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 ~~a~~ 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 SSBP Symposium.

SSBP=Society for the Study of Behavioural Phenotypes.

FXS Pathophysiology

- FXS is caused by the deficiency or absence of the FMR1 protein (FMRP)[1]
- FXS is typically caused by a trinucleotide repeat expansion of more than 200 CGG repeats in the 5’ untranslated region of the gene *(FMR1)* that codes for FMRP[2,3]
  - *FMR1* is located on the X chromosome[2,3]
  - CGG expansion leads to methylation of the promoter region of *FMR1*, an epigenetic modification of the gene that results in subsequent gene silencing and attenuation of FMRP expression in the majority of patients[4,5]
- In general, the FXS cognitive and emotional phenotype depends on the amount of FMRP that is produced, which is reflective of the degree of methylation of *FMR1*[6]
  - In males and females, there is an inverse correlation between methylation percentage of *FMR1* and the production of FMRP. FMRP levels in females are also partially determined by the level of X-inactivation[7,8]
  - Patients with higher degrees of methylation tend towards a more severe phenotype, including lower IQ and more severe symptoms of ASD[8]
- Patients without silencing of the gene may represent a different biologic population because of a combination of low FMRP and sometimes elevated mRNA[1,9]

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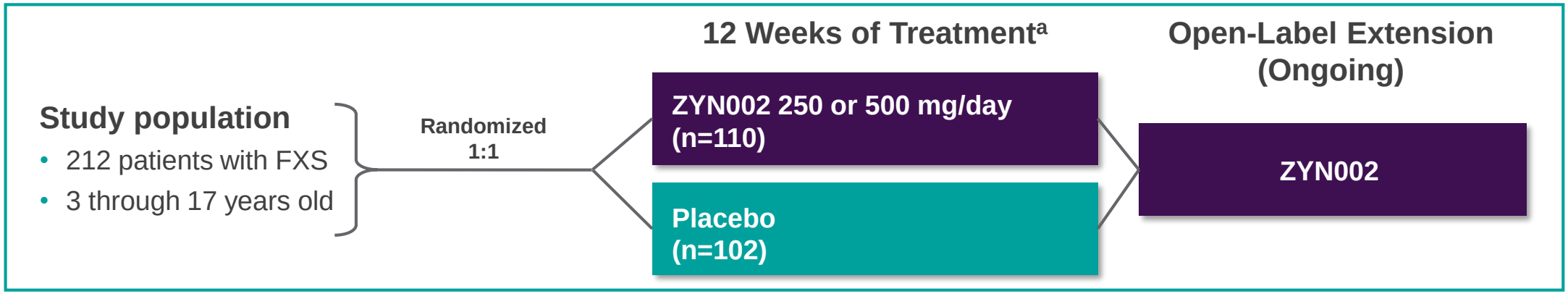
CONNECT-FX: Clinical study Of CaNNabidiol (CBD) in ChildrEn and AdolesCenTs with Fragile X

- CONNECT-FX was 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[b] was performed
- A post hoc analysis was also performed in patients with 100% methylation of the *FMR1* gene

[a]2-week placebo period followed by 12 weeks of treatment.
[b]*FMR1* methylation status was determined by using Southern blot analysis.

The ≥90% Methylation Group (n=169) Represented 80% of the Total Study Population

Baseline Characteristics in the ≥90% Methylation Group

The ≥90% methylation group had similar baseline characteristics to the full study population

	≥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,* %	65%	54%	59%

*Did not include sleep medications.
Data on file.

