 (3.0) and -3.6 (2.64) for ABC-C<sub>FXS</sub> SA
  - 9.8 (9.70) and -8.9 (9.43) for ABC-C<sub>FXS</sub> Irritability
  - 5.4 (6.46) and -6.8 (6.92) for ABC-C<sub>FXS</sub> SUL

Table 1. Mean Change Scores on the ABC-C<sub>FXS</sub> SA, Irritability, and SUL Subscales for Domain-Specific (DS) Behaviors and Overall Behavior (OB) by CaGI-S Change Categories

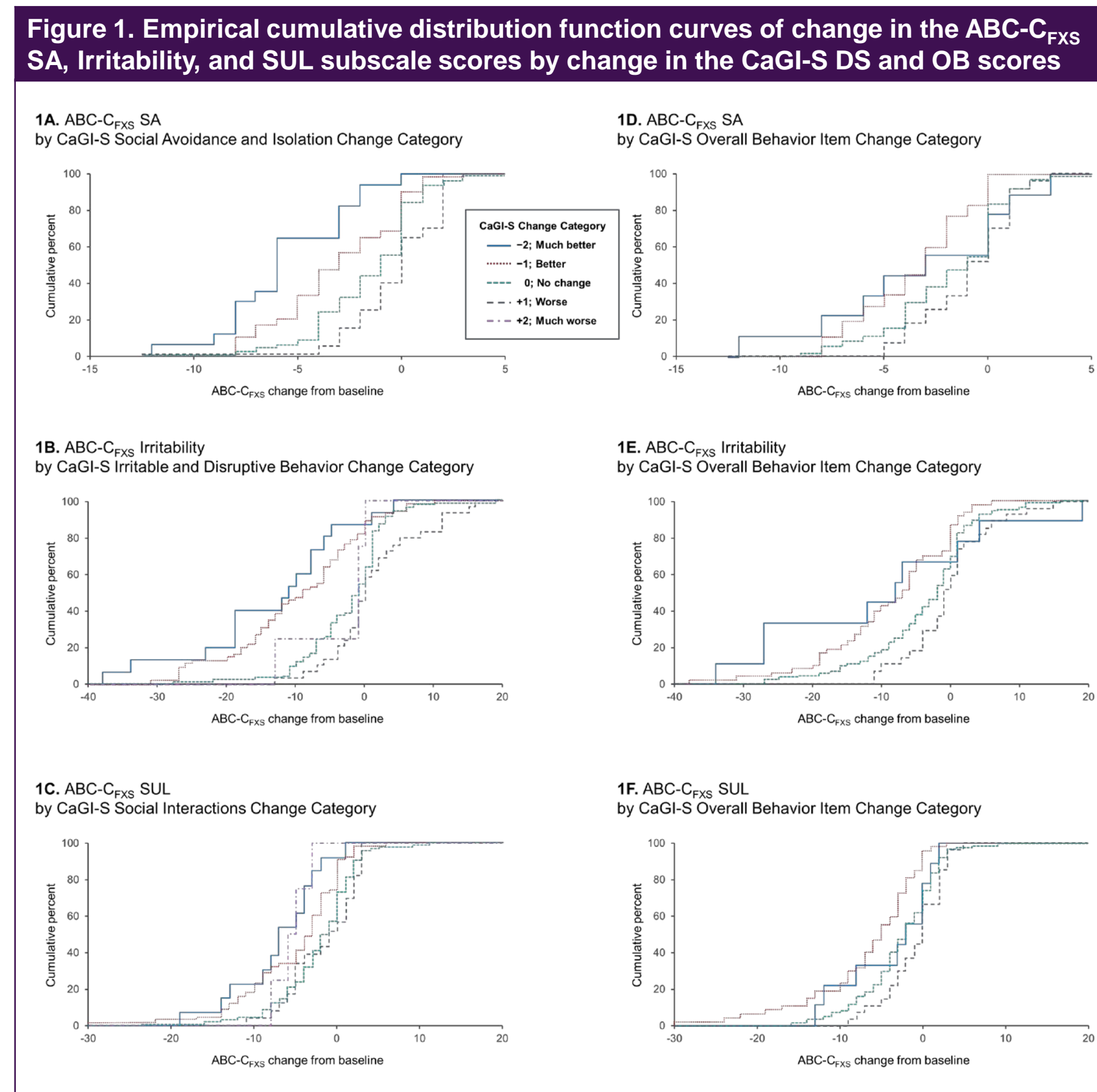
ABC-C <sub>FXS</sub>	CaGI-S Change Category <sup>a</sup>				
	Much better (-2)	Better (-1)	No change (0)	Worse (+1)	Much worse (+2)
<b>Social Avoidance</b>					
DS	-5.6 (3.06) (n=17)	-3.0 (3.0) (n=60)	-1.5 (2.44) (n=96)	-0.2 (1.91) (n=20)	N/A (n=0)
OB	-3.3 (4.85) (n=9)	-3.6 (2.64) (n=47)	-1.8 (2.85) (n=110)	-0.9 (2.22) (n=27)	N/A (n=0)
<b>Irritability</b>					
DS	-13.8 (11.73) (n=15)	-9.8 (9.7) (n=55)	-2.5 (6.34) (n=90)	1.2 (6.85) (n=29)	-3.8 (6.19) (n=4)
OB	-10.1 (17.06) (n=9)	-8.9 (9.43) (n=47)	-3.9 (8.01) (n=110)	-0.4 (4.14) (n=27)	N/A (n=0)
<b>Socially Unresponsive/Lethargic</b>					
DS	-7.2 (5.48) (n=13)	-5.4 (6.46) (n=55)	-2.3 (5.01) (n=98)	-1.7 (4.14) (n=23)	-5.5 (2.08) (n=4)
OB	-3.9 (5.69) (n=9)	-6.8 (6.92) (n=47)	-2.7 (4.76) (n=110)	-0.9 (3.55) (n=27)	N/A (n=0)

