

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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Disclosures

- 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
- Helen Heussler, Michael Duhig, Jonathan Cohen, and Caroline Buchanan have received research support from Zynerba Pharmaceuticals. Carol O'Neill and Stephen O'Quinn are employees of Zynerba Pharmaceuticals
- The trial was funded by Zynerba Pharmaceuticals



Background: 22q11.2 Deletion Syndrome (1 of 2)

- 22q11.2 deletion syndrome (22q) is the second most common chromosomal disorder after Down syndrome¹
- 22q occurs in 1 in 3000 to 1 in 6000 live births²
- The deletion of genes such as *TBX1* may be responsible for characteristic signs (such as heart defects, a cleft palate, distinctive facial features, hearing loss, and low calcium levels) and behavioral problems
- Children with 22q are at increased risk for several psychiatric disorders, including anxiety, social withdrawal, attention-deficit hyperactivity disorder, cognitive impairment, autism spectrum disorder (ASD), mood disorders, as well as psychotic disorders and schizophrenia (adolescence/adulthood)³

ASD, autism spectrum disorder.

1. Bassett AS, et al. *J Pediatr*. 2011;159(2):332-9.e1.

2. McDonald-McGinn DM, et al. *Nat Rev Dis Primers*. 2015;1:15071.

3. Swillen A, McDonald-McGinn DM. *Am J Med Genet C Semin Med Genet*. 2015;169(2):172-181.



Background: 22q11.2 Deletion Syndrome (2 of 2)

- Approximately 40% of these children suffer from some type of anxiety disorder¹
 - Specific phobias are most common, followed by generalized anxiety disorder, separation anxiety, and obsessive compulsive disorder²
- Early negative experience has been shown to increase the risk of anxiety and is associated with atypical development of the physiological stress response³
 - Serious medical complications such as congenital heart disease, feeding difficulties, and often multiple surgeries or hospitalizations may also predispose some children to anxiety disorders due to stressors associated with repeated medical procedures or poor sense of control over one's body⁴
- The presence of anxiety symptoms in children with 22q is negatively correlated with adaptive function and impacts everyday living skills⁵

1. Jolin EM, et al. *J Affect Disord.* 2012;136(3):222-228.

2. Feinstein C, et al. *Biol Psychiatry.* 2002; 51(4):312-318.

3. Elzinga BM, et al. *Psychoneuroendocrinology.* 2008; 33:227-237.

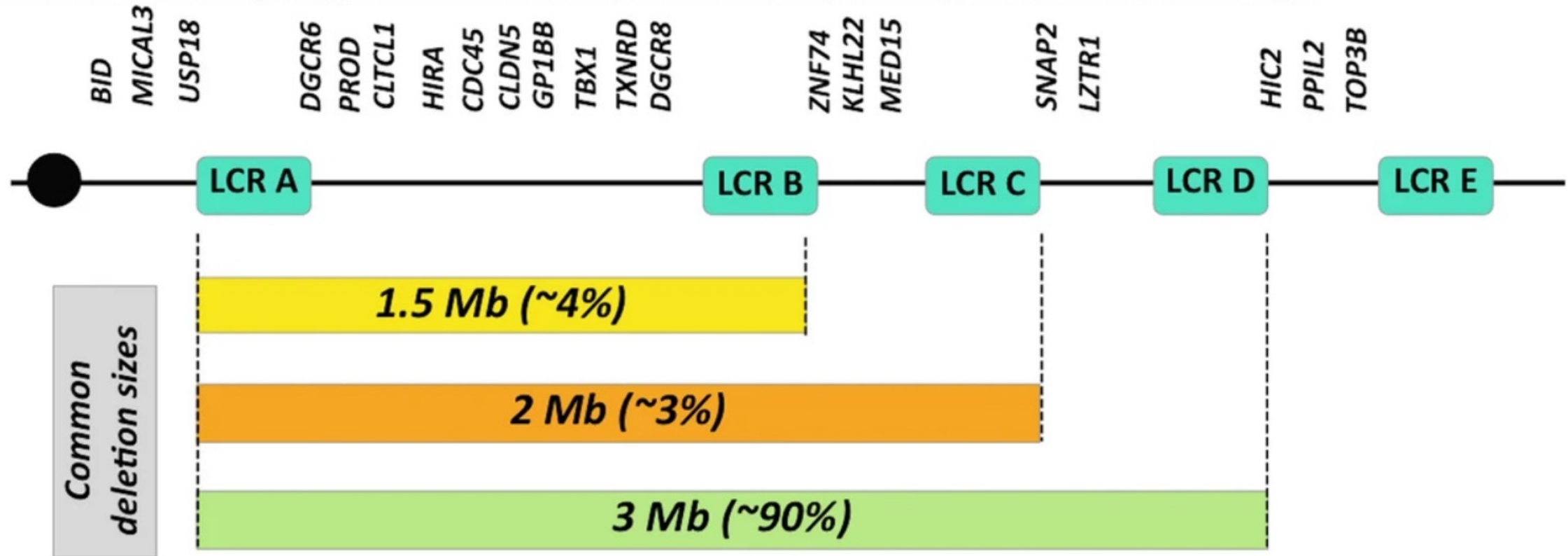
4. Beaton EA, Simon TJ. *J Neurodev Disord.* 2011; 3(1):68-75.

