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

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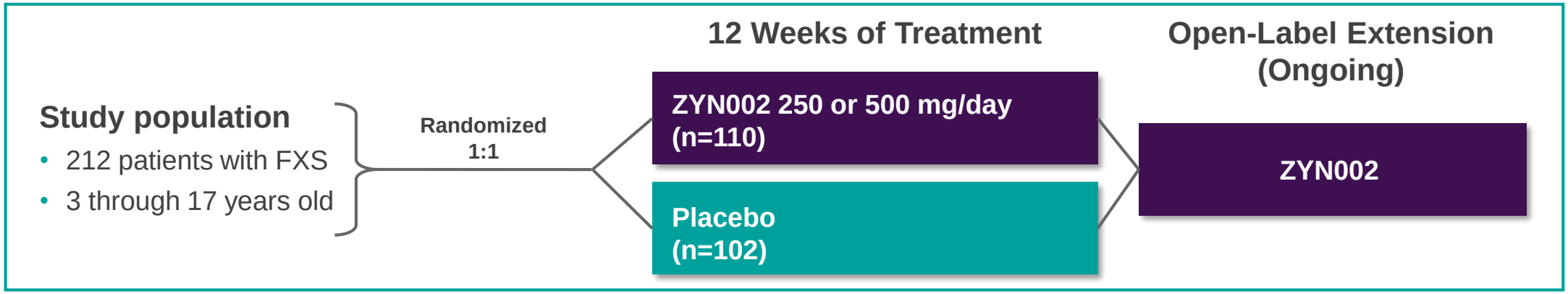
Disclaimers

- 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.

- This slide presentation is based on an abstract submitted and accepted for presentation at the 2021 Society of Developmental & Behavioral Pediatrics Annual Meeting.

CONNECT-FX: Clinical study Of CaNNabidiol (CBD) in ChildrEn and AdolesCenTs with Fragile X

- CONNECT-FX is a randomized, double-blind, multinational, 14-week pivotal study 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[a] was performed
  - The results suggest that ZYN002 may have benefit in patients with ≥90% methylation of the *FMR1* gene

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

In Patients With ≥90% Methylation of *FMR1*, Statistical Significance Was Achieved on Social Avoidance at Week 12 (ABC-C_{FXS})

- Mean (years): 9.6 (placebo), 9.2 (ZYN002)
- Male sex : 70% (placebo), 71% (ZYN002)

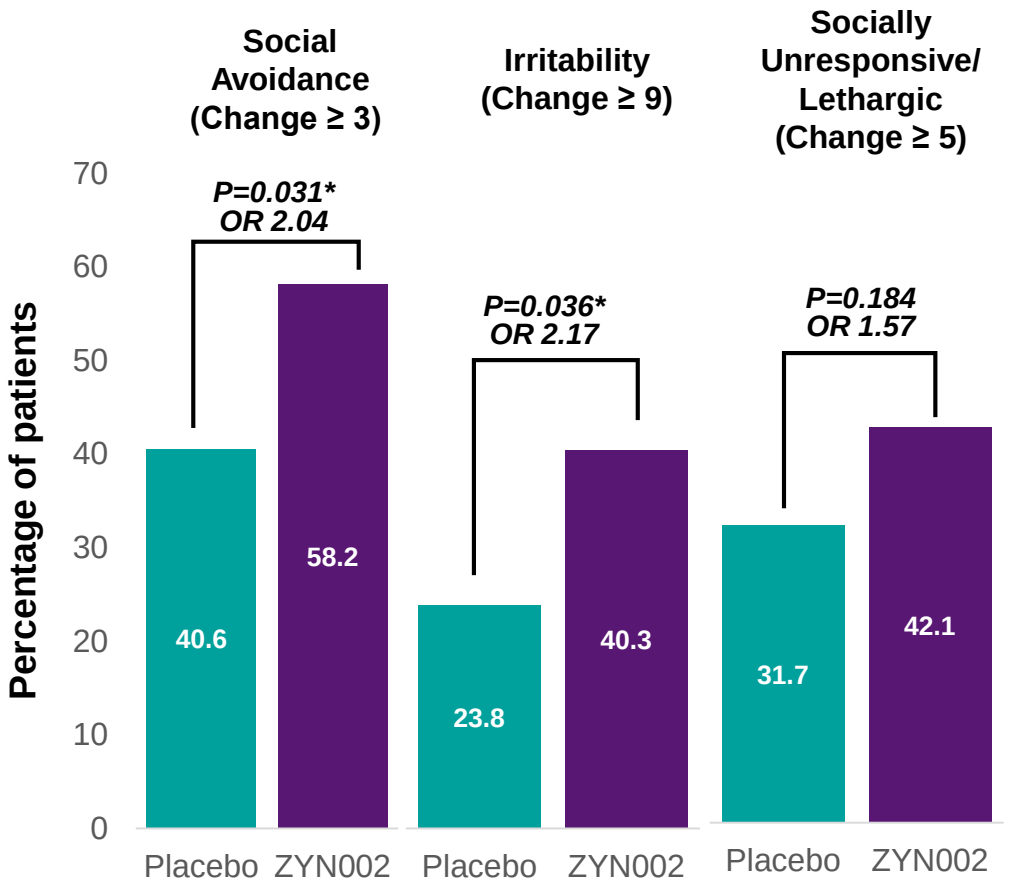
		Placebo N=76			ZYN002 N=91				
	Endpoints	Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Treatment Difference / Odds Ratio†	Treatment *p*-value
Primary Endpoint	Social Avoidance	7.18 (0.32)	5.41 (0.42)	-21.1	7.12 (0.29)	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

Trend level response achieved in Irritability and CGI-I
CGI-I defined as “any improvement”

