

ZYN002 Cannabidiol Gel Efficacy and Safety: Recent Clinical Research Advances in the Experimental Treatment of Autism and Developmental and Epileptic Encephalopathies and the Role of Methylation Status as a Correlate of Disease Severity and Therapeutic Response in Fragile X Syndrome

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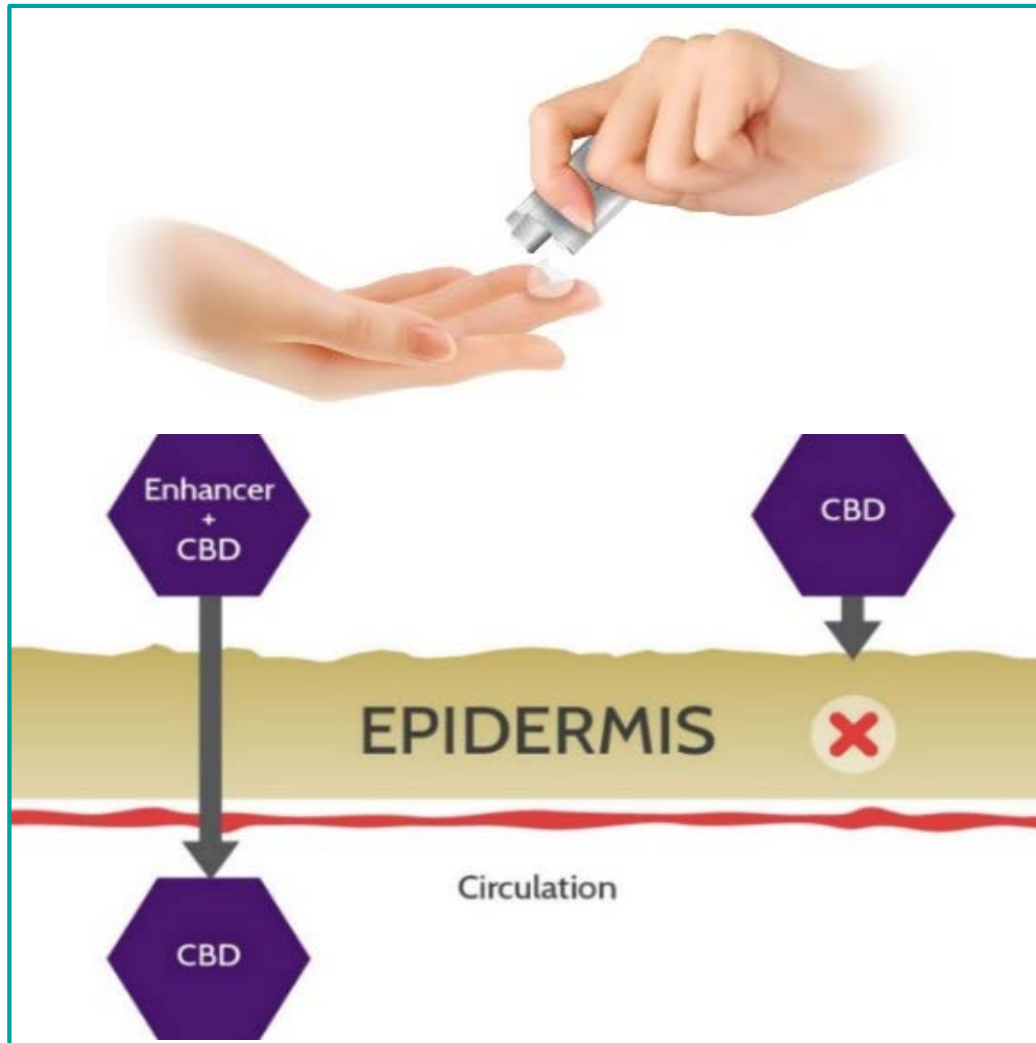


Disclaimers

- 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 2020 Synchrony Symposium.
- Joseph Palumbo is a full-time employee of Zynerba Pharmaceuticals, Inc.



Key Characteristics of ZYN002



Transdermal (non-oral).
Avoids first pass metabolism.
Associated with few gastrointestinal adverse events across our clinical development program.*

Pharmaceutically manufactured.
Known purity and consistency.
No potential for pesticides or heavy metals; regulated manufacturing.

THC not detected in urine or plasma.*
Supports the purity and stability of CBD in ZYN002.

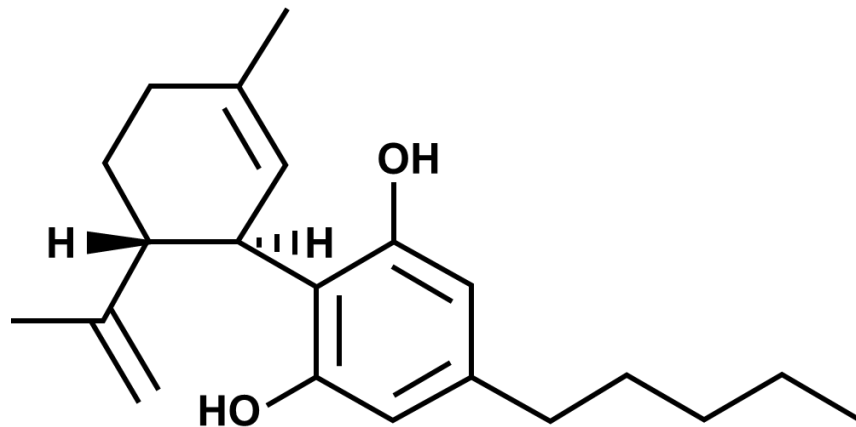
*Data on file.



Cannabidiol and Tetrahydrocannabinol

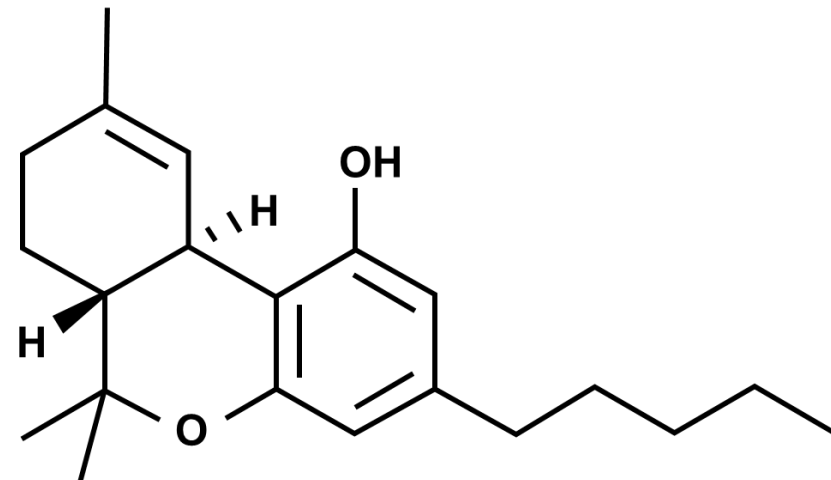
Cannabidiol (CBD)¹

CBD is the non-euphoric component of cannabis



Tetrahydrocannabinol (THC)¹

THC is the component of cannabis associated with euphoria



The Endocannabinoid System (ECS) in the CNS

- The ECS includes the cannabinoid G-protein-coupled receptors, CB₁ and CB₂, and the endocannabinoids^{1,2}:
 - Anandamide (AEA)
 - 2-Arachidonoylglycerol (2-AG)
- Evidence indicates that the ECS has an important role in the CNS
 - The endocannabinoids and their receptors, CB₁ and CB₂ are located in the CNS and in the periphery³⁻⁵
 - Alterations in the ECS in experimental animal models have resulted in profound changes in cognition and behavior^{6,7}
 - In particular, the endocannabinoid system appears to regulate neuronal development and function; particularly synaptic homeostasis and plasticity⁸

1. Mouslech, Z, Valla V. *Neuro Endocrinol Lett.* 2009;30(2):153-179.

2. Pacher, P, et al. *Pharmacol Rev.* 2006;58(3):389-462.

3. Fernandez-Ruiz, J, et al. *Eur Neuropsychopharmacol.* 2020;36:217-234.

4. Herkenham, M, et al. *Proc Natl Acad Sci U S A.* 1990;87(5):1932-1936.

5. Hoffman, AF, Lupica CR. *J Neurosci.* 2000;20(7):2470-2479.

6. Castillo, PE, et al. *Neuron.* 2012;76(1):70-81.

7. Ohno-Shosaku, T, Kano M. *Curr Opin Neurobiol.* 2014;29:1-8.

8. Katona, I, Freund TF. *Annu Rev Neurosci.* 2012;35:529-558.



ZYN002 Clinical Development Program in Autism Spectrum Disorder

| Study | Study Design | Key Findings |
|-------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BRIGHT | Open-label, Phase 2 study in children and adolescents with autism spectrum disorder (ASD) N=37 | <ul style="list-style-type: none"> Positive benefit-risk profile for ZYN002 when administered in addition to stable standard of care in children and adolescents with moderate-to-severe ASD ZYN002 showed improvement in all ASD measures |
| BELIEVE | Open-label, Phase 2 study in children and adolescents with developmental and epileptic encephalopathy (DEE) N=48 | <ul style="list-style-type: none"> Meaningful reductions in FIAS and TCS with ZYN002 treatment which was maintained through to 12 months In the subgroup of patients with ASD (n=14), ZYN002 demonstrated meaningful reductions in FIAS and TCS |
| CONNECT-FX | Randomized, controlled, Phase 3 study in children and adolescents with fragile X syndrome (FXS) N=212 | <ul style="list-style-type: none"> ZYN002 was superior to placebo in multiple analyses in the group of patients with $\geq 90\%$ methylation of their <i>FMR1</i> gene (80% of the full analysis set) ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set |

FXS is the most common cause of monogenic origin of ASD¹



Tolerability and Efficacy of ZYN002 Cannabidiol (CBD) Transdermal Gel in Children and Adolescents With Autism Spectrum Disorder: An Open-Label Phase 2 Study [BRIGHT (ZYN2-CL-030)]

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Disclosures: TH, CO, DG, and JP are employees of Zynerba Pharmaceuticals. HH and MD have received research support from Zynerba Pharmaceuticals. The study was funded by Zynerba Pharmaceuticals.



