

Long-term Safety and Sustained Efficacy of ZYN002 Cannabidiol Transdermal Gel in the Treatment of Behavioral Symptoms in Children and Adolescents with Fragile X Syndrome (ZYN2-CL-017)

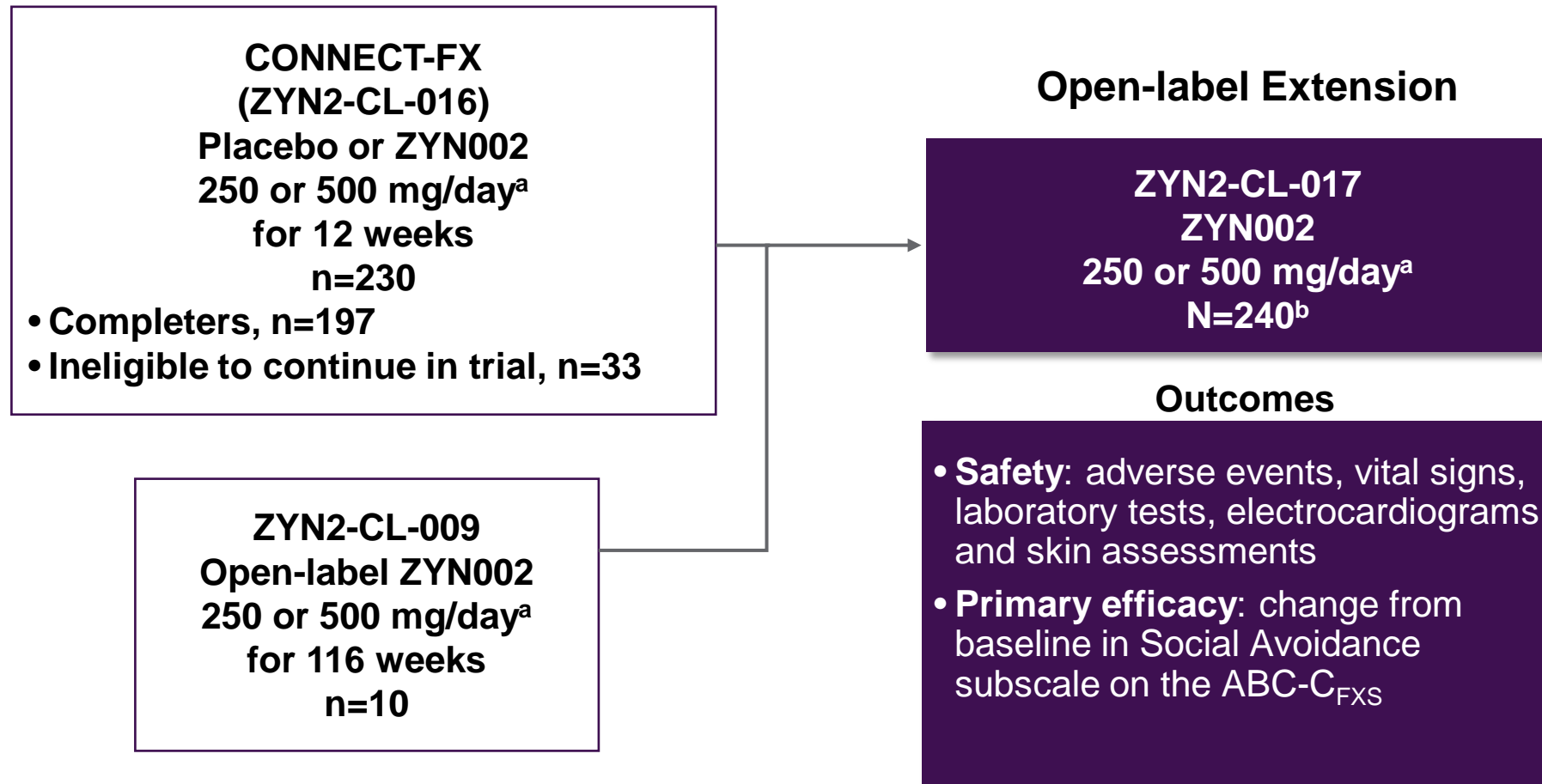
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Disclosures

- This presentation is intended to communicate scientific and medical information about data from clinical trials involving ZYN002. ZYN002 is an investigational treatment. This means that it is not approved for commercial distribution by government regulatory bodies, including the United States Food and Drug Administration (FDA). This presentation is not designed or intended to promote the use of ZYN002 or any other Company product in order to impact prescribing
- The trials were funded by Zynerba Pharmaceuticals

ZYN2-CL-017 Trial Design and Path of Patient Entry



^aWeight-based in 2 divided doses applied twice daily.