5. Angkustsiri et al. *J Dev Behav Pediatr.* 2012; 33(9): 713–720



Deletions Sizes and Impacted Genes in 22q11.2 Deletion Syndrome

From: [Association between phenotype and deletion size in 22q11.2 microdeletion syndrome: systematic review and meta-analysis](#)



Schematic overview of the chromosome 22q11.2 region. Centromere is represented by the black circle. LCR22 A to E are illustrated by the green boxes. Horizontal bars below the map represent the most common deletions at 22q11.2 region and their frequencies



Background: Cannabidiol and ZYN002

- Disruption in the endocannabinoid system (ECS) is one of the proposed mechanisms underlying symptoms affecting children with neurodevelopmental disorders¹
- Cannabidiol acts as a negative allosteric modulator at presynaptic CB₁ receptors²
- Cannabidiol has also shown activity at serotonin 5HT_{1A},³ GABA_A,⁴ and dopamine D₂ and D₃^{5,6} receptors
- ZYN002 is a pharmaceutically produced (not plant-derived) cannabidiol transdermal gel in clinical development for the treatment of behavioral symptoms associated with 22q and Fragile X Syndrome (FXS)
- ZYN002 does not contain THC and avoids conversion to THC in the stomach⁷

CB₁, cannabinoid receptor 1; ECS, endocannabinoid system; FXS, Fragile X syndrome; GABA, gamma-aminobutyric acid; THC, tetrahydrocannabinol.

1. Cheung KAK, et al. *Front Psychiatry*. 2021;12:643442.
2. Laprairie RB, et al. *Br J Pharmacol*. 2015;172(20):4790-4805.
3. Russo EB, et al. *Neurochem Res*. 2005;30(8):1037-1043.

4. Bakas T, et al. *Pharmacol Res*. 2017;119:358-370.
5. McGuire P, et al. *Am J Psychiatry*. 2018;175(3):225-231.
6. Bian YM, et al. *Acta Pharmacol Sin*. 2019;40(3):374-386.
7. Merrick J, et al. *Cannabis Cannabinoid Res*. 2016;1:102-112.