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

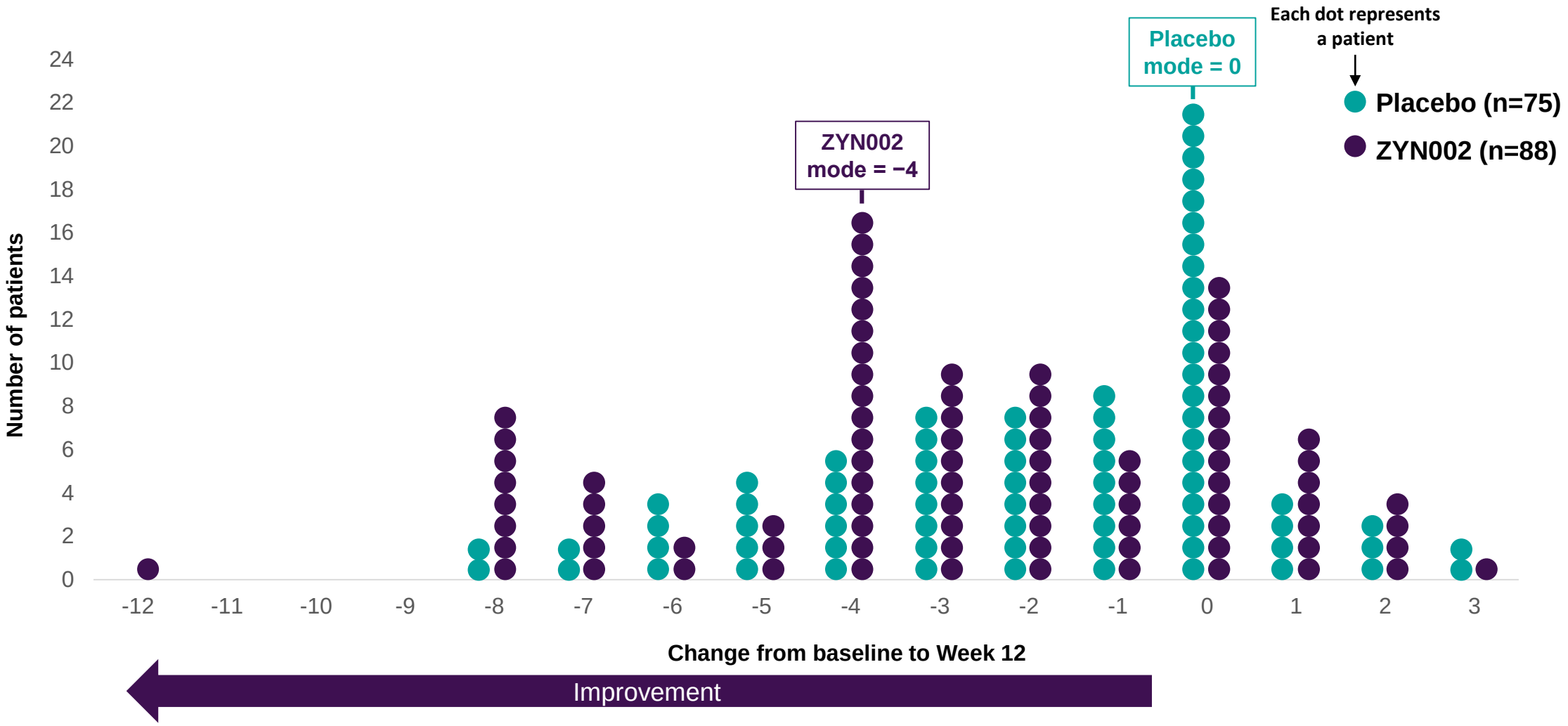
		Placebo N=76			ZYN002 N=91				
	Endpoints	Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Treatment Difference / Odds Ratio†	Treatment *p*-value
Primary Endpoint	**Social Avoidance**	7.18 (0.32)	5.41 (0.42)	-21.1	7.12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

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

From Baseline to Week 12, the ZYN002 group demonstrated greater improvement compared with placebo