Background

- Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by difficulties with behaviors, communication, and reciprocal social interaction^{1,2}
- Current management options for ASD symptoms are restricted to cognitive behavioral therapy and a limited number of approved pharmacologic treatments, highlighting the substantial unmet need for novel therapies in this population²
- The endocannabinoid system is a key modulator of emotion and social behavior and is dysregulated in ASD³
- It is therefore possible that cannabidiol (CBD) may provide therapeutic benefit in ASD; however, the efficacy and safety of CBD in patients with ASD have not been well established³
- BRIGHT (ZYN2-CL-030) is an exploratory, single-center, open-label Phase 2 study evaluating the safety and tolerability and efficacy of ZYN002 in children and adolescents with ASD who are 4 to <18 years old*

1. Masi A et al. *Neurosci Bull.* 2017;33(2):183-193.

2. Sanchack KE, Thomas CA. *Am Fam Physician.* 2016;94(12):972-979.

3. Poleg S et al. *Prog Neuropsychopharmacol Biol Psychiatry.* 2019;89:90-96.

*One 3-year-old participant was enrolled.



Methods

- The study enrolled patients with Clinical Global Impression (CGI)–Severity score ≥ 4 (moderate or greater) and Aberrant Behavior Checklist-Community (ABC-C) Irritability score ≥ 18
- Primary objective: to evaluate the safety and tolerability of ZYN002 in patients aged 4 to <18 years,^a for up to 38 weeks (14-week treatment period and a 6-month extension period)
 - Safety assessments included adverse events (AEs), laboratory tests, and electrocardiograms (ECGs)
- The primary efficacy assessments included ABC-C and CGI
- Secondary objectives comprised evaluation of the efficacy of ZYN002 in the treatment of symptoms of ASD, including measuring parental/caregiver stress (APSI^b), Autism Impact Measure (AIM), and qualitative caregiver reported behavioral problems, assisting us to appreciate the voice of the patient and family
- Patients received ZYN002 250 mg or 500 mg (weight-based dose) daily for 14 weeks in addition to stable standard of care medications (including antipsychotic agents, when prescribed)

^aOne 3-year-old participant was enrolled.

^bAPSI=Autism Parenting Stress Index.



Baseline Demographics

| Characteristic | BRIGHT Participants N=37 |
|-------------------------|-----------------------------|
| Age, mean years (range) | 9.2 (3-16) |
| Sex, n (%) | |
| Male | 34 (91.9) |
| Female | 3 (8.1) |
| Race, % | |
| White | 75.7 |
| Indigenous Australian | 5.4 |
| Asian | 8.1 |
| Other | 10.8 |



Baseline Disease Characteristics

| Characteristic | BRIGHT Participants N=37 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Time since diagnosis, n Mean years (range) | 37 5.4 (0.07-15.7) |
| ABC-C Irritability subscale score, n Mean (range) | 36 ^a 30.3 (18-43) |
| PRAS-ASD score, n Mean (range) >52, n (%) | 36 ^a 40.8 (21-68) 9 (24.3) |
| AIM domain scores, n Atypical behavior, mean (range) Communication, mean (range) Peer interaction, mean (range) Repetitive behavior, mean (range) Social reciprocity, mean (range) | 36 ^a 44.0 (16-56) 39.3 (17-60) 31.2 (13-40) 54.0 (24-80) 33.9 (14-48) |
| DSM-5 severity level ^b Level 1 (mild), n (%) Level 2 (moderate), n (%) Level 3 (severe), n (%) | 3 (8.1) 15 (40.5) 19 (51.4) |
| ADOS [®] -2 comparison score, n <5, n (%) 5-7, n (%) 8-10, n (%) | 36 ^a 2 (5.6) 19 (52.8) 15 (41.7) |

PRAS-ASD: 24% of participants had scores >52, indicating possible clinical anxiety

DSM-5: 92% of participants had moderate to severe symptoms of ASD

ADOS-2: 94% of participants had moderate to severe symptoms of ASD

ABC-C=Aberrant Behavior Checklist-Community; ADOS[®]-2=Autism Diagnostic Observation Schedule[®], 2nd edition; AIM=Autism Impact Measure; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PRAS-ASD=Parent Rated Anxiety Scale—Autism Spectrum Disorder.

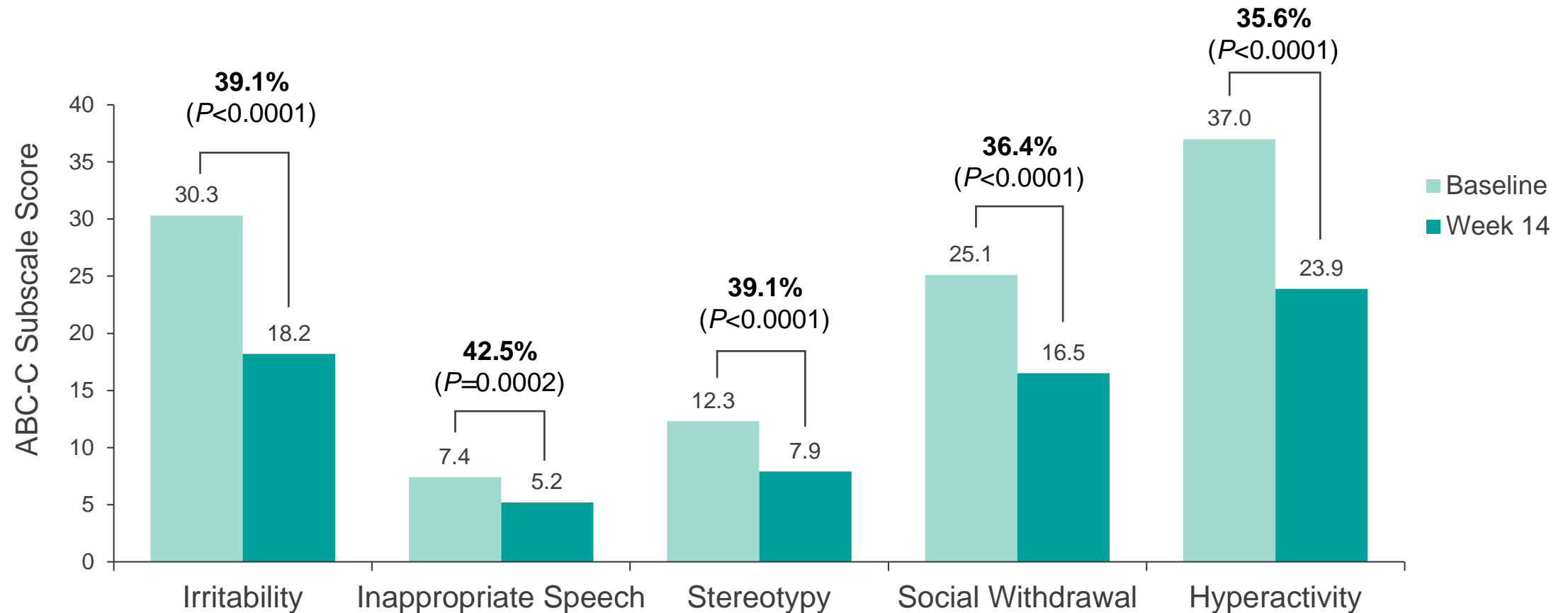
^aOne patient had missing data.

^bDSM-5 severity levels are based on degree of social communication impairment and behavioral flexibility. The levels indicate patients “requiring support” (level 1), “requiring substantial support” (level 2), and “requiring very substantial support” (level 3).¹



Efficacy: Statistically Significant Improvements in All ABC-C Subscale Scores

Mean Percent Improvement at Week 14 vs Baseline



n=28 (n=26 for Inappropriate Speech)

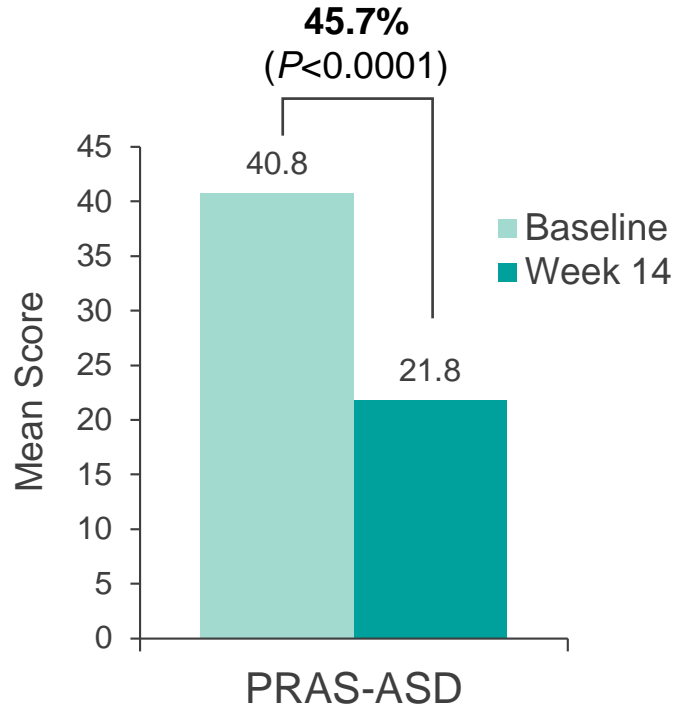
*Lower values reflect improvement in each ABC-C subscale



