ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Fragile X Syndrome: Role of Methylation Status as a Correlate to Disease Severity and as a Prognostic Biomarker

Elizabeth Berry-Kravis,[1] Craig Erickson,[2] Randi Hagerman,[3] Nicole Tartaglia,[4] Jonathan Cohen,[5] Terri Sebree,[6] Donna Gutterman,[6] Nancy Tich,[6] Thomas Dobbins,[7] **Joseph M. Palumbo[6]**

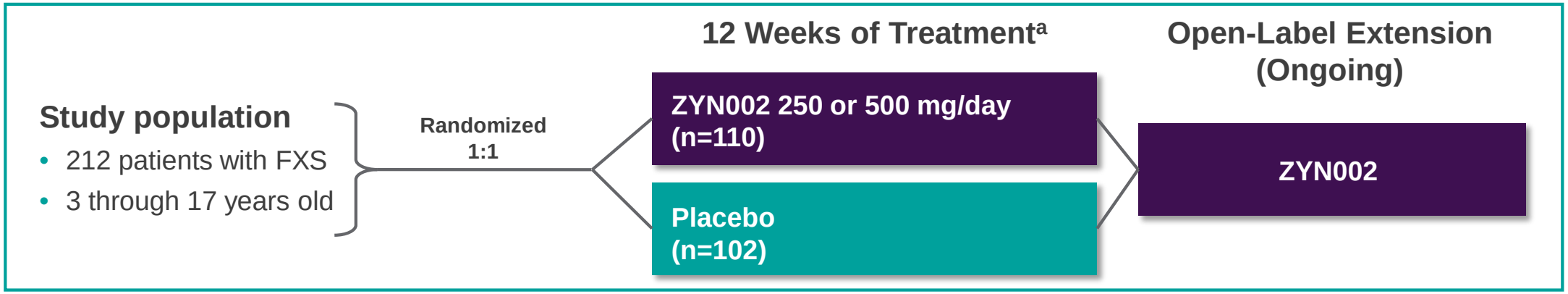
[1]Rush University Medical Center, Chicago, IL, USA; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [3]University of California Davis Medical Center, Department of Pediatrics and MIND Institute, Sacramento, CA, USA; [4]Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA; [5]Fragile X Alliance, North Caulfield, VIC, Australia; [6]Zynerba Pharmaceuticals, Devon, PA, USA; [7]Dobbins Statistical Consulting, Blue Bell, PA, USA

Acknowledgements: *p*-value communications provided editorial support.

Disclosures: TS, DG, N Tich, and JP are employees of Zynerba Pharmaceuticals. TD is a contractor for Zynerba Pharmaceuticals. EBK, CE, RH, N Tartaglia, and JC have received research support from Zynerba Pharmaceuticals. The study was funded by Zynerba Pharmaceuticals.

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

- ZYN002 is a pharmaceutically manufactured transdermal cannabidiol (CDB) gel in development for the treatment of behavioral symptoms in Fragile X syndrome (FXS)



- 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 ("full methylation" or FMet) of the impacted *FMR1* gene[b] was performed
  - The results suggest that ZYN002 may have benefit in patients with full 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.

FMet Group Represented 80% of the Total Study Population

FMet Baseline Characteristics

The FMet group had similar baseline characteristics to the full study population

	FMet 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.