^bThrough January 23, 2023.

ABC-C_{FXS}=Aberrant Behavior Checklist-Community for fragile X syndrome.

Safety Results

- ZYN002 was safe and well tolerated in the ZYN2-CL-017 extension trial in patients with a median duration of exposure of 20 months (range 21 days to 45 months) since trial entry
- Treatment-emergent adverse events, whether related or unrelated to study drug, were reported by 66.7% of patients; most were related to conditions commonly reported in children and adolescents
- Treatment-related adverse events were reported in 13.3% of patients; the most common was application site pain (6.7%)
 - Application site pain was transient and reported as mild in 15 and moderate in 1 patient
- Three patients had increases in ALT of $\geq 3x$ ULN (2 of the patients had suspected fatty liver disease and 1 patient was receiving valproic acid)
- No clinically significant changes were observed in vital signs or electrocardiograms

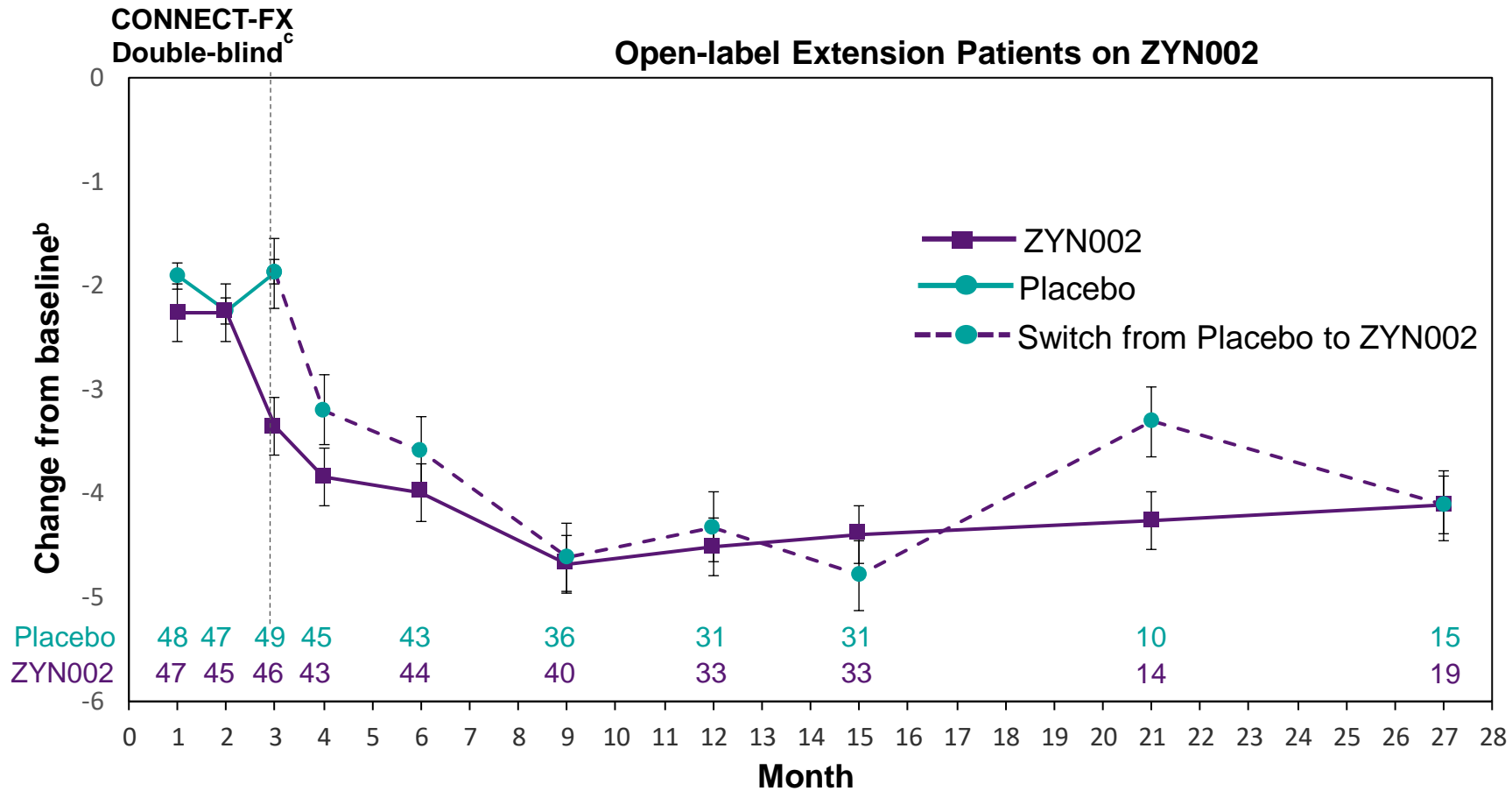
ZYN002 OLE Trial Interim Safety Data – Adverse Events