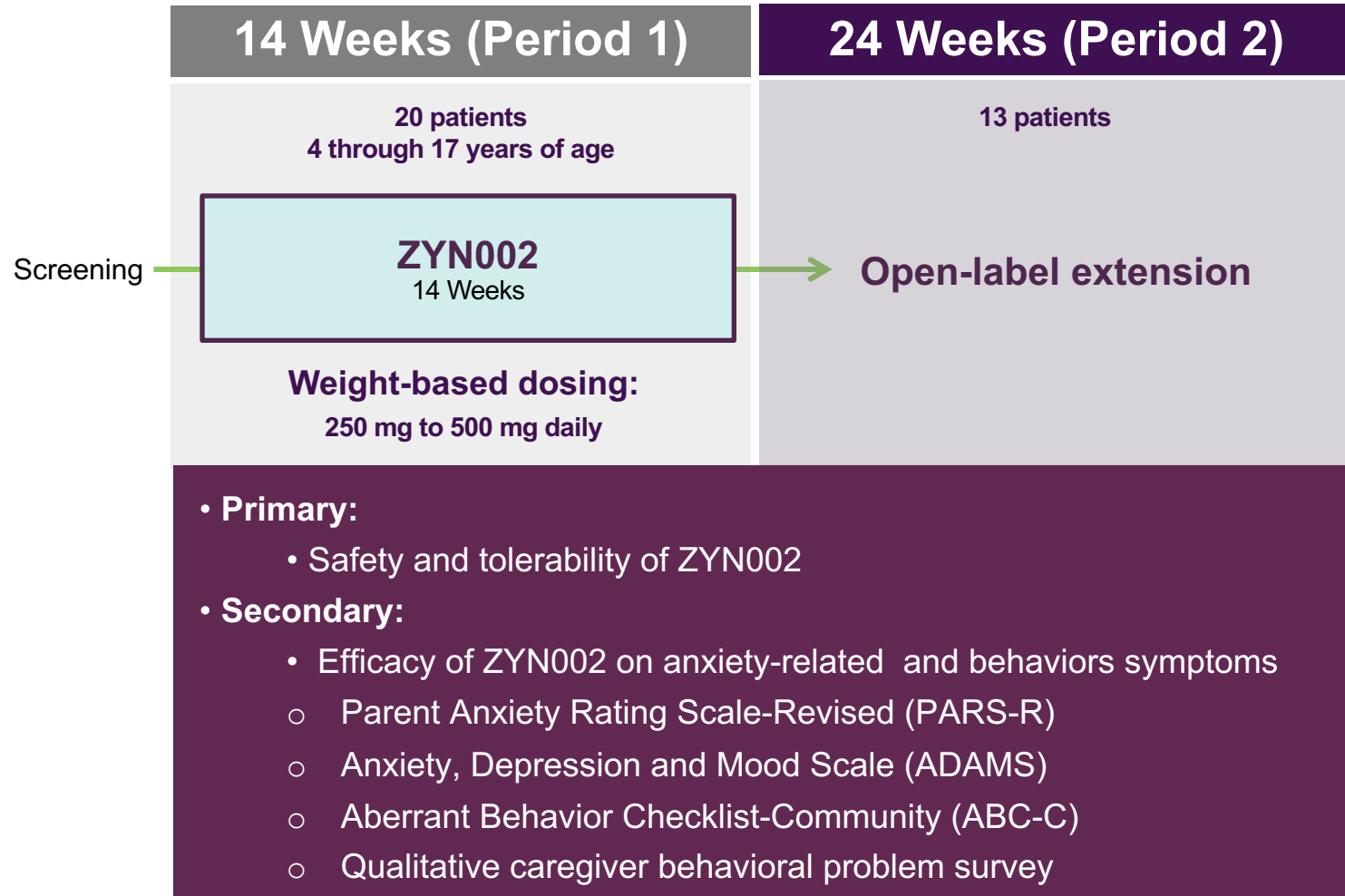
Methods

- 3 sites: 2 in Australia and 1 in the United States
- Children and adolescents ages 4 through 17 with genetically confirmed 22q
 - Clinical Global Impression-Severity (CGI-S) score of ≥ 4 at Screening and Visit 2 (Day 1)
 - Pediatric Anxiety Rating Scale-Revised (PARS-R) score of ≥ 10 at Screening and Visit 2 (Day 1)
- Primary outcome measure was incidence of treatment-emergent adverse events
- Secondary outcome measures to assess efficacy included:
 - PARS-R
 - Anxiety, Depression, and Mood Scale (ADAMS)
 - Aberrant Behavior Checklist-Community (ABC-C)
 - Clinical Global Impression-Improvement (CGI-I)
 - Qualitative Caregiver Reported Behavioral Problems Survey
- Patients received ZYN002 250 mg (weight ≤ 35 kg) or 500 mg (weight > 35 kg) daily, in divided doses every 12 hours as an add-on to standard-of-care medications. At Week 6, if the patient had less than a 25% improvement from baseline in the ABC-C irritability subscale, the investigator could increase the dose, as follows:
 - Patients who weigh ≤ 35 kg receiving a total daily dose of 250 mg CBD could increase to a daily dose of 500 mg
 - Patients who weigh > 35 kg receiving a daily dose of 500 mg CBD could increase the dose to 750 mg/day
- Patients demonstrating improvement were allowed to continue treatment for an additional 24 weeks (Period 2)

