A Pivotal Study of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Fragile X Syndrome (CONNECT-FX [ZYN2-CL-016])

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BACKGROUND

- ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel in development for the treatment of behavioral symptoms in Fragile X syndrome (FXS)
- CONNECT-FX was a randomized, double-blind, multinational, 14-week pivotal study to evaluate the efficacy and safety of ZYN002 in children/adolescents with a full *FMR1* gene mutation (**Figure 1**)
  - ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set
- FXS is defined as full mutation of the *FMR1* gene with silencing of the gene, which may require complete or near complete methylation of the gene.
- Patients without silencing of the gene may represent a different biologic population[1,2]
- A pre-planned ad hoc analysis of patients having at least 90% methylation of the *FMR1* gene[a] was performed

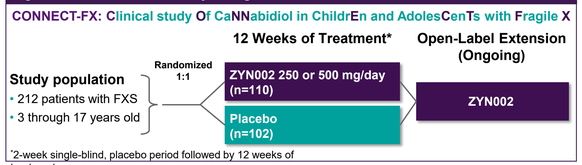
OBJECTIVE

- To describe the results of the CONNECT-FX (ZYN2-CL-016) study in children/adolescents with FXS with complete or near complete methylation of their *FMR1* gene

METHODS

- Patients were randomized to 12-weeks of ZYN002 (250 mg or 500 mg daily [weight-based]) or placebo, as add-on to standard of care
- The primary endpoint was change in the Social Avoidance subscale of the Aberrant Behavior Checklist–Community FXS (ABC–C_{FXS})
- Key secondary endpoints
  - Change from baseline to end of the treatment in ABC-C_{FXS} Irritability and Socially Unresponsive/Lethargic subscale scores
  - Improvement in Clinical Global Impression (CGI-I) at end of treatment, anchored to FXS behaviors
- Safety assessments included adverse events, laboratory tests, and electrocardiograms in the full study population
- Efficacy results are reported for the group with ≥90% methylation of *FMR1*

Figure 1. CONNECT-FX Study Design



*2-week single-blind, placebo period followed by 12 weeks of treatment.

[a]*FMR1* methylation status was determined using Southern blot analysis.

RESULTS

BASELINE DEMOGRAPHICS

- The ≥90% methylation group represented 80% of the study population
- Baseline characteristics are shown in **Table 1**

Table 1. Baseline Demographics, ≥90% Methylation Group

	Placebo	ZYN002	Total
n	77	92	169
Age (years)	9.6	9.2	9.4
Sex – Males	54 (70%)	65 (71%)	119 (70%)
Weight (kg)			
Median	33.9	35.7	35.0
Range (Min, Max)	15.6, 104.7	14.6, 87.0	14.6, 104.7
>35 kg, %	46%	53%	50%
Baseline psychoactive medications,[a] %	65%	54%	59%

[a]Did not include sleep medications.

EFFICACY RESULTS

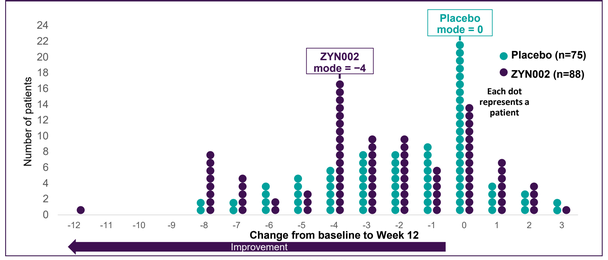
- The ≥90% methylation group achieved statistically significant improvement in the primary endpoint of ABC-C_{FXS} Social Avoidance at Week 12 (*P*=0.020, **Table 2 and Figure 2**)

Table 2. CONNECT-FX Results: ≥90% Methylation Group

		Placebo N=76			ZYN002 N=91				
	Endpoints	Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Treatment Difference / Odds Ratio†	Treatment *p*-value
Primary Endpoint	Social Avoidance	7.18 (0.32)	5.41 (0.42)	−21.1	7.12 (0.29)	4.32 (0.33)	−40.0	−1.00	**0.020***
Secondary Endpoints	Irritability	28.0 (1.56)	24.11 (1.56)	−11.6	29.36 (1.37)	22.69 (1.42)	−24.3	−2.30	0.091
	Socially Unresponsive /Lethargic	13.17 (0.85)	10.29 (0.80)	−20.5	13.30 (0.68)	9.03 (0.67)	−30.8	−1.17	0.135
	CGI-I	-	35.7%		-	51.1%		1.88†	0.056

*Statistically significant.