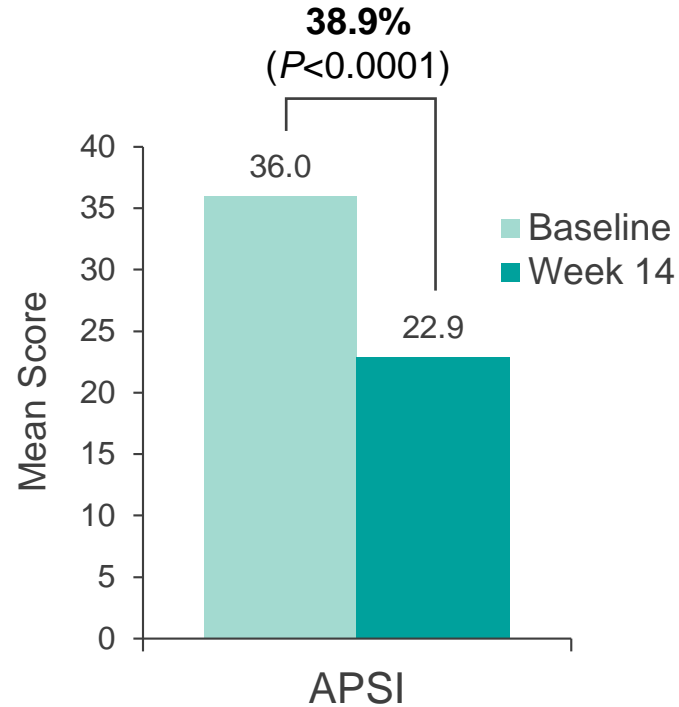
Efficacy: Statistically Significant Improvements in PRAS-ASD, APSI, and CGI-I

Mean Percent Improvement at Week 14 vs Baseline

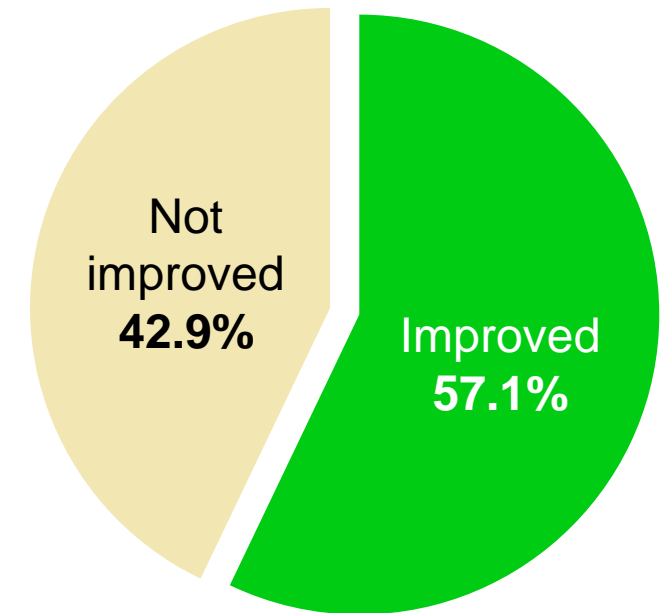
Parent-Rated Anxiety Scale-ASD



Autism Parenting Stress Index

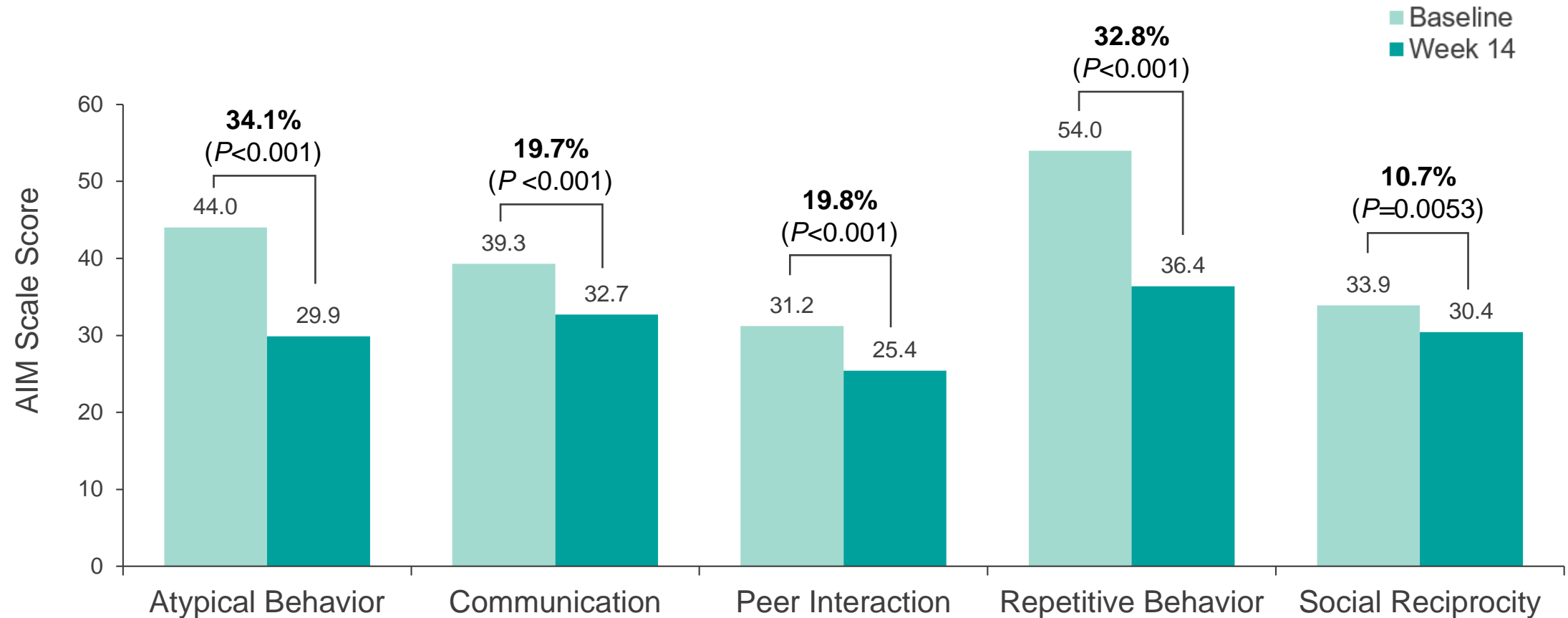


CGI-Improvement



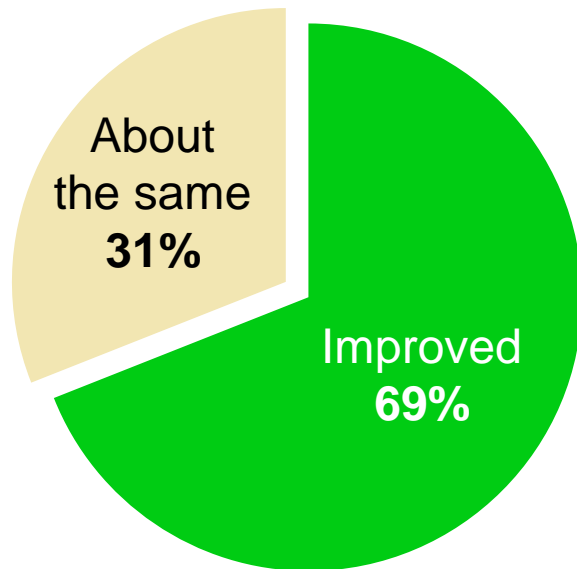
Efficacy: Statistically Significant Improvements in Autism Impact Measure Scores

Mean Percent Improvement at Week 14 vs Baseline

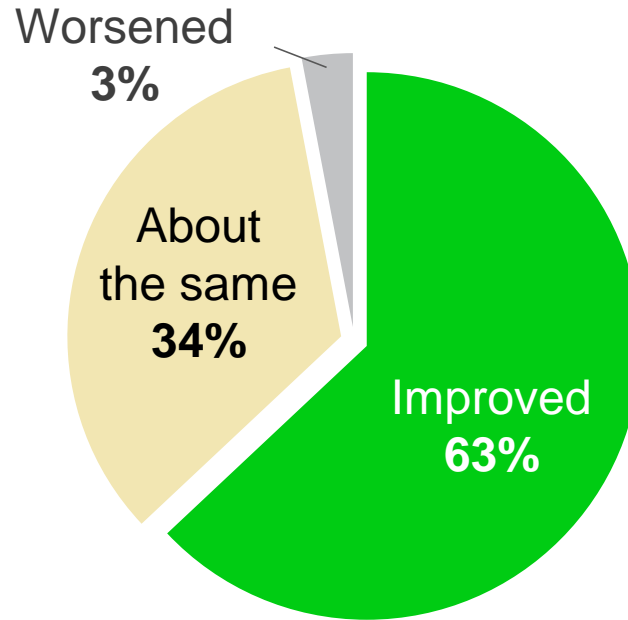


Efficacy: Notable Improvements in the **Qualitative Caregiver Behavioral Problems Survey** at Week 14