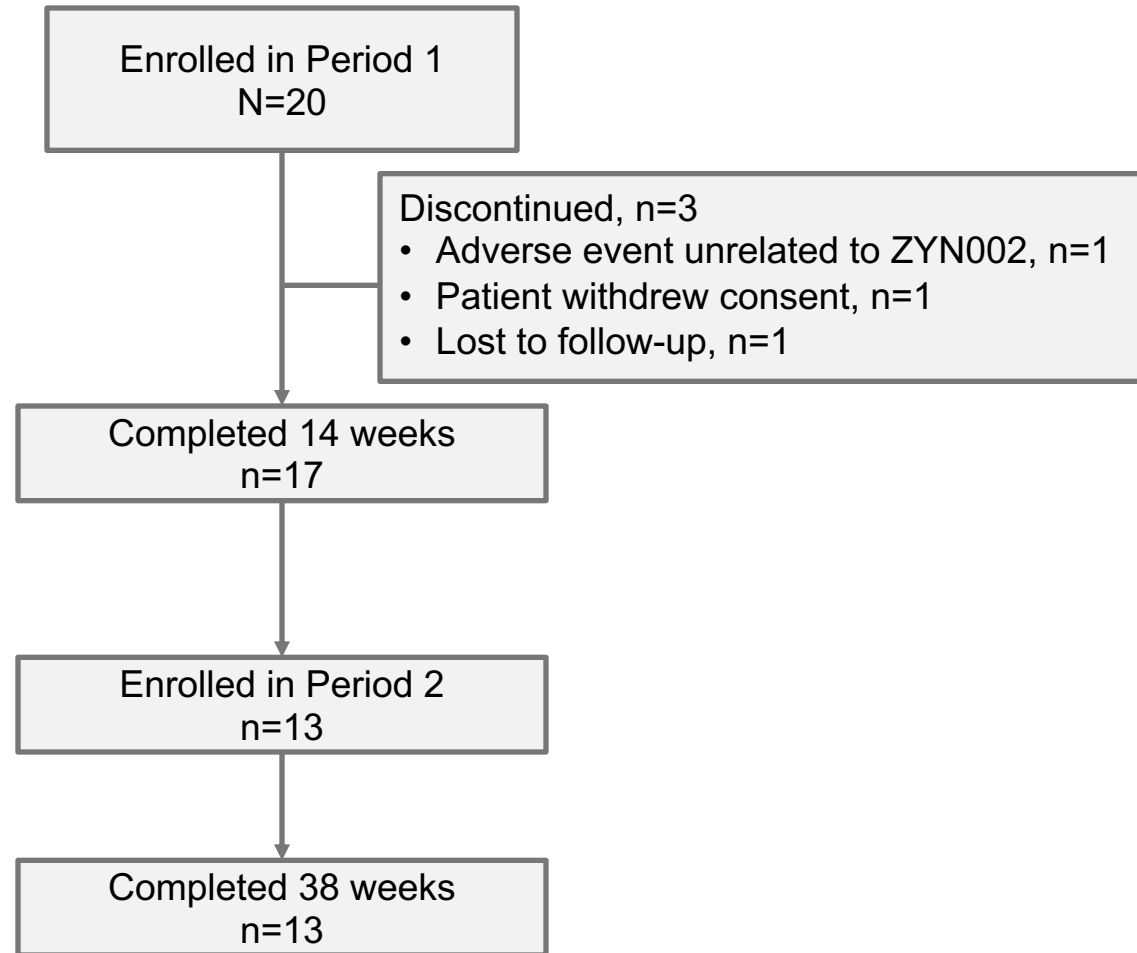


INSPIRE Phase 2 Trial Design

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



Patient Disposition



Baseline Demographics

	Period 1
N	20
Mean Age, years (range)	9.9 (4 to 15)
Sex, n (%)	
Male	12 (60.0)
Female	8 (40.0)
Race, n (%)	
White	18 (90.0)
Black or African American	1 (5.0)
Multiple	1 (5.0)
Median Weight (kg)	33.5
Range (min, max)	13.7, 79.8
Median BMI (kg/m ²)	17.9
Range (min, max)	13.4, 32.4

BMI, body mass index.



Select Disorders on Medical History at Baseline

Disorder on Medical History	n (%)
Congenital Disorders (eg aberrant aortic arch, cleft palate)	9 (45)
Ear and Labyrinth Disorder (eg conductive deafness)	8 (40)
Nervous System	12 (60)
Apraxia	2 (10)
Dyspraxia	1 (5)
Hypotonia	2 (10)
Intellectual Disability	5 (25)
Language Disorder	1 (5)
Sensory Processing Disorder	3 (15)
Speech Disorder Development	4 (20)
Psychiatric	16 (80)
Anxiety	6 (30)
Attention-Deficit Hyperactivity Disorder	6 (30)
Autism Spectrum Disorder (by history)	4 (20)
Behavior Disorder	2 (10)
Insomnia	5 (25)
Learning Disability	2 (10)
Obsessive-Compulsive Disorder	1 (5)
Separation Anxiety Disorder	1 (5)
Sleep Disorder	5 (25)

Autism Spectrum Disorder
By ADOS-2 at Screening
8 of 15 (53%) patients
assessed



Adverse Events and Safety Over 38 Weeks

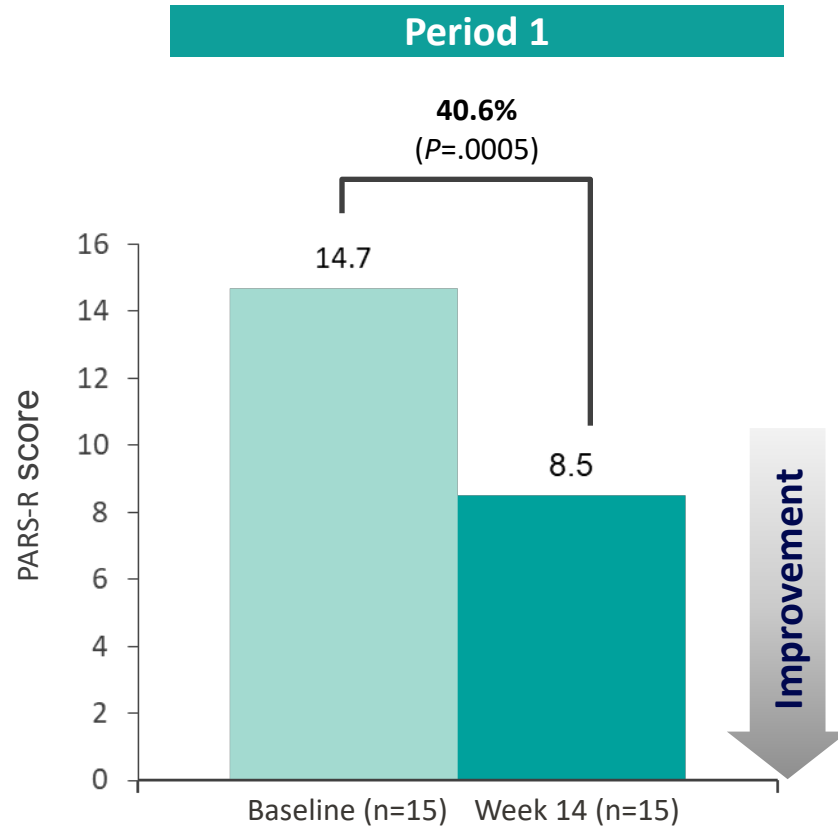
	Patients (n=20) % Patients (n patients or events)
Treatment-Emergent Adverse Events (TEAEs)^a	60% (12 patients; 28 events)
Mild in severity	85.7%
Treatment-Related AEs	15% (3 patients; 3 events)
Application site pain Application site itching <i>All were mild and transient</i>	10% (2 patients; 2 events) 5% (1 patient; 1 event)
Discontinuations due to TEAEs unrelated to ZYN002 (Worsening of ASD and ADHD on day 2)	1 patient
Serious AEs All unrelated to ZYN002 in Period 2 (hypocalcemia, testicular torsion, scrotal hematoma, lower respiratory tract infection)	4 (3 patients)
No clinically significant changes in laboratory, vital signs, or electrocardiograms	