Most related to conditions commonly reported in children and adolescents

Adverse Event Type	Patients (n = 240) or Events, %
Treatment Emergent Adverse Events (TEAE)^a	66.7%
Mild-to-moderate TEAEs	97.8% (events)
TEAEs (≥3% of patients)	
Upper respiratory infection	17.9%
COVID-19	7.1%
Application-site pain	6.7%
Nasopharyngitis	6.3%
Pyrexia	5.8%
Vomiting	5.4%
Diarrhea	5.0%
Ear infection	4.6%
Cough	4.2%
Influenza	4.2%
Anxiety	3.8%
Streptococcal pharyngitis	3.3%
Discontinuations due to TEAEs	2.9% (7 patients)
Serious AEs (all non-treatment-related)	11 events in 8 patients
Treatment-Related TEAEs	13.3%
Most common treatment-related AE (≥3% of patients)	
Application-site pain (transient; mild in 15 and moderate in 1 patient)	6.7%

^aTEAE, whether related or unrelated to study drug.

Sustained Improvement in ABC-C_{FXS} Social Avoidance in ZYN002 and Placebo Patients Who Switched to Open-label ZYN002: Patients With Complete Methylation of *FMR1*^a

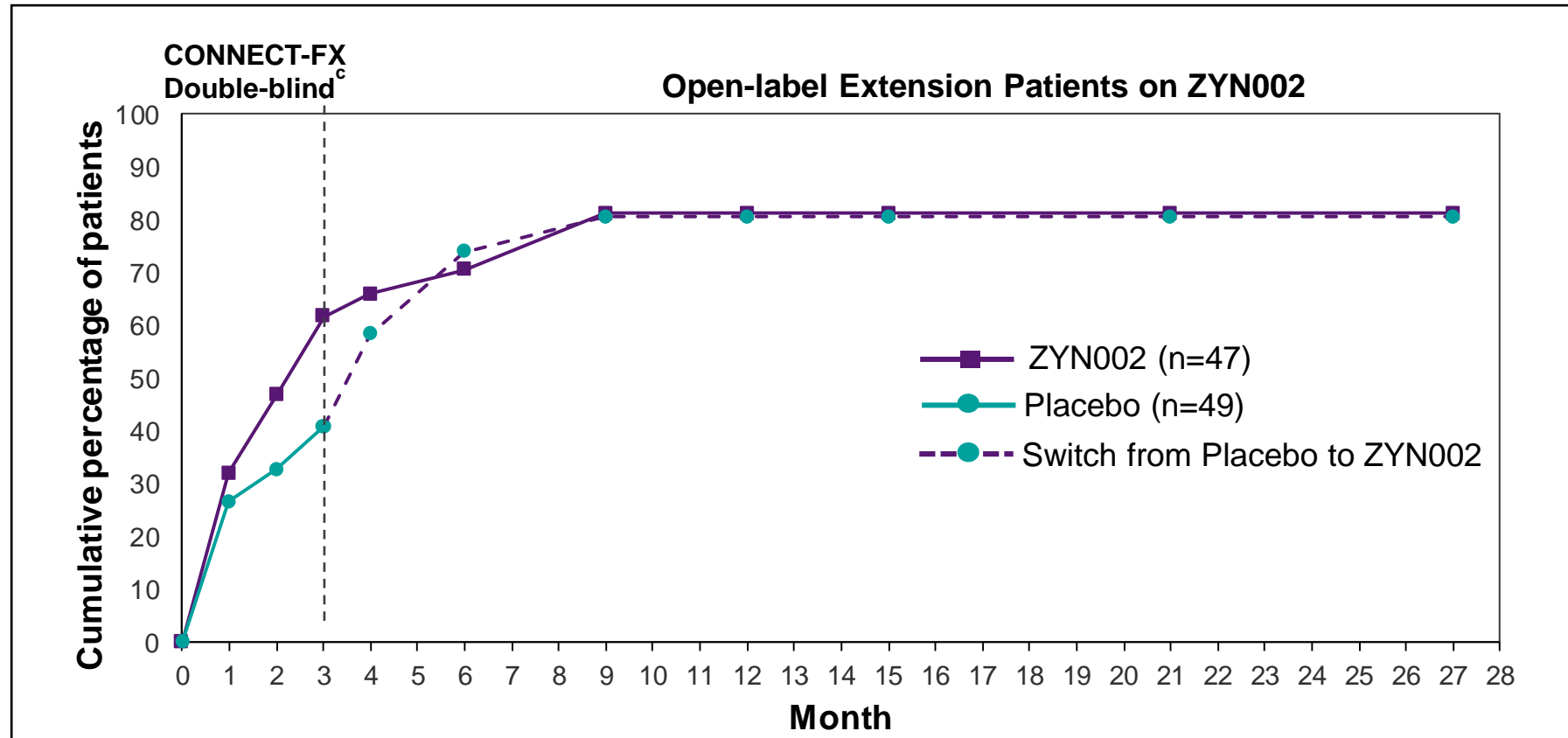


^aPatients matching primary efficacy population in RECONNECT.

^bLeast square mean \pm SE; reduction equals improvement.

^cZYN2-CL-016 (CONNECT-FX).

ZYN002-treated Patients Achieved and Maintained Clinically Meaningful Change^a in ABC-C_{FXS} Social Avoidance: Patients with Complete Methylation of *FMR1*^b



^aMeaningful change in Social Avoidance: ≥ 3 -point improvement from baseline; maintained for ≥ 2 consecutive visits.

^bPatients matching primary efficacy population in RECONNECT.

^cZYN2-CL-016 (CONNECT-FX).

Conclusions and Ongoing Trial in Fragile X Syndrome

- The interim results from this open-label extension trial support the long-term safety and effectiveness of ZYN002 in children and adolescents with fragile X syndrome, with the greatest improvements seen in those with complete methylation of their *FMR1* gene
- RECONNECT, an ongoing Phase 3, randomized, double-blind, placebo-controlled confirmatory trial evaluating the efficacy and safety of ZYN002 over 18 weeks (NCT04977986) in patients 3 through 22 years of age is actively enrolling
- For more information on RECONNECT, visit www.fragilexhelp.com