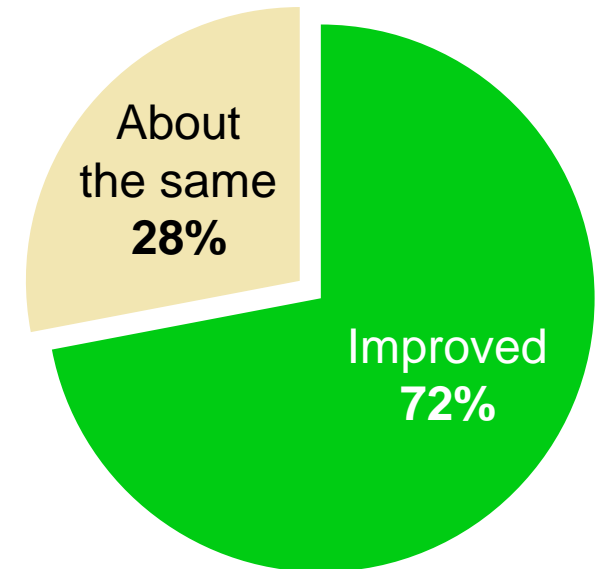
Behavioral



Social



Emotional



Examples at baseline

- Aggressive
- Refuses to go to school
- Repetitive phrases
- Self-harm

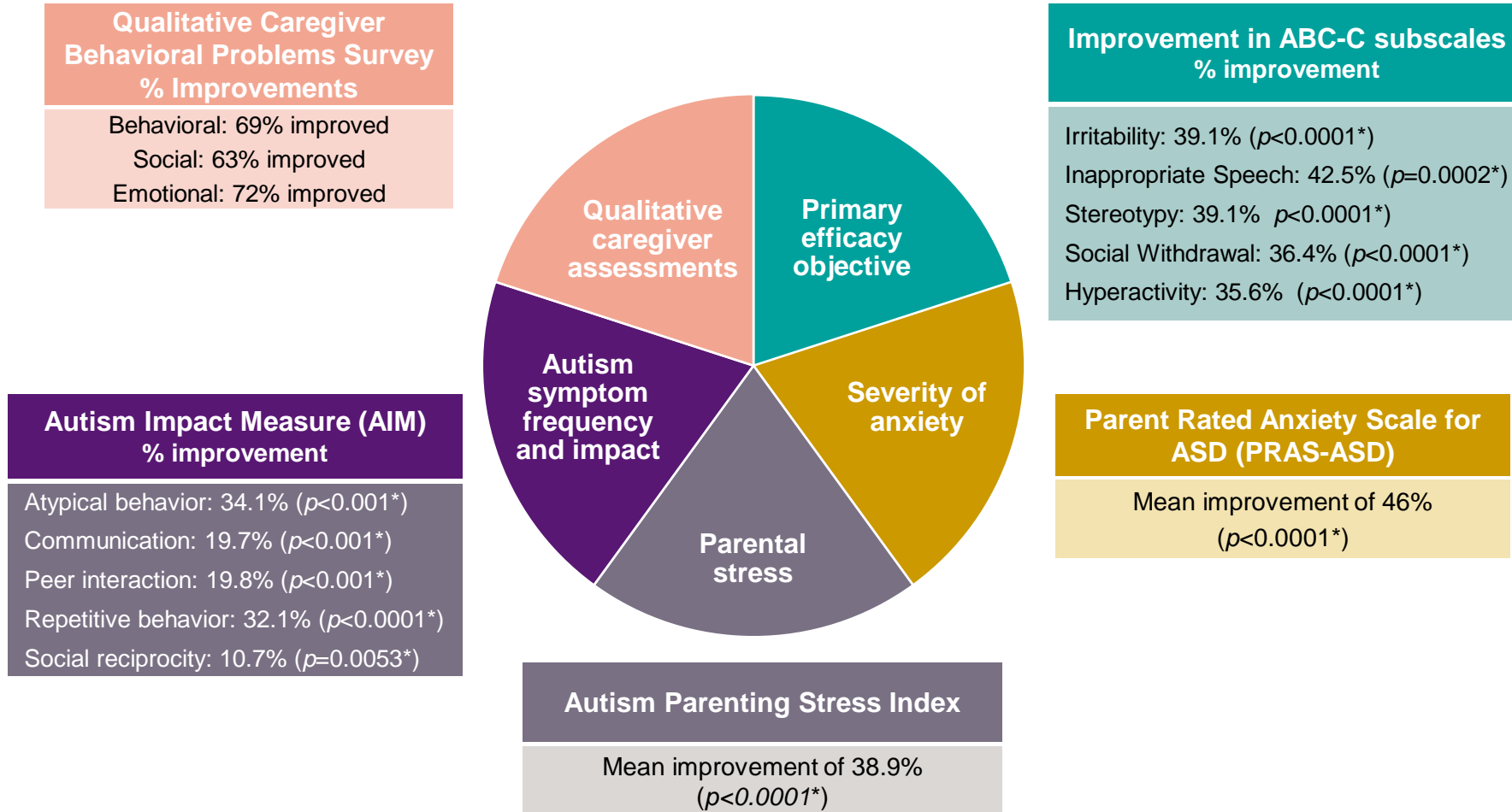
- Minimal social engagement
- No personal space
- No empathy for others
- Fear of new people

- Anxious
- Little self-regulation of emotions
- Easily offended



Summary of Efficacy Results: BRIGHT

Statistically Significant Results at Week 14 Compared to Baseline



* Statistically significant



Safety Assessments and Conclusions Through 14 Weeks

- All TEAEs were mild (75%) or moderate (25%) and reported in 49% of patients
- Treatment-related TEAEs were reported in 14% of patients
 - Most were mild and transient
- No serious or severe AEs or clinically significant changes in laboratory tests or ECGs were reported

TEAEs experienced by ≥ 2 patients through 14 weeks

| Description | Number of Patients N=37 | Number of AEs |
|-------------------------------|----------------------------|---------------|
| Patients with at least 1 TEAE | 18 (48.6%) | 24 |
| Application site pain | 2 (5.4%) | 2 |
| Application site pruritus | 2 (5.4%) | 3 |
| Ear infection | 2 (5.4%) | 2 |
| Nasopharyngitis | 2 (5.4%) | 2 |

Conclusions

- Through 14 weeks of treatment, BRIGHT provides initial evidence suggesting a positive benefit-risk profile for ZYN002 when administered in addition to stable standard of care in children and adolescents with moderate-to-severe ASD
- ZYN002 showed improvement in all ASD measures (ABC-C, AIM, PRAS-ASD, CGI and Qualitative Caregiver Assessments)
- Further controlled studies are warranted in this difficult-to-treat population



ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Developmental and Epileptic Encephalopathies: An Open-Label Clinical Trial [BELIEVE (ZYN2-CL-025)]

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Disclosures: DG and TS are employees of Zynerba Pharmaceuticals. JH is a paid consultant to Zynerba Pharmaceuticals through Paradigm Neuroscience. JM is a paid consultant to Zynerba Pharmaceuticals. IS, SA, NK, and LS have received research support and consulting fees from Zynerba Pharmaceuticals. The study was funded by Zynerba Pharmaceuticals.



Background

- Developmental and epileptic encephalopathies (DEEs) are a severe group of neurodevelopmental disorders characterized by seizures and abnormal electroencephalogram activity that negatively impact development¹
- DEEs include, but are not limited to, West syndrome, Lennox-Gastaut syndrome (LGS), and Dravet syndrome²
- DEEs with onset ≤ 18 months have an incidence of 1 in 2000 live births³
- Seizures are generally refractory to antiseizure medications (ASMs)⁴
- Oral administration of ASMs can be difficult due to behavioral and cognitive impairments
- Children with DEEs are medically fragile and have multiple comorbidities including motor and cognitive impairments, autism spectrum disorder (ASD), and sleep disturbance, which further increase disability^{3,5,6}

1. Scheffer IE et al. *Epilepsia*. 2017;58(4):512-521.

2. Aaberg KM et al. *Epilepsia*. 2017;58(11):1880-1891.

3. Howell KB et al. *Epilepsia*. 2018;59:1177-1187.

4. Vigeveno F et al. *Epilepsia*. 2013;54(suppl 8):45-50.

5. Turner SJ et al. *Neurology*. 2017;88(8):743-749.

6. Rodda JM et al. *Arch Neurol*. 2012;69:873-878.



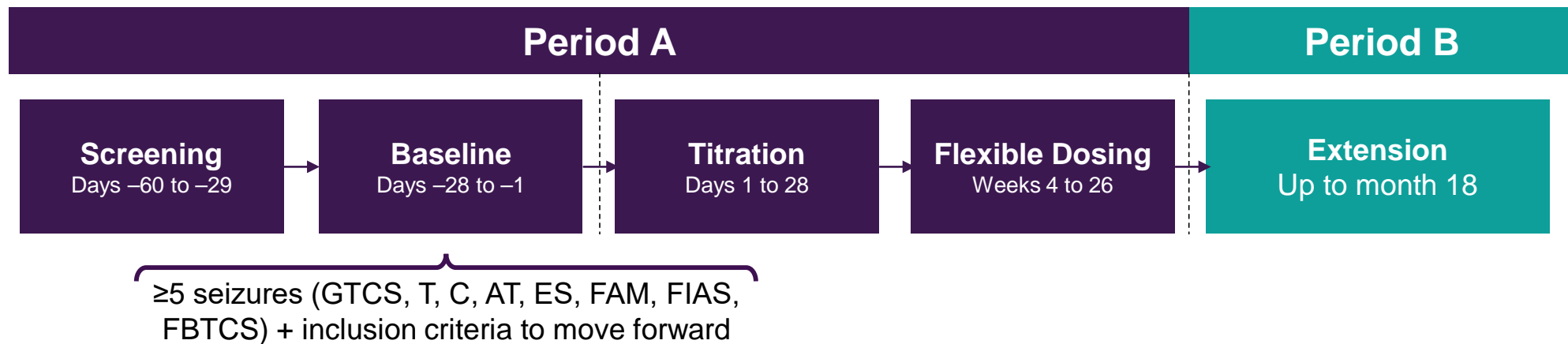
Objectives and Study Design

Objectives

- To evaluate the efficacy (current data through month 12) and safety and tolerability (18 months) of ZYN002 in children and adolescent patients with DEEs
- An exploratory analysis to evaluate efficacy of ZYN002 in DEE patients with ASD