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

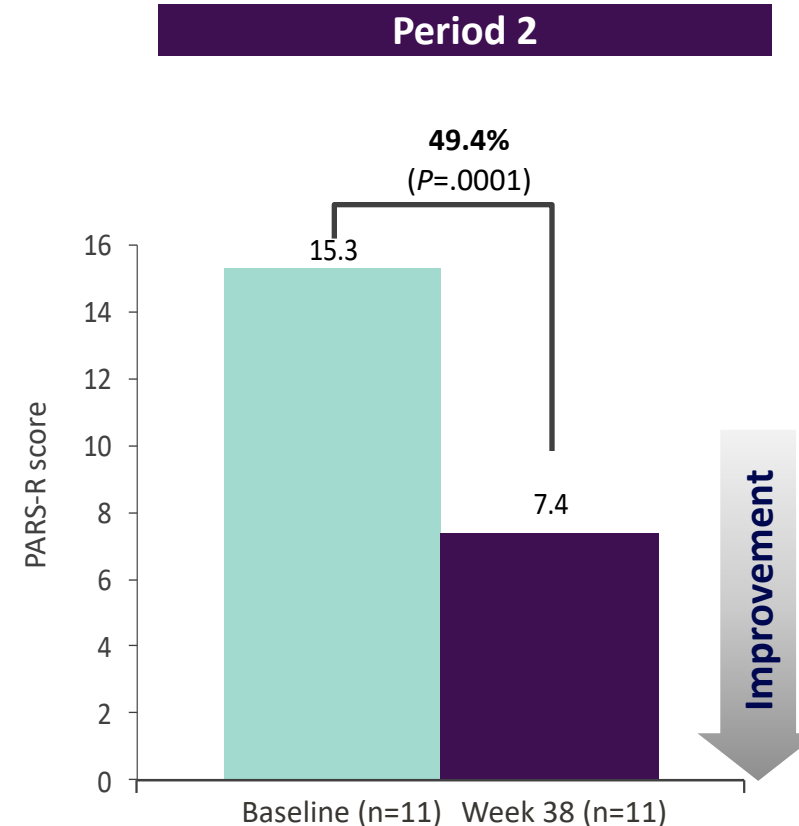


Significant Improvement from baseline in Anxiety as Measured by the PARS-R

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).



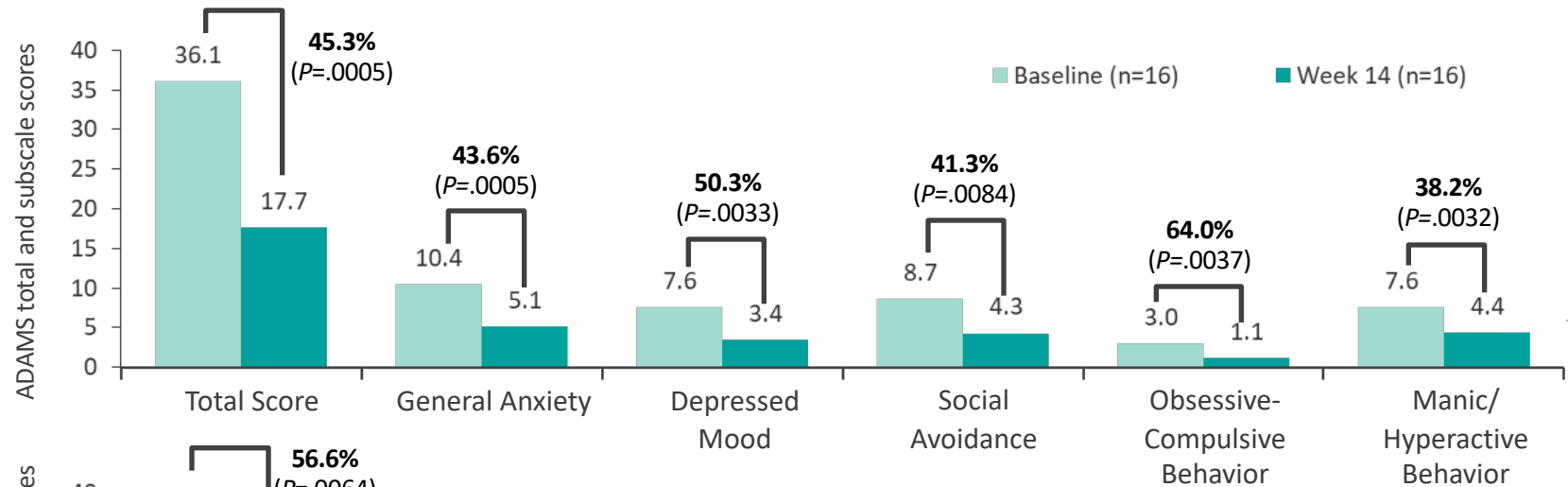
The efficacy analysis for Period 2 included 11 patients; 1 patient who completed Week 38 stopped drug prior to completion.