CONNECT-FX: Pre-Planned Ad hoc Analysis

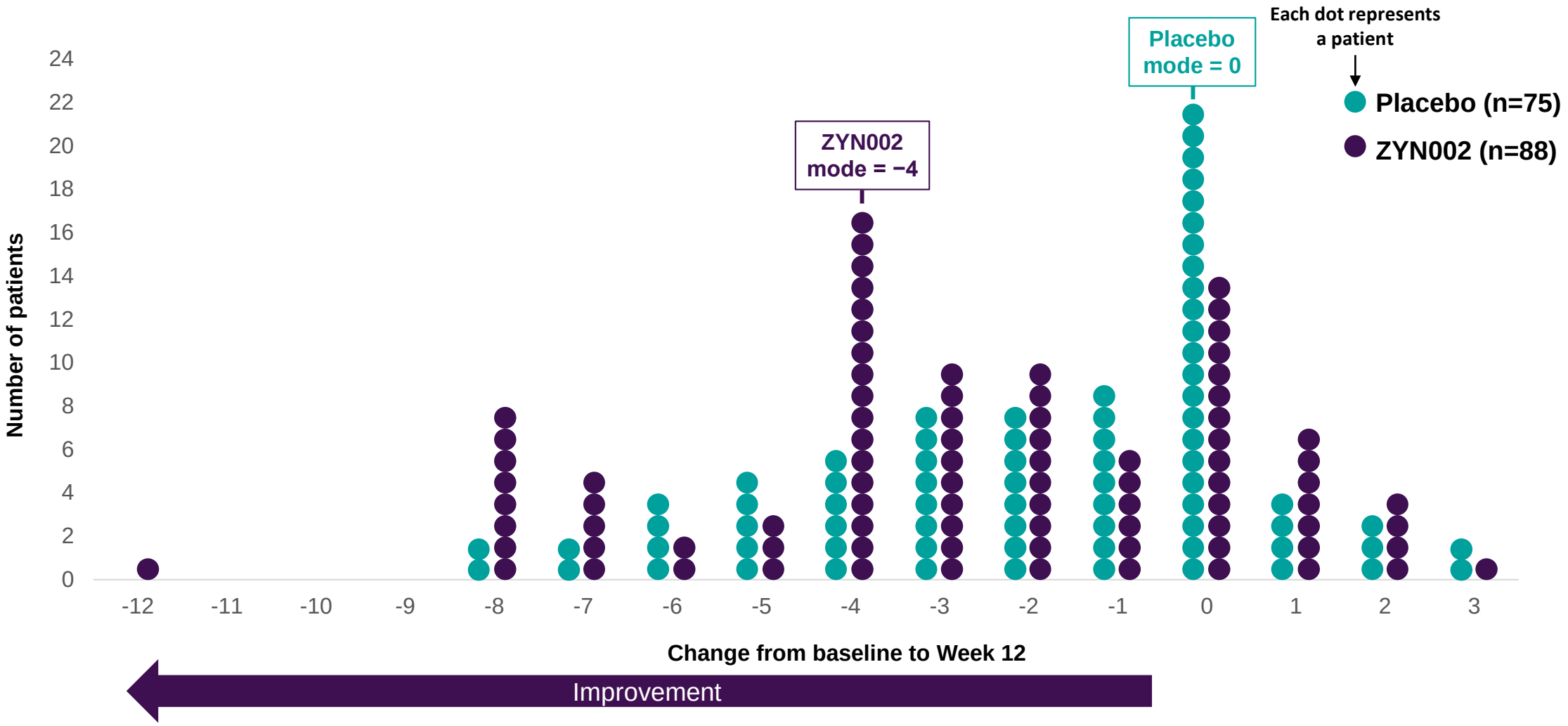
Achieved Statistical Significance on Social Avoidance at Week 12 (ABC-C_{FXS})

		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

*Statistically significant.
Data on file.

ABC-C_{FXS} Social Avoidance: FMet 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}

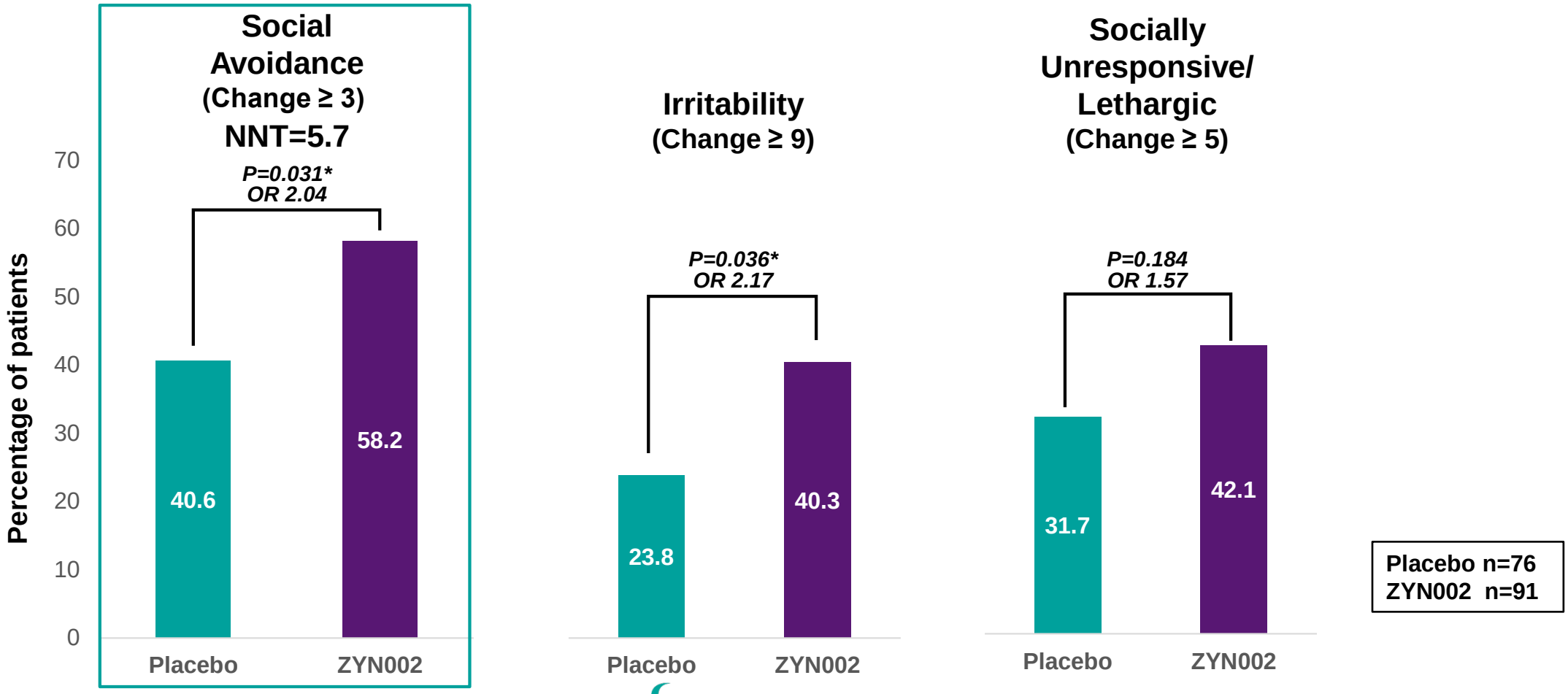
3-point improvement determined to be clinically meaningful for Social Avoidance