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

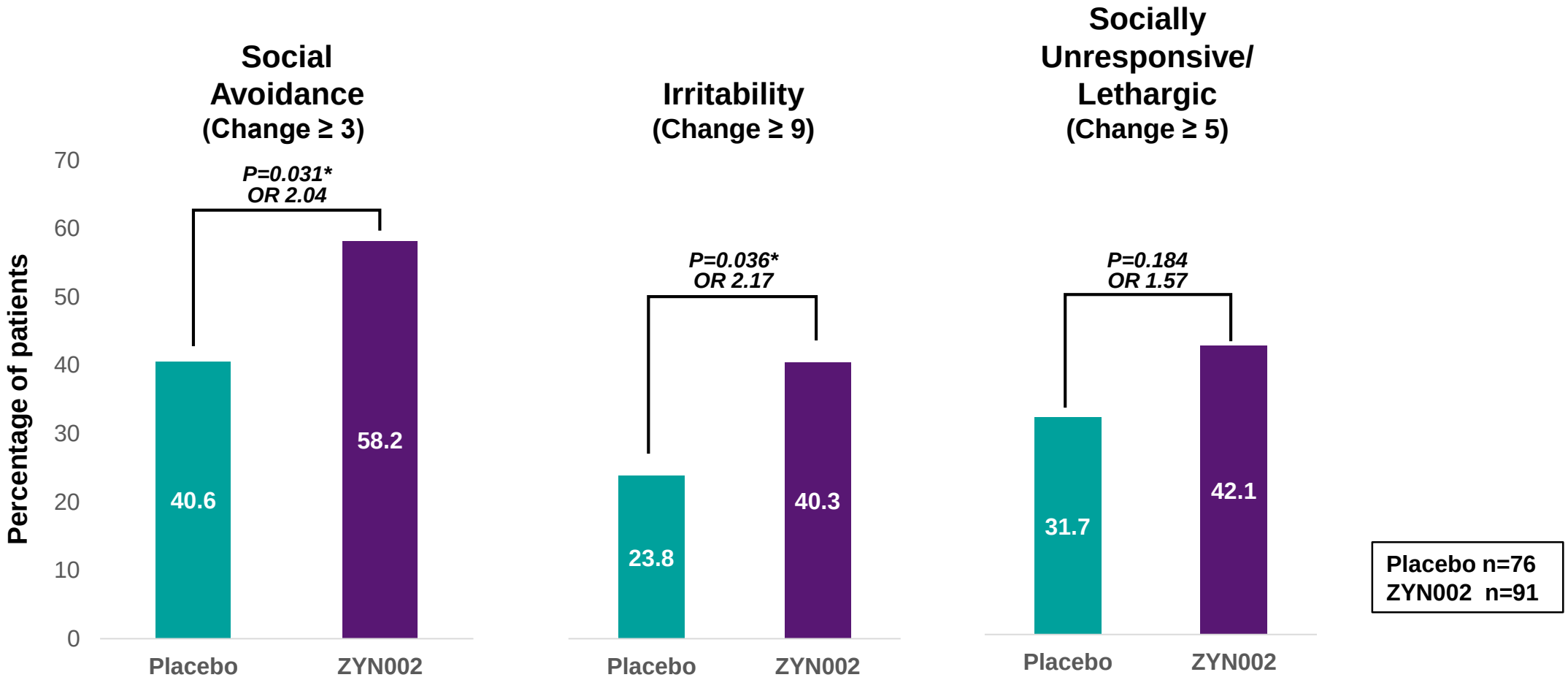
Psychometric Analyses Determined Clinically Meaningful Changes for ABC-C_{FXS}

3-point improvement determined to be clinically meaningful for Social Avoidance

- CONNECT-FX data were used to determine what constitutes meaningful within-subject change from Baseline to Week 12 in the ABC-C_{FXS} subscale scores using anchor-based methods
- The analyses support defining a clinically meaningful treatment response over 12 weeks of treatment as an improvement of:
  - 3 points for the Social Avoidance subscale
  - 9 points for the Irritability subscale
  - 5 points for the Socially Unresponsive / Lethargic subscale

Greater Percentages of Participants Achieved Meaningful Change in ABC-C_{FXS} Social Avoidance and Irritability With ZYN002 vs Placebo