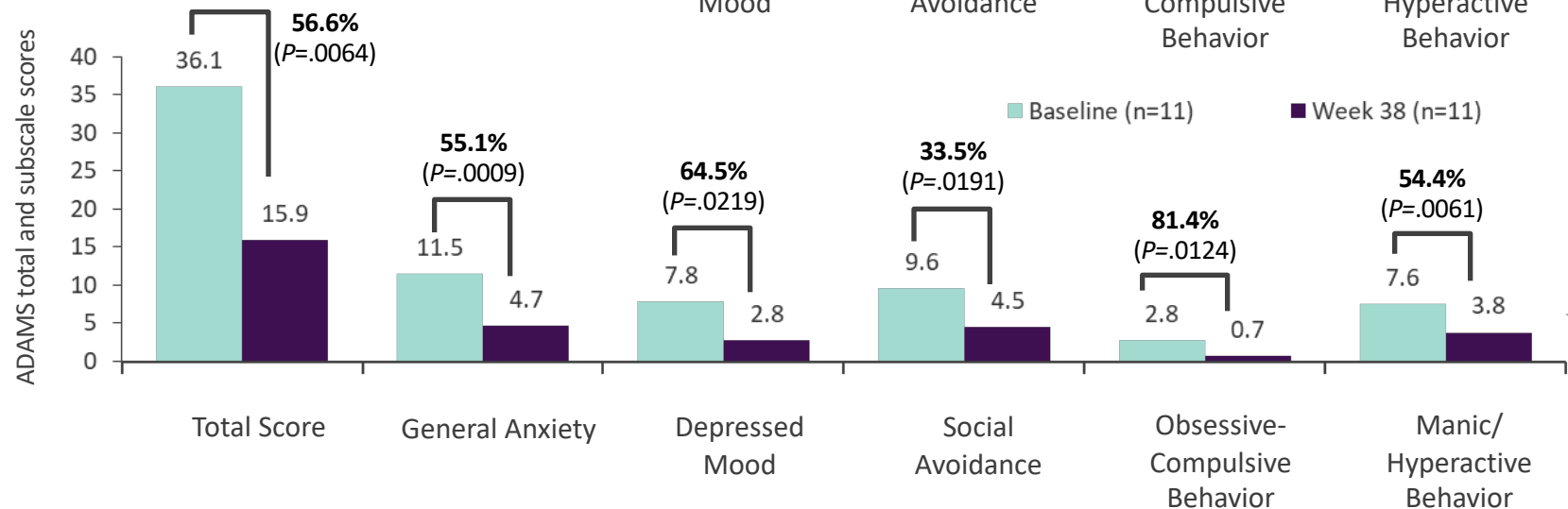
Significant Improvements from baseline in ADAMS Total Score and All Subscales

Mean Scores and Percentage Improvement

Period 1



Period 2



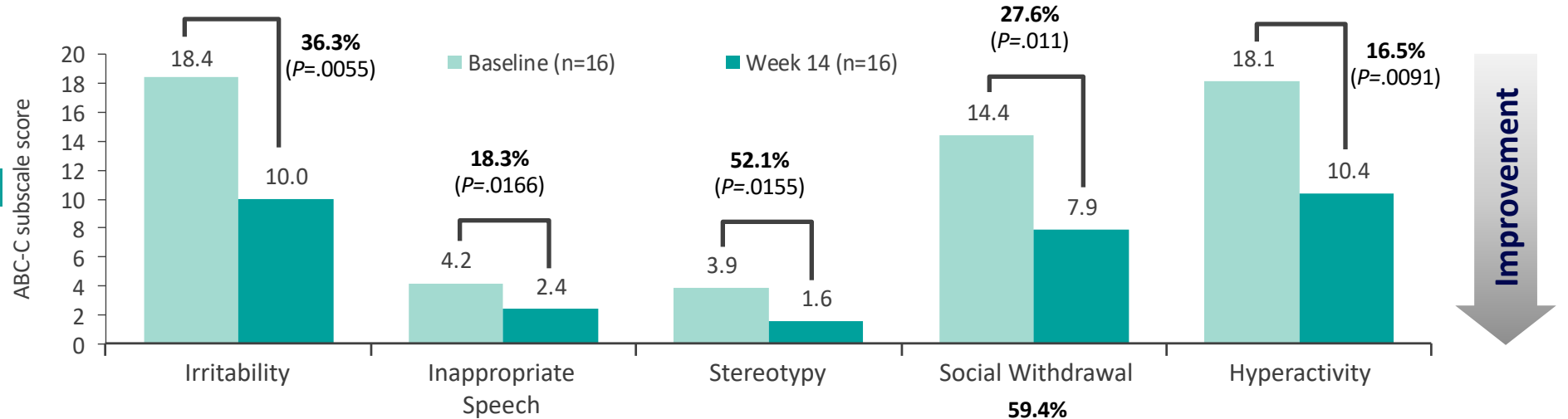
The efficacy analysis for Period 1 included 16 patients for ADAMS (1 patient did not have a valid assessment at Week 14).
 The efficacy analysis for Period 2 included 11 patients; 1 patient who completed Week 38 stopped drug prior to completion.
 Total Score and Obsessive/Compulsive Behavior N=10 as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