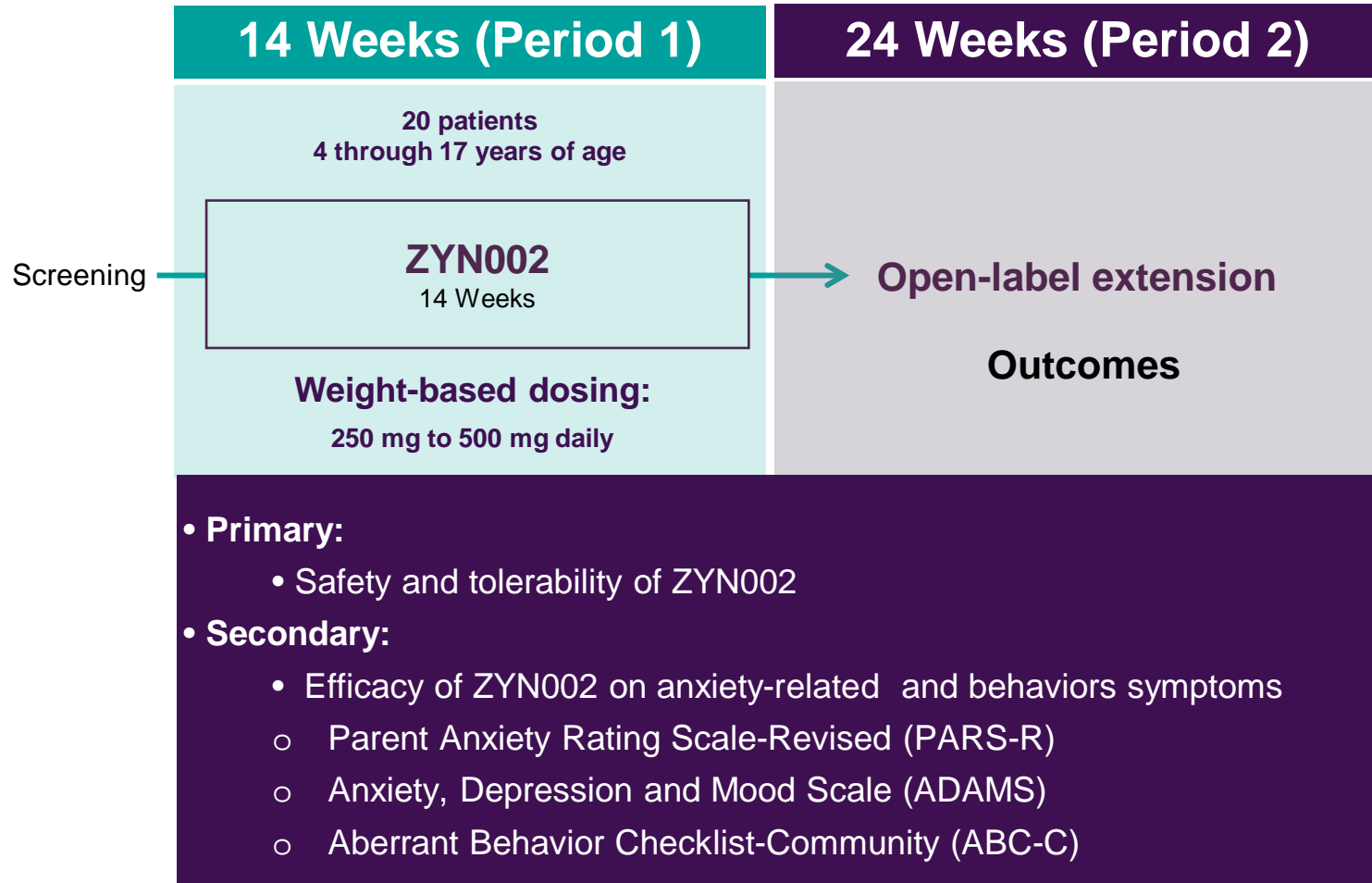
An Open-label Trial Assessing Short- and Long-term Tolerability and Efficacy of ZYN002 (Cannabidiol) Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome (INSPIRE)

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INSPIRE Phase 2 Trial Design

Assessing the Impact of ZYN002 (Transdermal CBD Gel) on Pediatric Behavioral and Emotional Symptoms of 22q11.2 Deletion Syndrome (NCT05149898, ZYN2-CL-031)