Study design

- Open-label, 2-center, multiple-dose, phase 2 study in patients aged 3 to <18 years with DEEs



Baseline Demographics

| Demographic or Disease Characteristic | Safety Analysis Set (N = 48) |
|------------------------------------------------|------------------------------|
| Age, years Mean (range) | 10.5 (3, 16) |
| Sex, n (%) | |
| Male | 26 (54.2) |
| Female | 22 (45.8) |
| Seizure type, ^{a,b} n (%) | |
| Focal impaired awareness | 26 (54.2) |
| Tonic-clonic | 21 (43.8) |
| Generalized tonic-clonic | 14 (29.2) |
| Focal to bilateral tonic-clonic | 7 (14.6) |
| Autism spectrum disorder, ^{c,d} n (%) | 14 (29.2) |
| Seizure type in ASD patients, n (%) | |
| Focal impaired awareness | 6 (42.9) |
| Tonic-clonic | 8 (57.1) |
| Generalized tonic-clonic | 5 (35.7) |
| Focal to bilateral tonic-clonic | 3 (21.4) |
| Number of concomitant ASMs, mean | 2.7 |

ASD, autism spectrum disorder; ASM, antiseizure medication.

^aDuring the 4-week baseline period.

^bFor seizure type, N=33. Thirty-three patients with focal impaired awareness and/or tonic-clonic seizures; patients could have more than one seizure type.

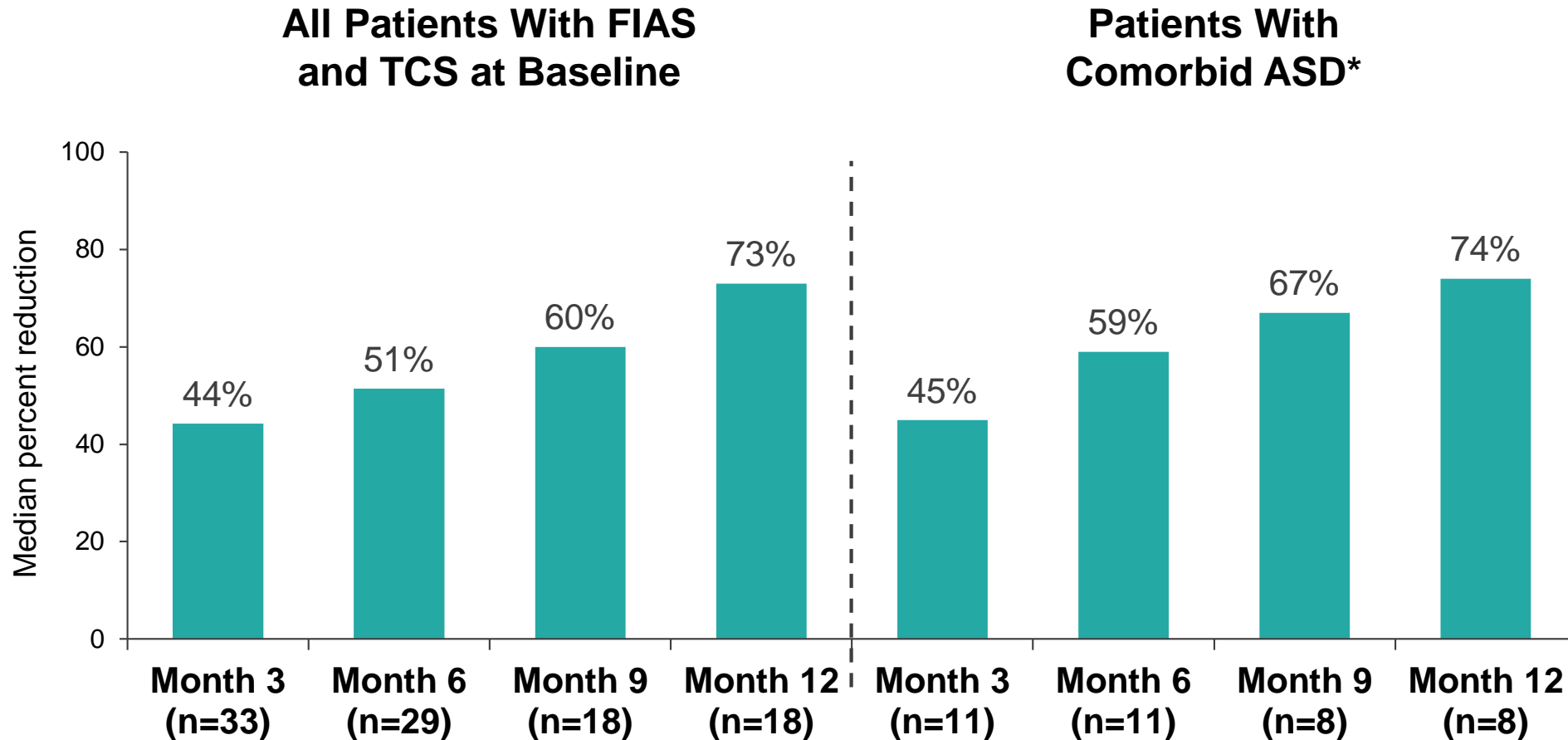
^cASD diagnosis per investigator.

^dFor seizure type, N=11. Eleven patients with focal impaired awareness and/or tonic-clonic seizures; patients could have more than one seizure type



Efficacy: Meaningful Reductions in Seizure Frequencies

Median Percentage Reduction From Baseline in 28-Day Frequency of FIAS and TCS

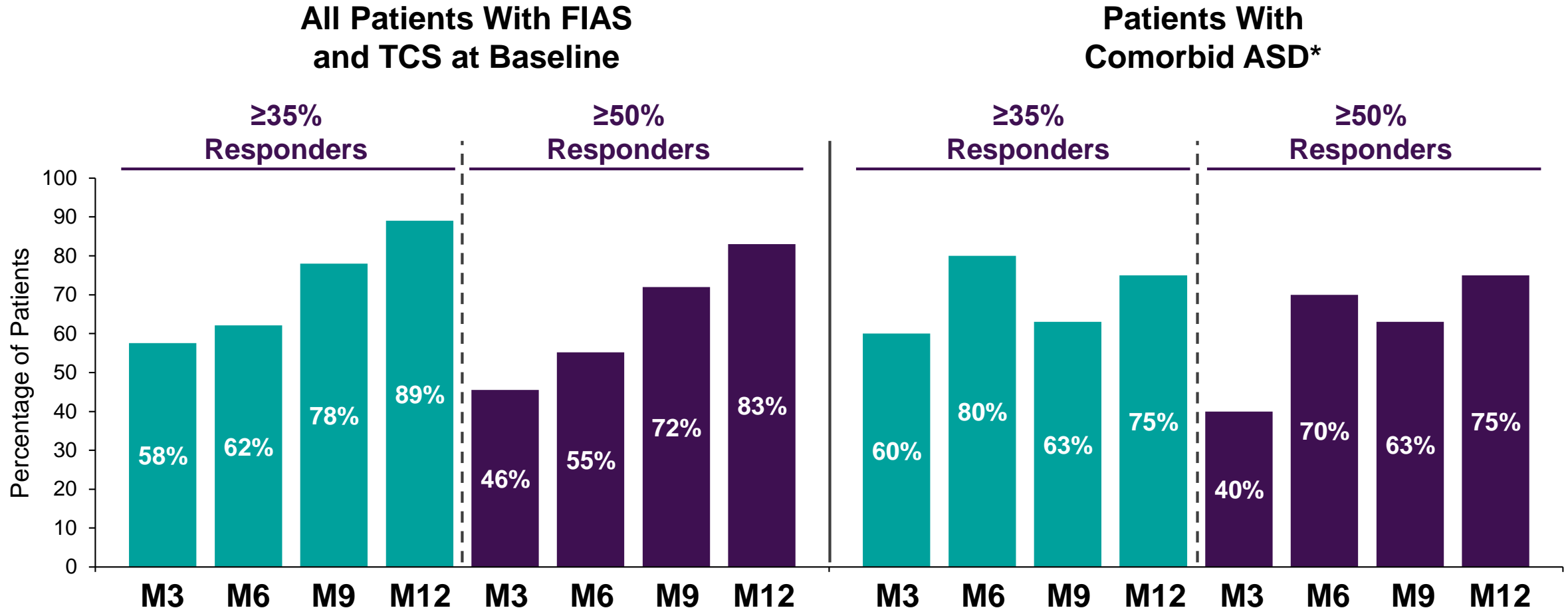


*Post hoc analysis.

FIAS=focal impaired awareness; TCS=tonic-clonic seizures.