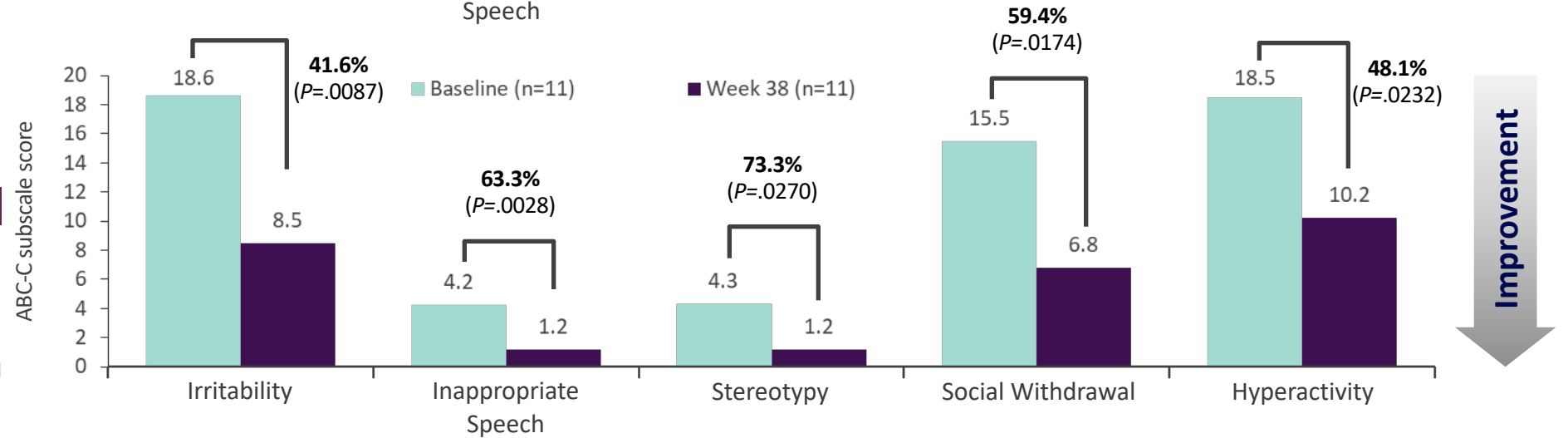
Significant Improvement from baseline in all ABC-C Subscale Scores