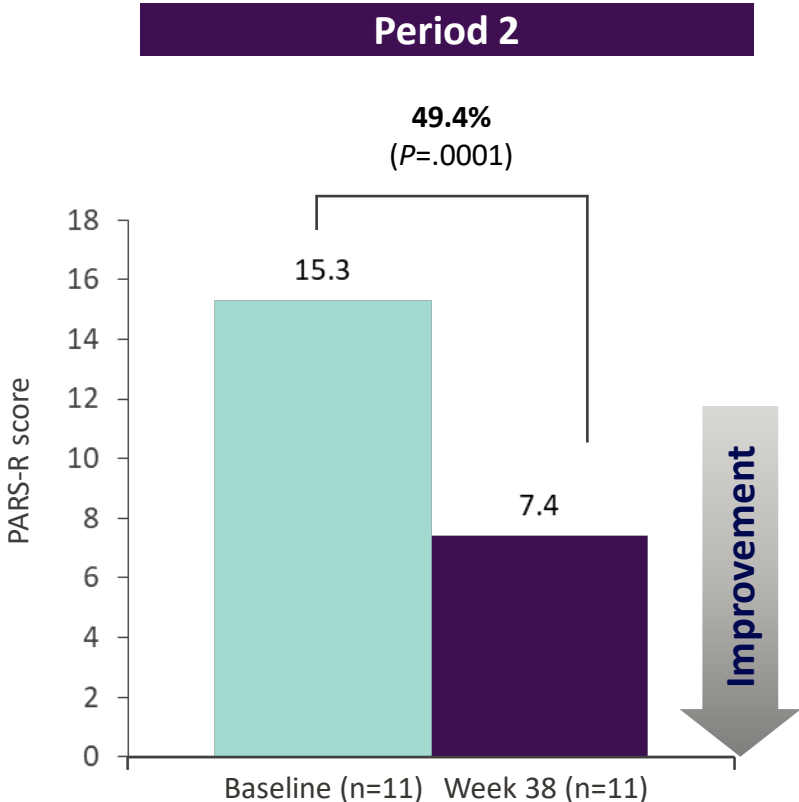
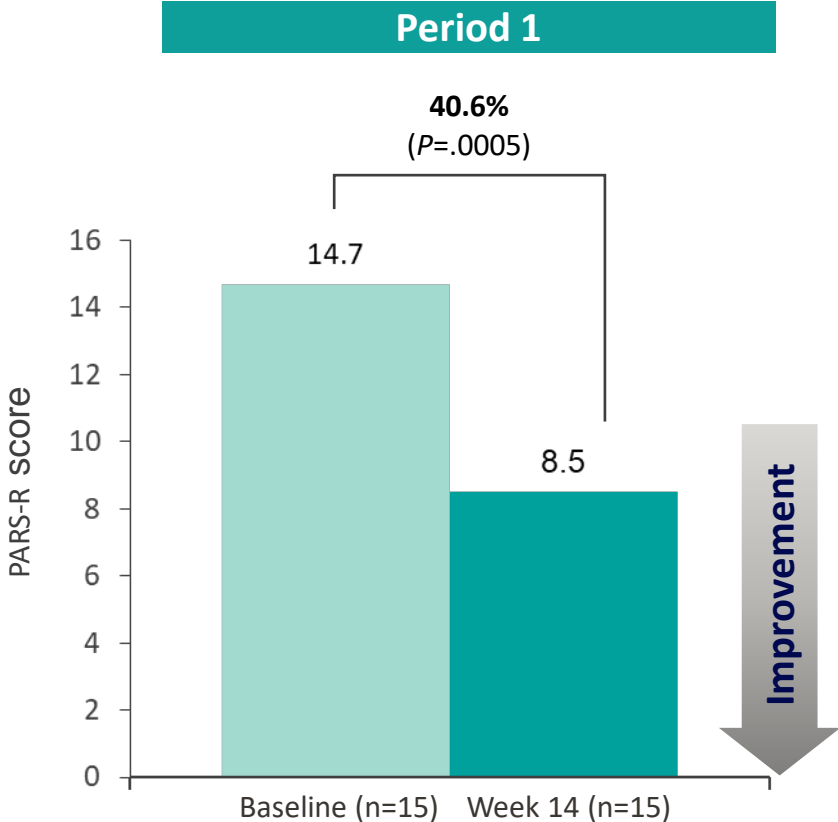
Adverse Events and Safety Over 38 Weeks

	Patients (n=20) % Patients (n patients or events)
Treatment-Emergent Adverse Events (TEAEs)^a	65% (13 patients; 30 events)
Mild in severity	86.7%
Treatment-Related AEs	15% (3 patients; 3 events)
Application site pain	10% (2 patients; 2 events)
Application site itching	5% (1 patient; 1 event)
<i>All were mild and transient</i>	
Discontinuations due to TEAEs unrelated to ZYN002	1 patient
Serious AEs	3 (3 patients)
All unrelated to ZYN002 in Period 2	
No clinically significant changes in laboratory, vital signs, or electrocardiograms	

^aTreatment-emergent adverse events are any events, whether related or unrelated to ZYN002