Efficacy: Responder Analysis

Percentage of Patients With 35% and 50% Reduction in FIAS and TCS

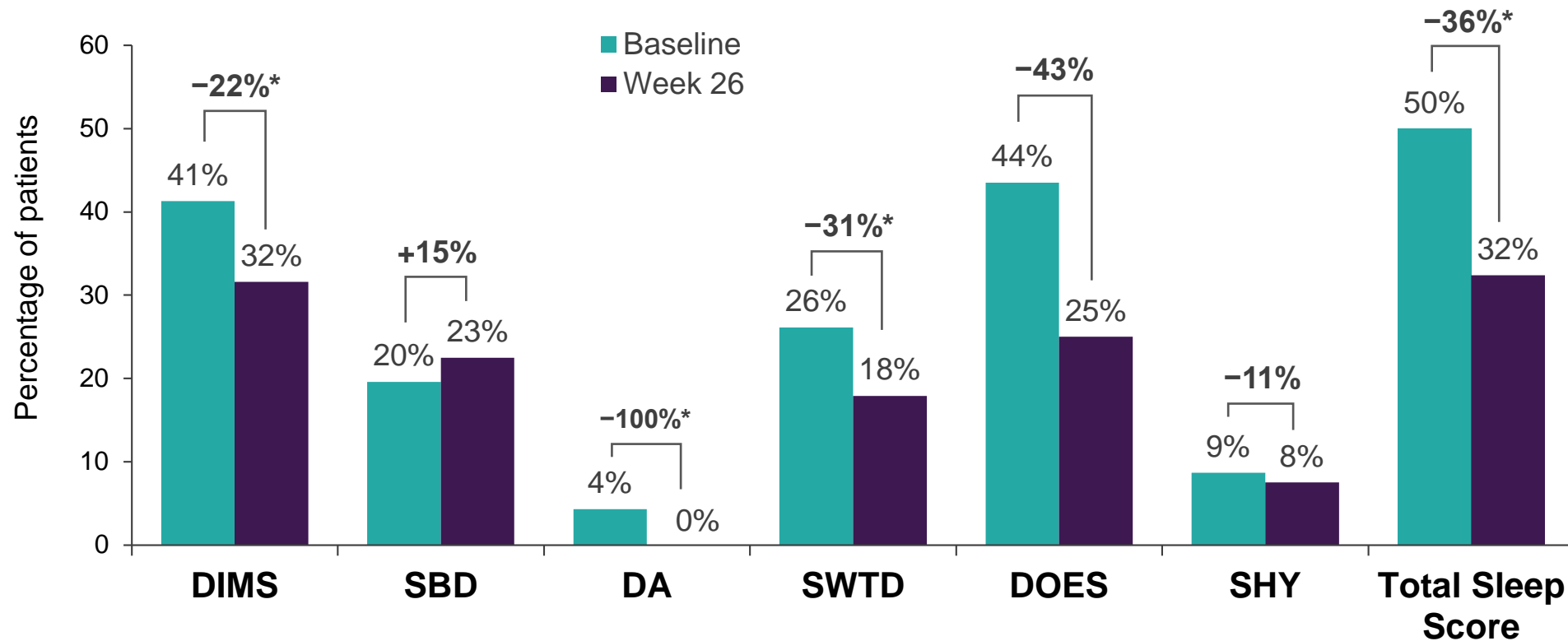


*Post hoc analysis.

FIAS=focal impaired awareness; TCS=tonic-clonic seizures.

Efficacy in Sleep Disturbance: Full DEE Population^a

Sleep Disturbance Scale for Children (SDSC)– Percentage of Patients Above Threshold for Clinically Significant Sleep Problems at Baseline and Week 26



^aAnalysis of sleep disturbance in patients with comorbid ASD is being conducted.

* $P < 0.05$ for change from baseline to week 26.

DA=disorders of arousal/nightmares; DIMS=disorders of initiating or maintaining sleep; DOES= disorders of excessive somnolence; SBD=sleep breathing disorders; SHY=sleep hyperhidrosis; SWTD=sleep wake transition disorder.

Efficacy: Significant Improvements in Quality of Life Full DEE Population

Improvements from baseline in mean Epilepsy and Learning Disabilities Quality of Life (ELDQOL) subscale scores for seizure severity, behavior, and mood at week 26

| Change From Baseline in Mean ELDQOL Subscale Scores, mITT Population (N = 40) ^a | | | |
|--------------------------------------------------------------------------------------------|-----------|---------------------|--------------|
| | Mean (SD) | Change ^b | P value |
| ELDQOL subscale | | | |
| Seizure severity | | | |
| Baseline (n = 40) | 26 (54.2) | | |
| Week 26 (n = 40) | 22 (45.8) | -0.19 | 0.008 |
| Behavior | | | |
| Baseline (n = 40) | 8 (16.7) | | |
| Week 26 (n = 40) | 5 (10.4) | -0.21 | 0.001 |
| Mood | | | |
| Baseline (n = 40) | 26 (54.2) | | |
| Week 26 (n = 40) | 21 (43.8) | -0.15 | 0.001 |

^aIncludes patients who completed both baseline and week 26 ELDQOL assessments; 6 patients completed the baseline assessment but did not complete the week 26 assessment.

^bNegative change from baseline reflects an improvement.

Summary of Efficacy Results: BELIEVE

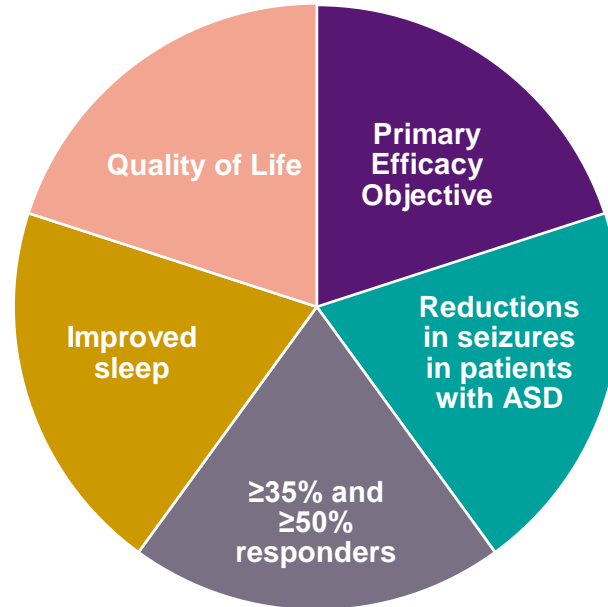
Clinically Meaningful Improvements in FIAS / TCS, Sleep and QoL vs. Baseline

Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale

Statistically significant reductions in subscale scores for seizure severity ($p < 0.008$), behavior, and mood ($p < 0.001$) observed at 26 weeks

Sleep Disturbance Scale for Children (SDSC) % improvement

Statistically significant improvements observed in
 Disorders of initiating/maintaining sleep: 22%; $p = 0.006$
 Disorders of Arousal/Nightmares: 100%; $p = 0.031$
 Sleep wake transition disorder: 31%; $p = 0.030$
 Total Score: 36%; $p = 0.012$



Mean % Reductions in Seizures

Month 3 (n=33): 44%
 Month 6 (n=29): 51%
 Month 9 (n=18): 60%
 Month 12 (n=18): 73%

Mean % Reductions in Seizures: Comorbid ASD

Month 3 (n=33): 45%
 Month 6 (n=29): 59%
 Month 9 (n=18): 67%
 Month 12 (n=18): 74%

% of patients with ≥35% and ≥50% Reductions in FIAS and TCS All Patients / Comorbid ASD

| ≥35% reductions | ≥50% reductions |
|---------------------|---------------------|
| Month 3: 58% / 60% | Month 3: 46% / 40% |
| Month 6: 62% / 80% | Month 6: 55% / 70% |
| Month 9: 78% / 63% | Month 9: 72% / 63% |
| Month 12: 89% / 75% | Month 12: 83% / 75% |



Safety

- ZYN002 was well tolerated in BELIEVE
- Most treatment-emergent adverse events (TEAEs) (any event, whether unrelated or related to study drug) were mild or moderate
- There were 30 serious adverse events reported by 14 patients over the 18 month treatment period, of which two (lower respiratory tract infection and status epilepticus) were considered possibly drug related
- One patient, with a history of keratosis pilaris, discontinued study medication due to an AE (intense application site erythema); dermatologic patch testing showed this was not caused by allergic contact dermatitis from ZYN002 and was likely irritant contact dermatitis complicated by a secondary bacterial infection
- There were no clinically significant changes in vital signs, ECGs, or laboratory findings except for 1 patient with a transient, benign, isolated elevation of alkaline phosphatase at week 26 ($1.69 \times \text{ULN}$) that was not considered related to study medication



Conclusions

- BELIEVE is the first clinical trial of ZYN002 (transdermal CBD) in DEEs
- These data suggest meaningful reductions in refractory FIAS and TCS with ZYN002 treatment which is maintained through to 12 months
- In the subgroup of patients with ASD, ZYN002 demonstrated meaningful reductions in refractory FIAS and TCS, on top of standard of care, with most children reaching the 35% or 50% responder threshold by Month 3 and Month 6 respectively
- Clinically meaningful improvements initiating and maintaining sleep, disorders of arousal/nightmares, sleep wake transition, and overall sleep were observed in the overall DEE population
- ZYN002 was well tolerated over 18 months of treatment in a medically fragile patient population of children and adolescents with DEEs
- The positive benefit/risk profile of ZYN002 in this trial supports further study in patients with DEEs and FIAS and TCS
- The data also support further study of ZYN002 in patients with ASD and comorbid refractory seizures



ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Fragile X Syndrome: Role of Methylation Status as a Correlate to Disease Severity and Therapeutic Response (CONNECT-FX [ZYN2-CL-016])

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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.