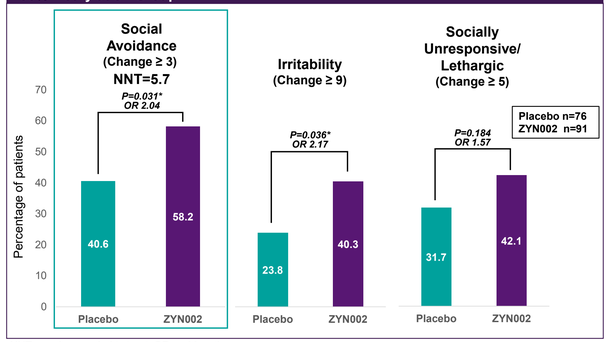
Figure 2. ABC-C_{FXS} Social Avoidance: ≥90% Methylation Group



Data represent observed cases: 4 patients did not have Week-12 ABC-C_{FXS} assessment.

- Clinically meaningful within-subject change was determined by psychometric analyses (SOBP Poster by Merikle E. et al. entitled "Cannabidiol in Fragile X Syndrome (FXS): Proposed Mechanism of Action Translates Into Meaningful Clinical Benefits (CONNECT-FX [ZYN2-CL-016])")
- Significantly more ZYN002-treated patients in the ≥90% methylation group had a meaningful change in ABC-C_{FXS} subscales for Social Avoidance and Irritability (*P*=0.031 and *P*=0.036, respectively) (**Figure 3**)
- The number needed to treat (NNT) for Social Avoidance was 5.7 (Cohen's d of 0.52)

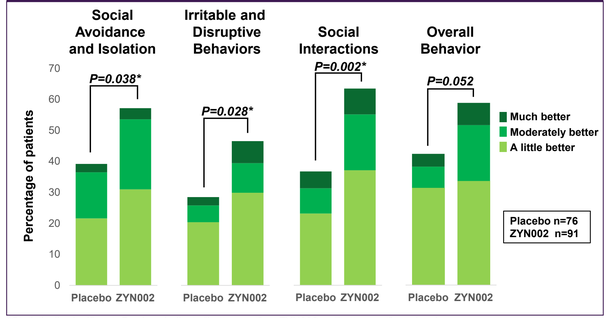
Figure 3. Greater Percentages of Participants Achieved Meaningful Change in ABC-C_{FXS} Social Avoidance and Irritability With ZYN002 vs Placebo in the ≥90% Methylation Group



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

- The ≥90% methylation group achieved statistically significant improvements in Caregiver Global Impression-Change in Social Avoidance and Isolation, Irritable and Disruptive Behaviors, and Social Interactions (*P*=0.038, *P*=0.028, and *P*=0.002) (**Figure 4**)

Figure 4. Caregiver Global Impression-Change: ≥90% Methylation Group



*Statistically significant; *P*-values indicate "betterment" on ZYN002 vs "betterment" on placebo.

SAFETY RESULTS

- ZYN002 was very well tolerated in CONNECT-FX
- There were no serious or severe adverse events reported during the study
- All treatment-emergent adverse events (TEAEs) (any event, whether unrelated or related to study drug) were mild or moderate
  - The most common treatment-related TEAE was application site pain (ZYN002: 6.4%; placebo: 1.0%)
- Laboratory values for chemistry and hematology, and electrocardiogram parameters were comparable between the placebo and ZYN002 treatment groups, and there were no clinically relevant abnormalities in either group
  - There were no clinically significant changes to liver function tests

CONCLUSIONS

- To our knowledge, CONNECT-FX is the largest controlled study ever performed in FXS
- ZYN002 was well tolerated
- In the ≥90% methylation group, ZYN002 was superior to placebo in multiple analyses
  1. Statistically significant mean change in Social Avoidance vs placebo
  2. Proportion of patients attaining threshold of clinically meaningful change in Social Avoidance and Irritability
  3. Caregiver reported improvements including Social Avoidance, Social Interaction, and Irritable behaviors
- The data suggest that effective silencing of the *FMR1* gene may have led to differences in treatment response in patients with ≥90% methylation of the *FMR1* gene
- These results may represent an important step forward in further understanding FXS and the importance of methylation of the *FMR1* gene
- A follow-up phase 3 study is being conducted to confirm these results

REFERENCES

1. Hagerman, RJ, et al. *Nat Rev Dis Primers.* 2017;3:17065.
2. Schneider, A, et al. *Transl Psychiatry.* 2020;10(1):205.

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