Significant Improvement in Anxiety as Measured by the PARS-R

Moderate anxiety improved to minimal or mild anxiety



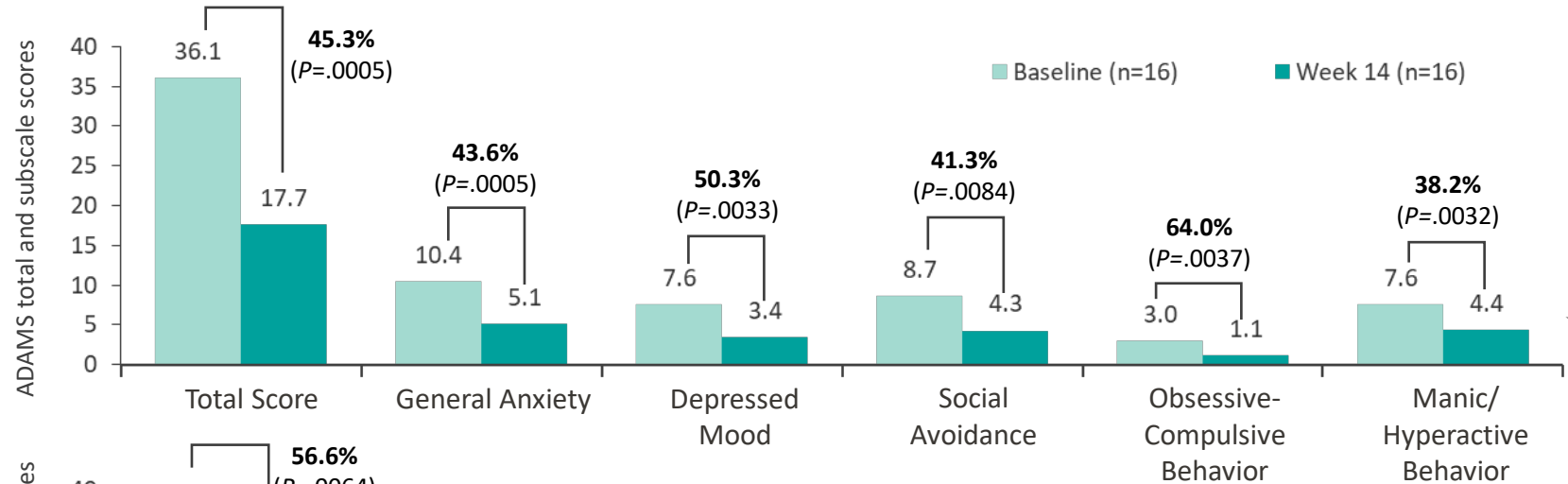
The efficacy analysis for Period 1 included 15 patients for PARS-R (2 patients did not have valid assessments at Week 14).

The efficacy analysis for Period 2 included 11 patients; 1 patient who completed Week 38 stopped drug prior to completion.

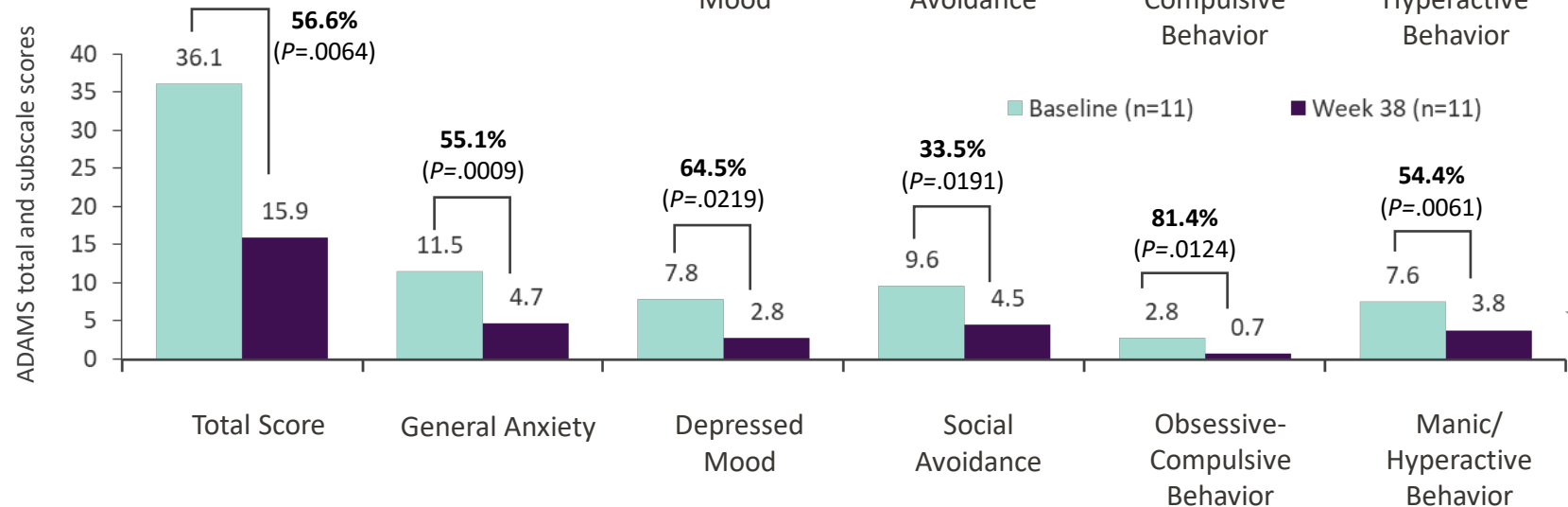
Significant Improvements in ADAMS Total Score and All Subscales