Mean Scores and Percentage Improvement

Period 1



Period 2

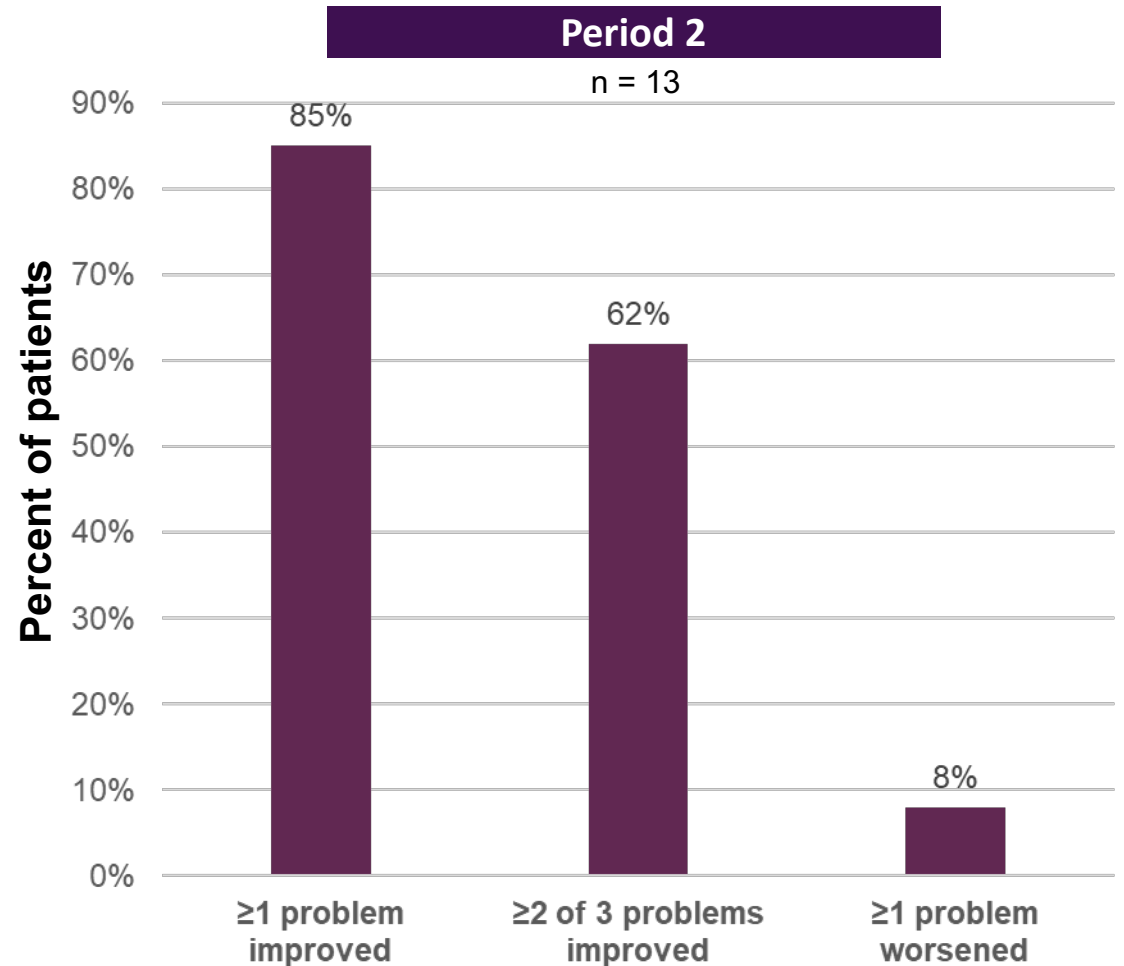
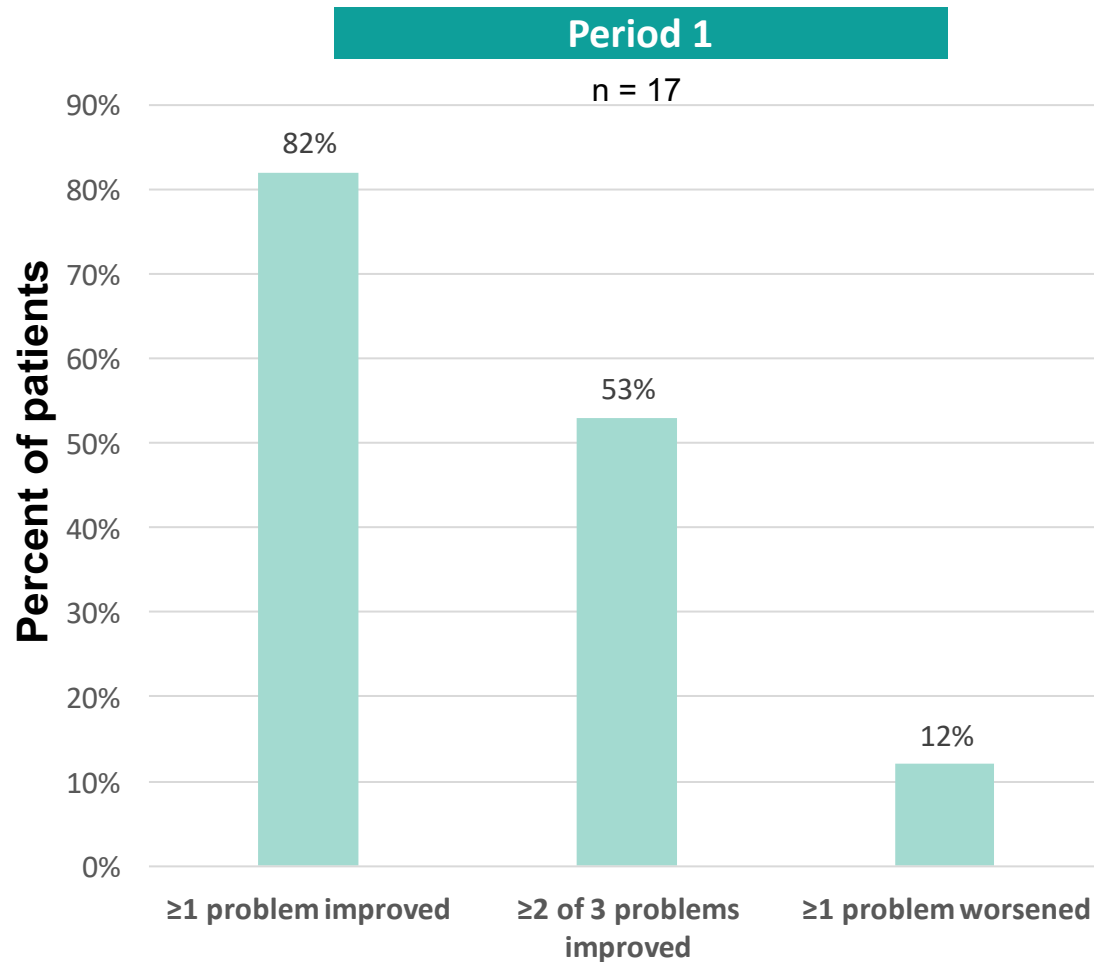


The efficacy analysis for Period 1 included 16 patients for ABC-C (1 patient did not have a valid assessment at Week 14).

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



Caregivers reported improvement in the most impactful self-identified behavioral, emotional, or social problems



Q: What are the three behavioral, emotional, or social problems that most impacted your son/daughter and his/her family in approximately the past year?



Conclusions

- INSPIRE provides initial evidence suggesting a positive risk-benefit profile for ZYN002 in improving anxiety-related and behavioral symptoms in children and adolescents with 22q when added to a stable standard of care of 38 weeks
- 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
- Caregivers reported improvement in the most impactful self-identified behavioral, emotional, or social problems
- These findings warrant further study of ZYN002 in children and adolescents with 22q