Background

- Fragile X syndrome (FXS) is a rare genetic disorder that has a prevalence of approximately 1 in 4000 males and 1 in 6000 females¹
- FXS is associated with a variety of intellectual and emotional disabilities, including autism spectrum disorder (ASD), anxiety, aggression toward others, irritability, temper tantrums, shyness, preference of solitary activities^{2,3}
- FXS is the most common cause of monogenic origin of ASD⁴
- Despite decades of preclinical research and interventional clinical trials, there are no approved treatments for FXS

1. Coffee, B, et al. *Am J Hum Genet.* 2009;85(4):503-514.

2. Hagerman, RJ. *West J Med.* 1997;166(2):129-137.

3. Tranfaglia, MR. *Dev Neurosci.* 2011;33(5):337-348.

4. Salcedo-Arellano, MJ, et al. *Neurotherapeutics.* 2020. [Epub ahead of print]



FXS Pathophysiology

- FXS is caused by the deficiency or absence of the FMR protein¹
- 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^{4,5}
- In general, the FXS cognitive and emotional phenotype depends on the amount of FMRP that is produced and 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 ASD⁸

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2. Pieretti, M, et al. *Cell*. 1991;66(4):817-822.

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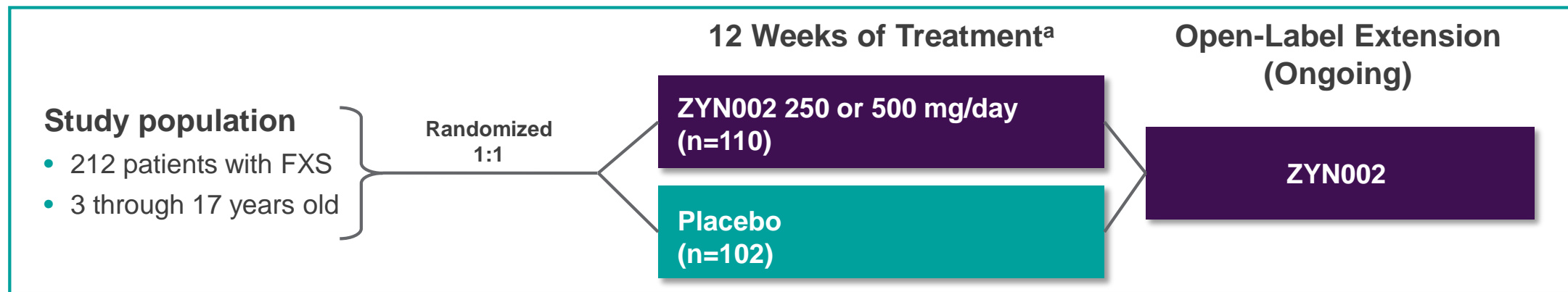
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CONNECT-FX: Clinical study Of CaNNabidiol (CBD) in ChildrEn and AdolesCenTs with Fragile X

- 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^b was performed
 - The results suggest that ZYN002 may have benefit in patients with $\geq 90\%$ methylation of the *FMR1* gene

^a2-week placebo period followed by 12 weeks of treatment.

^b*FMR1* methylation status was determined by using Southern blot analysis.



The $\geq 90\%$ Methylation Group Represented 80% of the Total Study Population

Baseline Characteristics in the $\geq 90\%$ Methylation Group

The $\geq 90\%$ methylation group had similar baseline characteristics to the full study population

| | $\geq 90\%$ 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 $\geq 90\%$ 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 <i>p</i> -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 |

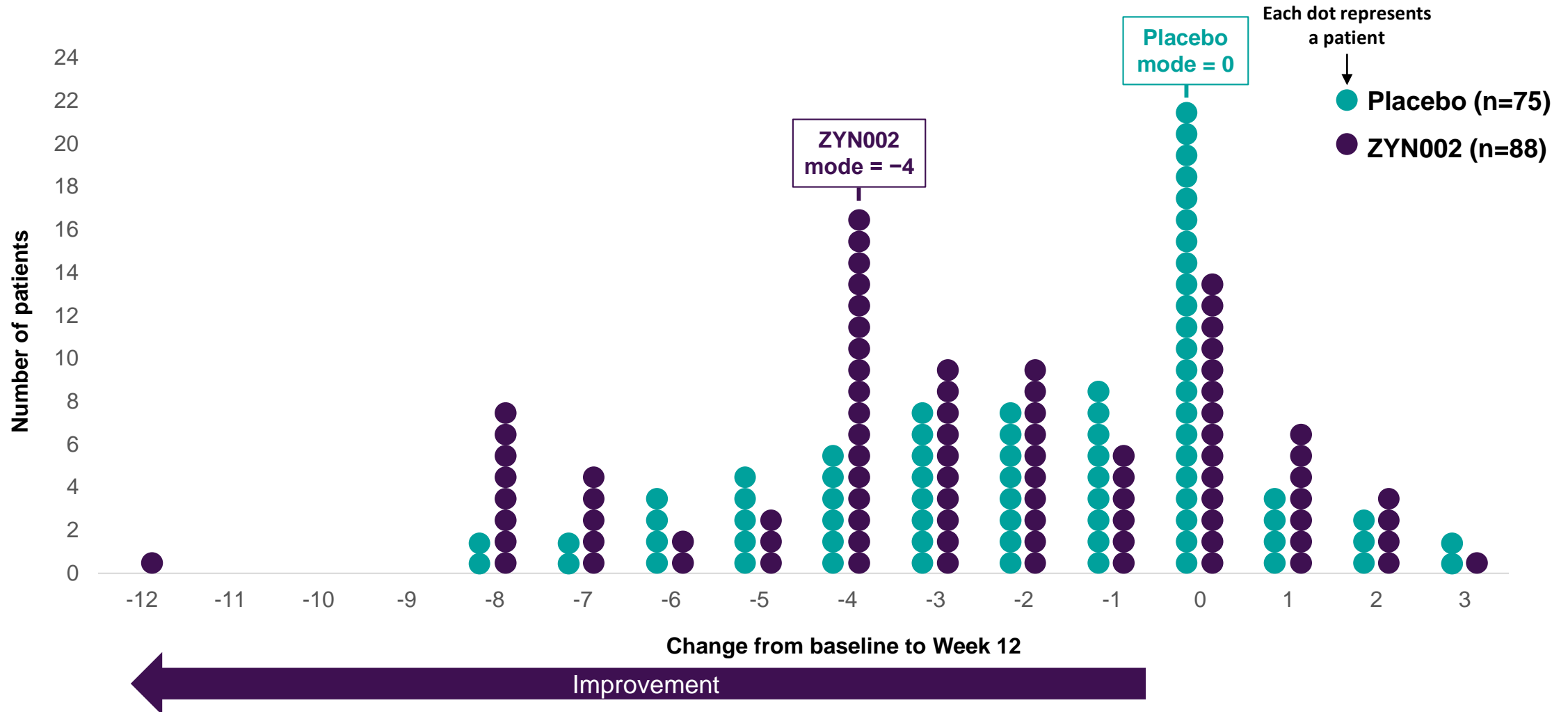
Trend level response achieved in Irritability and CGI-I

*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}

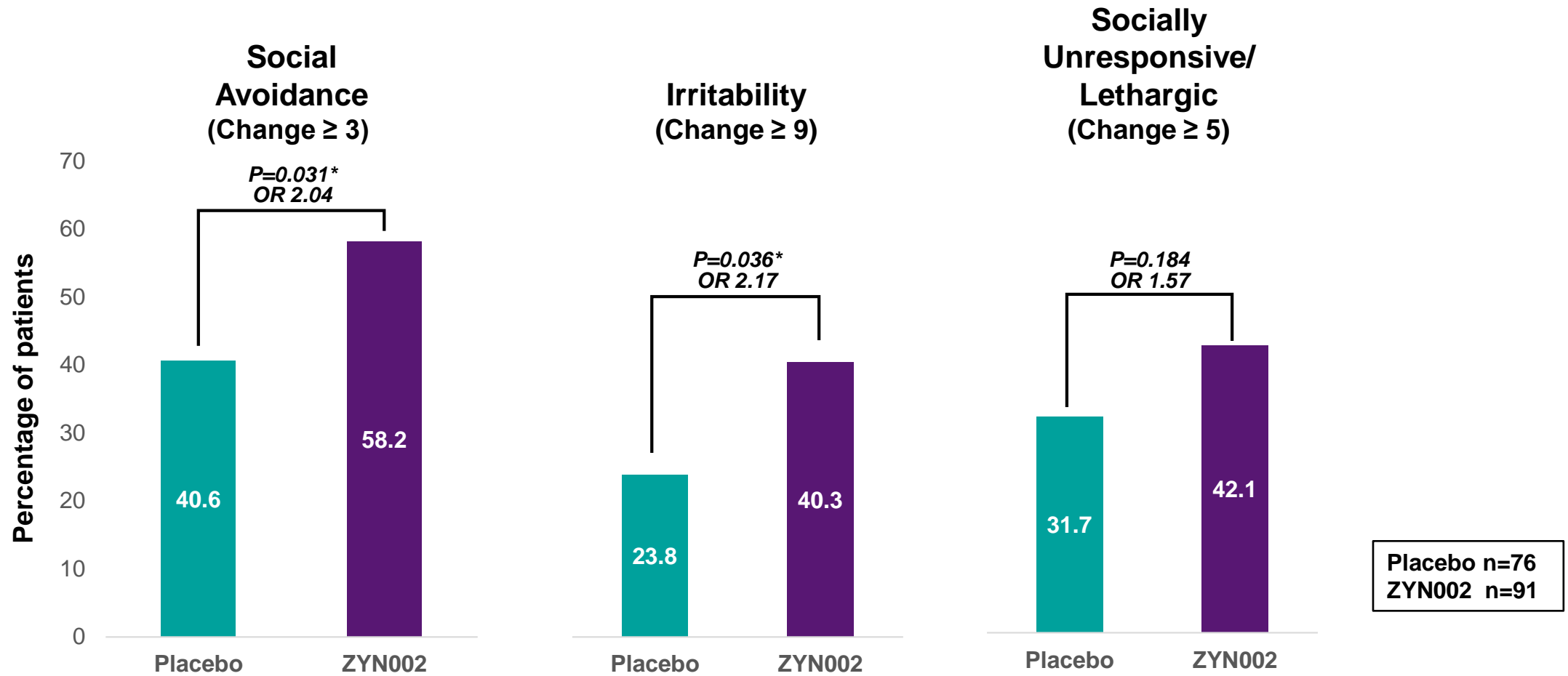
3-point improvement determined to be clinically meaningful for Social Avoidance