Mean Scores and Percentage Improvement

Period 1



Period 2

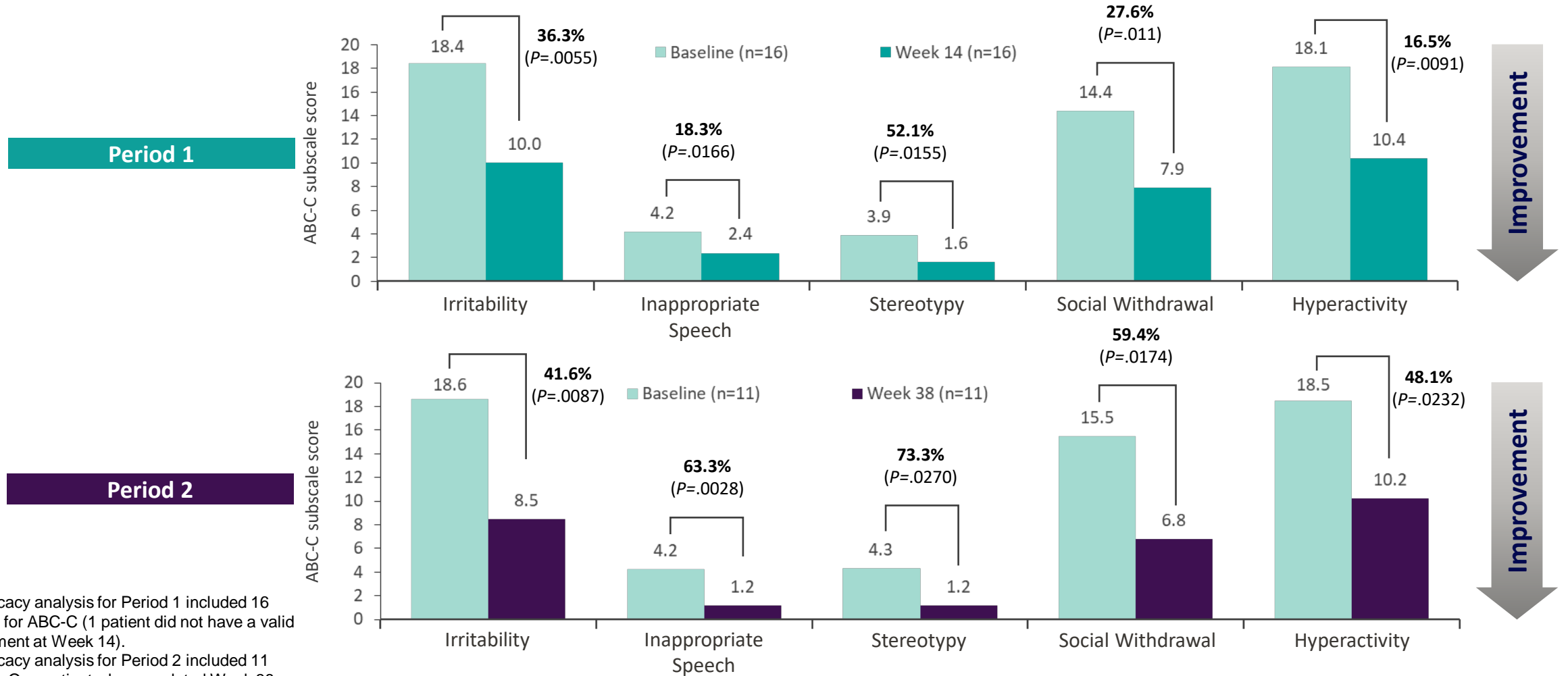


The efficacy analysis for Period 1 included 16 patients for ADAMS (1 patient did not have a valid assessment at Week 14). The efficacy analysis for Period 2 included 11 patients; 1 patient who completed Week 38 stopped drug prior to completion. Total Score and Obsessive/Compulsive Behavior N=10 as the score for item #16 was missing at Week 38.



Significant Improvement in all ABC-C Subscale Scores

Mean Scores and Percentage Improvement



The efficacy analysis for Period 1 included 16 patients for ABC-C (1 patient did not have a valid assessment at Week 14).

The efficacy analysis for Period 2 included 11 patients. One patient who completed Week 38 stopped drug prior to completion.

Conclusions

- ZYN002 was well tolerated with a safety profile consistent with other ZYN002 clinical trials
- Statistically significant improvements were reported in anxiety-related and behavioral symptoms:
 - PARS-R
 - Total score and all 5 subscales of ADAMS
 - All 5 subscales of ABC-C
- These findings warrant further study of ZYN002 in children and adolescents with 22q