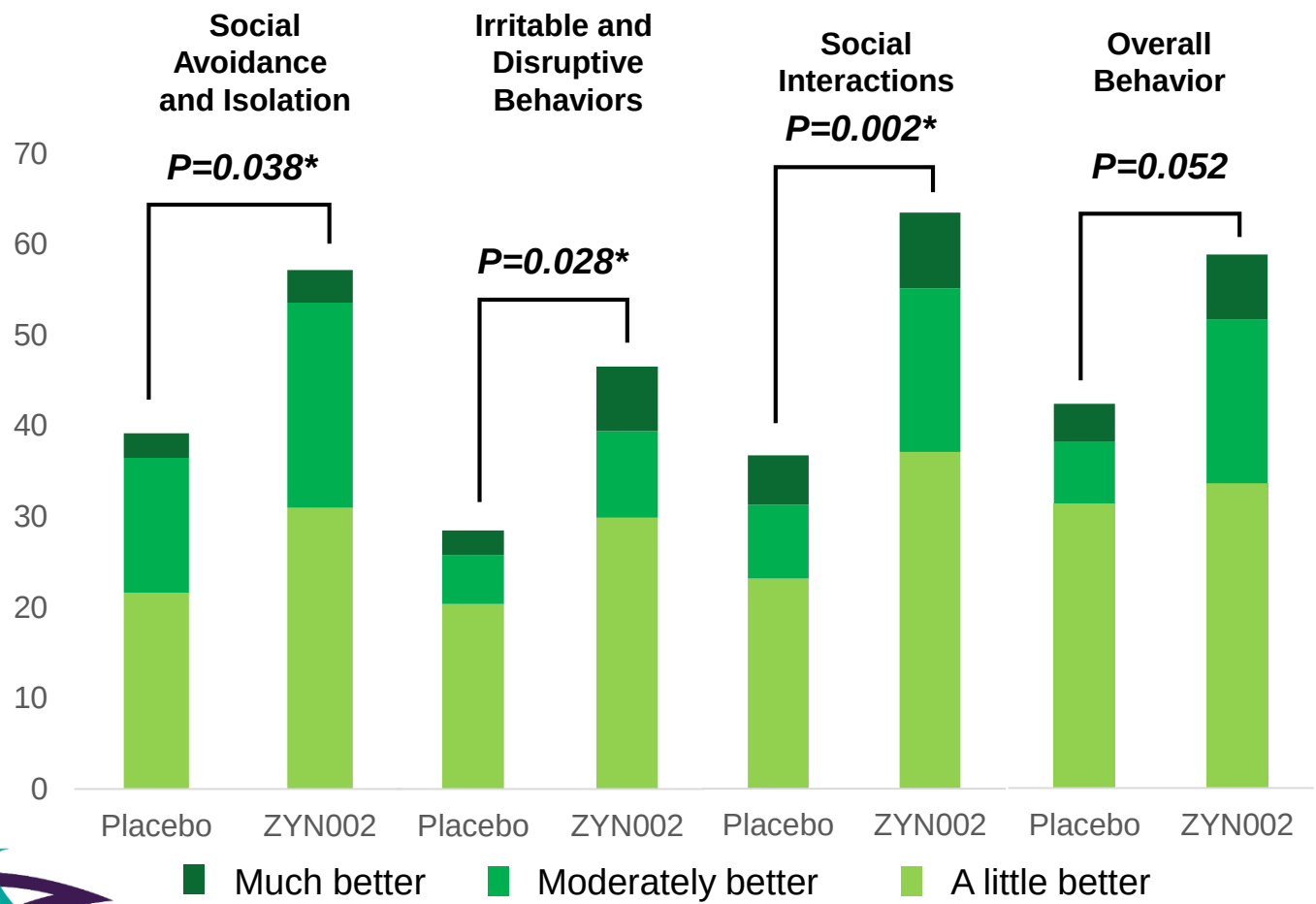
*Statistically significant.
Data on file.

Meaningful Change in ABC-C_{FXS} Social Avoidance and Irritability and Caregiver Global Impression of Change With ZYN002 vs Placebo

ABC-C_{FXS} Social Avoidance and Irritability



Caregiver Global Impression of Change



OR= odds ratio
*Statistically significant. LS Means

Placebo n=76
ZYN002 n=91

Data on File.

Post-hoc analysis in the 100% Methylation Population Representing 65% of Patients

Significant treatment effect also demonstrated in the smaller, complete methylation population, further supporting importance of methylation of *FMR1* gene

Endpoint 12 weeks post baseline	ZYN002 N = 72	Placebo** N = 64	Treatment Difference / Odds Ratio	p value
ABC-C_{FXS} Social Avoidance Mean change	- 2.92	- 1.84	- 1.08	0.027*
% change (median)	- 40%	- 20%		
Meaningful Change (≥ 3 points) ***Social avoidance / isolation***	56%	37%	2.25	0.03*
Caregiver global impression-Change (≥ 1 point) ***Social interactions***	63%	37%	2.91	0.005*
Caregiver global impression-Change (≥ 1 point) ***Irritable / disruptive behaviors***	54%	33%	2.36	0.027*

* Statistically significant

**Placebo N = 65, however, one patient did not have a post-baseline efficacy measure and was therefore not included in the efficacy analysis

CONNECT-FX Safety

Safety

- 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 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

Data on File.

CONNECT-FX: ZYN002 in Fragile X Syndrome

Summary

- ZYN002 was well tolerated
- In the ≥90% and 100% methylation groups, ZYN002 was superior to placebo in multiple analyses
- 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, RECONNECT [ZYN2-CL-033], is being conducted to confirm these results in patients with complete (100%) and partial methylation (<100%)