- 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 $\geq 90\%$ methylation group

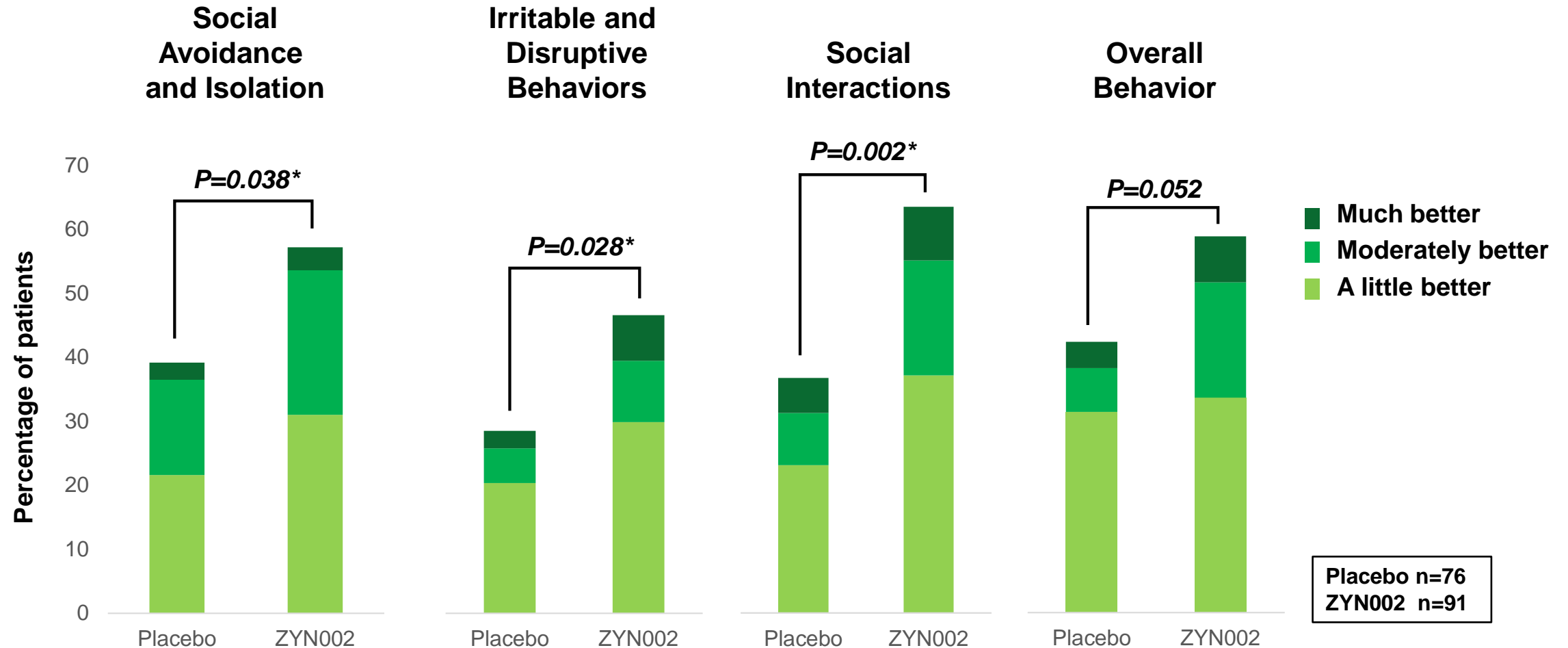


OR= odds ratio
*Statistically significant. LS Means



Caregiver Global Impression-Change: ≥90% Methylation Group

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

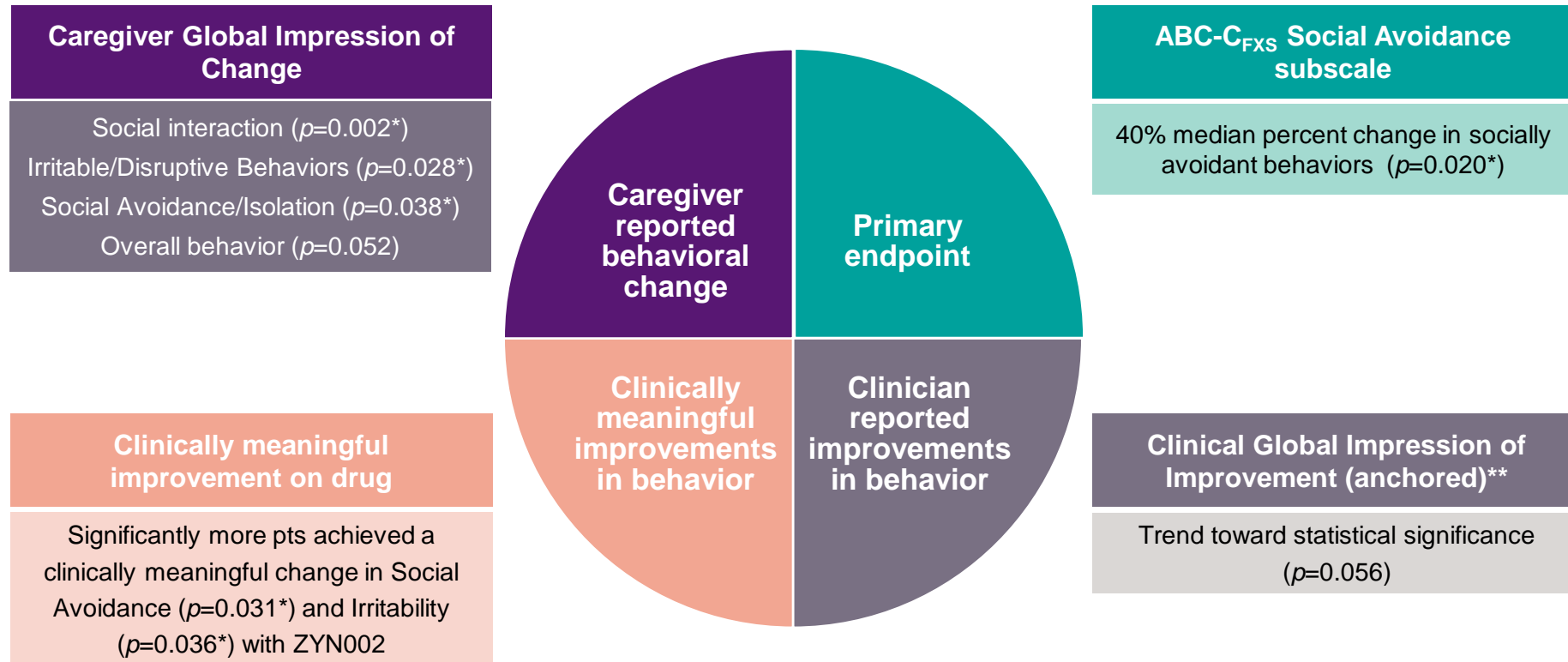


*Statistically significant.
 P-values indicate “betterment” on ZYN002 vs “betterment” on placebo.
 Psychometric analysis indicated that “any improvement” is meaningful.



Summary of Efficacy Results: $\geq 90\%$ Methylation Group

Consistent Improvements Observed with ZYN002 vs. Placebo



* Statistically significant

** Not specific to Social Avoidance



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



ZYN002 in FXS

Summary

- To our knowledge, CONNECT-FX is the largest controlled study ever performed in FXS
- ZYN002 was well tolerated
- In the $\geq 90\%$ 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

These results may represent an important step forward in the determination of biologically important constructs of pharmacotherapeutic response in FXS



Overall Summary

- The ECS plays an important role in the CNS and in neurodevelopmental disorders
- In BRIGHT, in children and adolescents with ASD, ZYN002 showed improvement in all ASD measures
- In BELIEVE, children and adolescents with DEE experienced meaningful improvements in seizures and sleep disorders with ZYN002 treatment
- In BELIEVE seizure improvements were also seen in patients with co-diagnosed ASD
- In CONNECT-FX, ZYN002 was well tolerated and was superior to placebo in multiple analyses in the group of patients with $\geq 90\%$ methylation of their *FMR1* gene
- These data support the concepts that ZYN002 was well tolerated and may have benefit in behavioral symptoms in patients diagnosed with ASD, as well as in patients diagnosed with FXS, the most common monogenic cause of ASD
- Potential benefit was also shown in the treatment of refractory seizures in DEE patients co-diagnosed with ASD





Thank You!