N/A, not applicable.  
<sup>a</sup>Data are mean change from Baseline (Visit 3, randomization) to Week 12 (Visit 6) (standard deviation).

- A similar pattern of mean change on the ABC-C<sub>FXS</sub> SA, Irritability and SUL subscales was observed for the CaGI-C DS and OB items

### Visual Plots

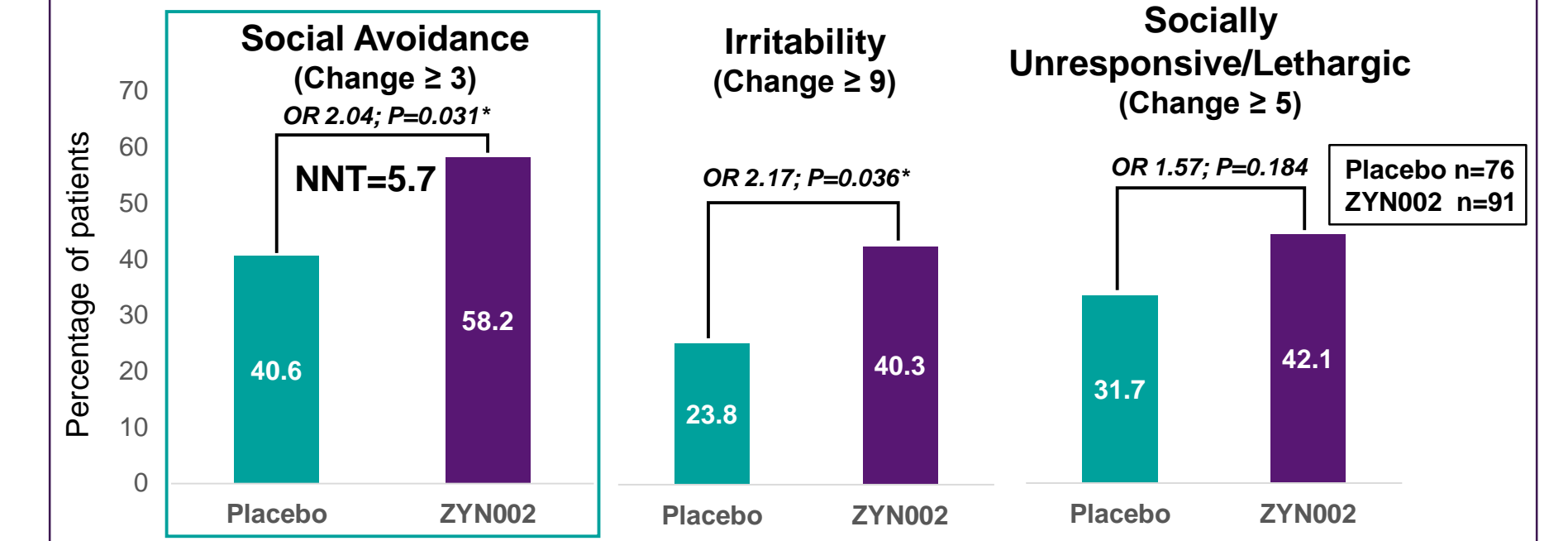
- Empirical cumulative distribution function curves of change in the ABC-C<sub>FXS</sub> SA, Irritability, and SUL subscale scores from Baseline to Week 12 by change in the CaGI-S DS and OB scores support the responder thresholds identified in the anchor-based analyses (Figure 1)



### Responder Threshold

- Triangulating the results from the anchor-based analyses, the visual plots, and the levels of meaningful change reported by caregivers in the cognitive interview study, patients who experienced a reduction of 3 or more points on the ABC-C<sub>FXS</sub> SA subscale, 9 or more points on the ABC-C<sub>FXS</sub> Irritability subscale, and 5 or more points on the ABC-C<sub>FXS</sub> SUL subscale from Baseline to Week 12 in CONNECT-FX achieved a meaningful behavioral response to treatment
- More patients in the ≥90% methylation group treated with ZYN002 than placebo met the responder threshold at Week 12 for SA (Figure 2)

Figure 2. Greater Percentages of Participants Achieved Meaningful Change in ABC-C<sub>FXS</sub> Social Avoidance and Irritability With ZYN002 in the ≥90% Methylation Group



\*Statistically significant, LS means. NNT=number needed to treat; OR= odds ratio

## CONCLUSIONS

- Responder thresholds for meaningful within-patient behavioral change on key domains of the ABC-C<sub>FXS</sub> were determined using anchor-based methods based upon FDA guidance for caregiver-reported outcomes
- The responder thresholds for meaningful within-patient behavioral change in CONNECT-FX corresponded to the following reductions
  - 3 or more points on the ABC-C<sub>FXS</sub> Social Avoidance subscale
  - 9 or more points on the ABC-C<sub>FXS</sub> Irritability subscale
  - 5 or more points on the ABC-C<sub>FXS</sub> Socially Unresponsive/Lethargic subscale
- These thresholds serve as a basis for evaluating clinically meaningful treatment effects at the individual patient level in clinical trials of children and adolescents with FXS as demonstrated for ZYN002 in CONNECT-FX
- ZYN002 provided meaningful improvements in behavioral symptoms of FXS in patients with ≥90% methylation of the *FMR1* gene

## REFERENCES AND ACKNOWLEDGMENTS

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### Disclosures

NT, TS, and JP are employees of Zynerba Pharmaceuticals. SO is a consultant for Zynerba Pharmaceuticals. TD is a contractor for Zynerba Pharmaceuticals. EM and VPP are employees of Covance by Labcorp which has received research funding from Zynerba. The study was funded by Zynerba Pharmaceuticals.