- 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

Data on File.

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

Meaningful within subject change in FMet groups

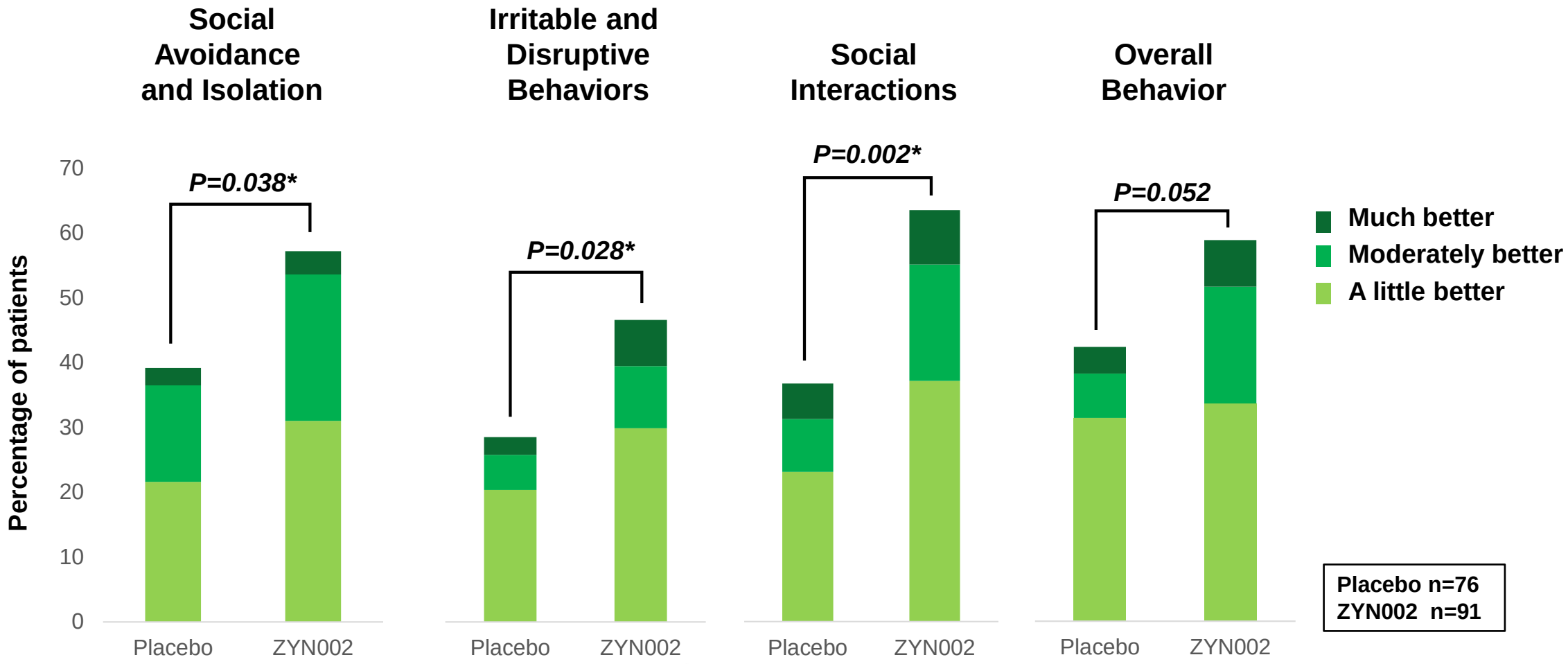


NNT=number needed to treat; OR= odds ratio
*Statistically significant. LS Means

Data on File.

Caregiver Global Impression-Change: FMet Group

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



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

Data on file.

CONNECT-FX

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.

ZYN002 in FXS

Summary

- To our knowledge, CONNECT-FX is the largest controlled study ever performed in FXS
- ZYN002 was well tolerated
- In the FMet 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
- Zynerba will be meeting with the FDA in Q4 2020

These results may represent an important step forward in biomarker-driven prediction of response in FXS and neuroscience.