Meaningful within-subject change in ≥90% methylation group



OR= odds ratio
*Statistically significant. LS Means

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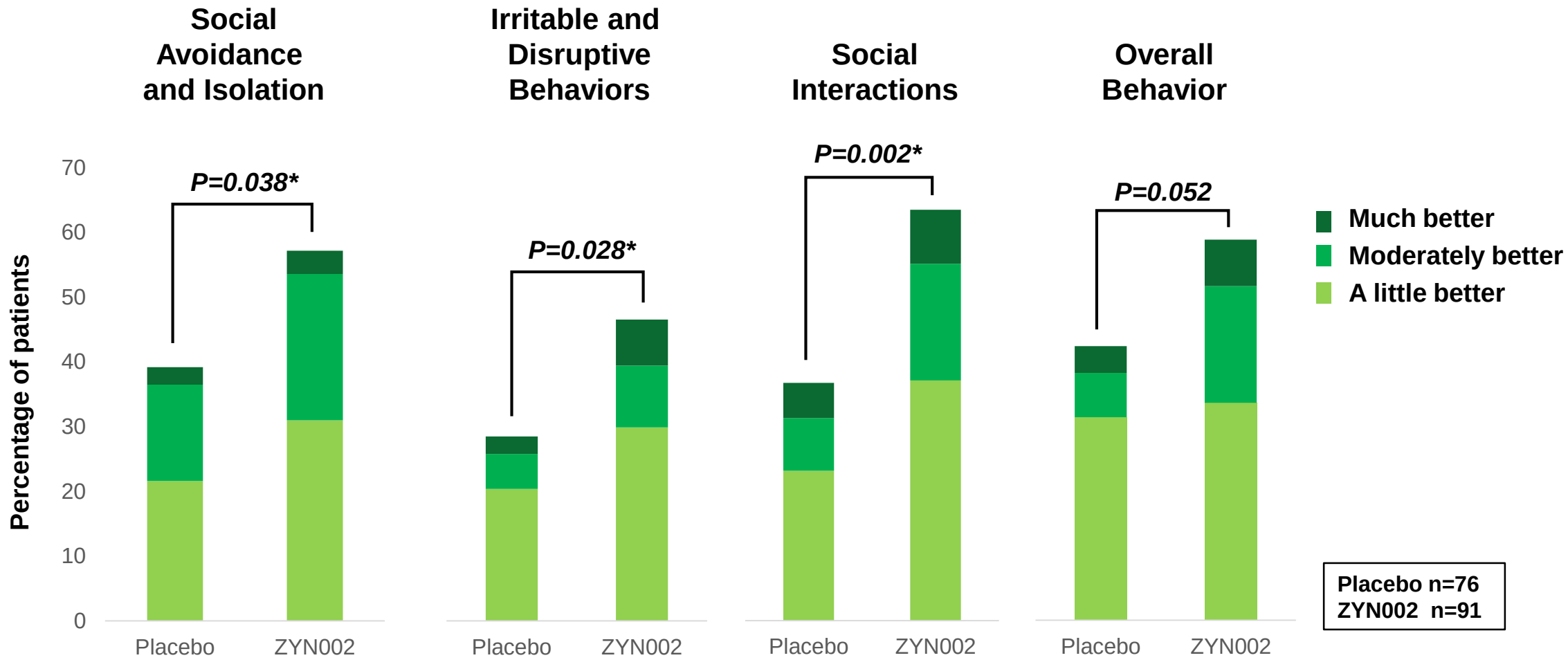
Caregiver Global Impression-Change: ≥90% Methylation Group

Change From Baseline to Week 12: Broad Shifts Toward Global Improvement



*Statistically significant.
P-values indicate "betterment" on ZYN002 vs "betterment" on placebo.
Psychometric analysis indicated that "any improvement" is meaningful.

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: ZYN002 in Fragile X Syndrome

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%)