

# An Open-Label, Tolerability and Efficacy Study of ZYN002 (Cannabidiol) Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome (INSPIRE)

Helen Heussler<sup>1</sup>, Jonathan Cohen<sup>2</sup>, Caroline Buchanan<sup>3</sup>, Carol O'Neill<sup>4</sup>, Terri Sebree<sup>4</sup>, Stephen O'Quinn<sup>4</sup>

<sup>1</sup>Centre for Clinical Trials in Rare Neurodevelopmental Disorders, Children's Health Queensland Hospital and Health Services, South Brisbane, Queensland, AU; <sup>2</sup>Genetic Clinics Australia, North Caulfield, Victoria, AU; <sup>3</sup>Greenwood Genetic Center, Greenville, SC, USA; <sup>4</sup>Zynerba Pharmaceuticals, Devon, PA, USA



# 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, Jonathan Cohen, and Caroline Buchanan have received research support from Zynerba Pharmaceuticals. Carol O'Neill, Terri Sebree, 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 syndrome<sup>1</sup>
- 22q occurs in 1 in 3000 to 1 in 6000 live births<sup>2</sup>
- 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)<sup>3</sup>

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 disorder<sup>1</sup>
  - Specific phobias are most common, followed by generalized anxiety disorder, separation anxiety, and obsessive compulsive disorder<sup>2</sup>
- Early negative experience has been shown to increase the risk of anxiety and is associated with atypical development of the physiological stress response<sup>3</sup>
  - 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 body<sup>4</sup>
- The presence of anxiety symptoms in children with 22q11.2DS is negatively correlated with adaptive function and impacts everyday living skills<sup>5</sup>

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.

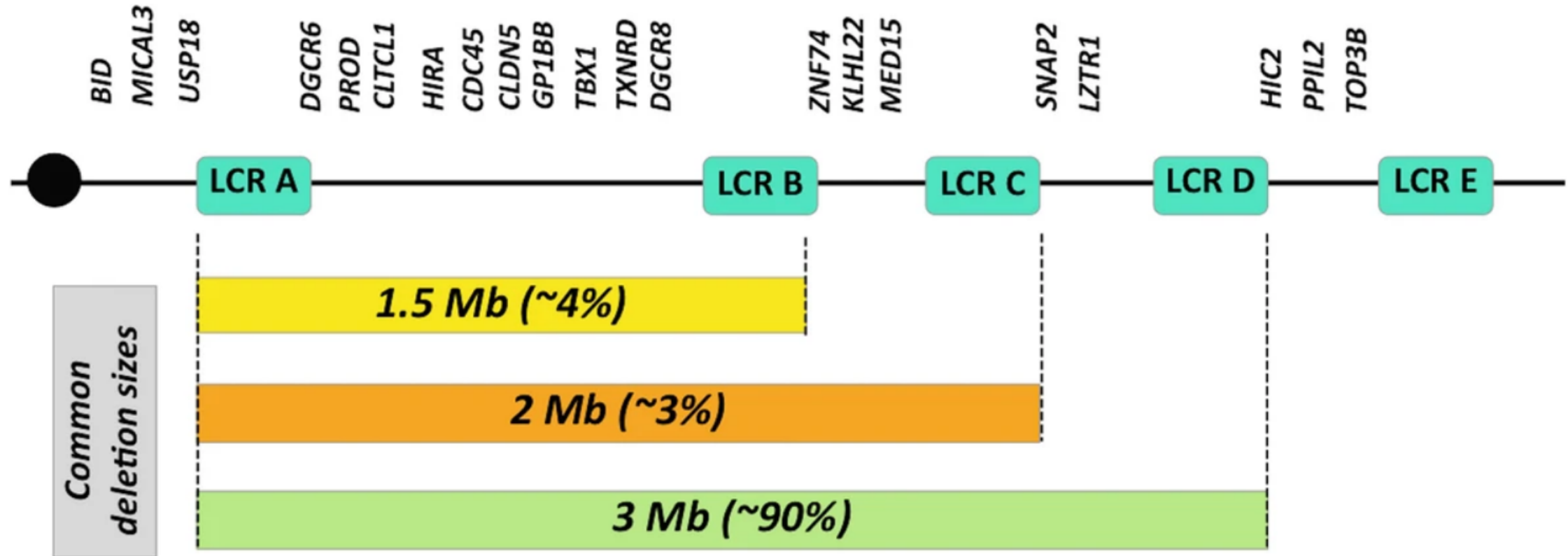
4. Beaton EA, Simon TJ. *J Neurodev Disord.* 2011; 3(1):68-75.

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 disorders<sup>1</sup>
- Cannabidiol acts as a negative allosteric modulator at presynaptic CB<sub>1</sub> receptors<sup>2</sup>
- Cannabidiol has also shown activity at serotonin 5HT<sub>1A</sub>,<sup>3</sup> GABA<sub>A</sub>,<sup>4</sup> and dopamine D<sub>2</sub> and D<sub>3</sub><sup>5,6</sup> receptors
- ZYN002 is a pharmaceutically produced (not plant-derived) cannabidiol transdermal gel in clinical development for the treatment of behavioral symptoms associated with 22q, Fragile X Syndrome (FXS), and ASD
- ZYN002 does not contain THC and avoids conversion to THC in the stomach<sup>7</sup>

CB<sub>1</sub>, cannabinoid receptor 1; ECS, endocannabinoid system; FXS, Fragile X syndrome; GABA, gamma-aminobutyric acid; THC, tetrahydrocannabinol.

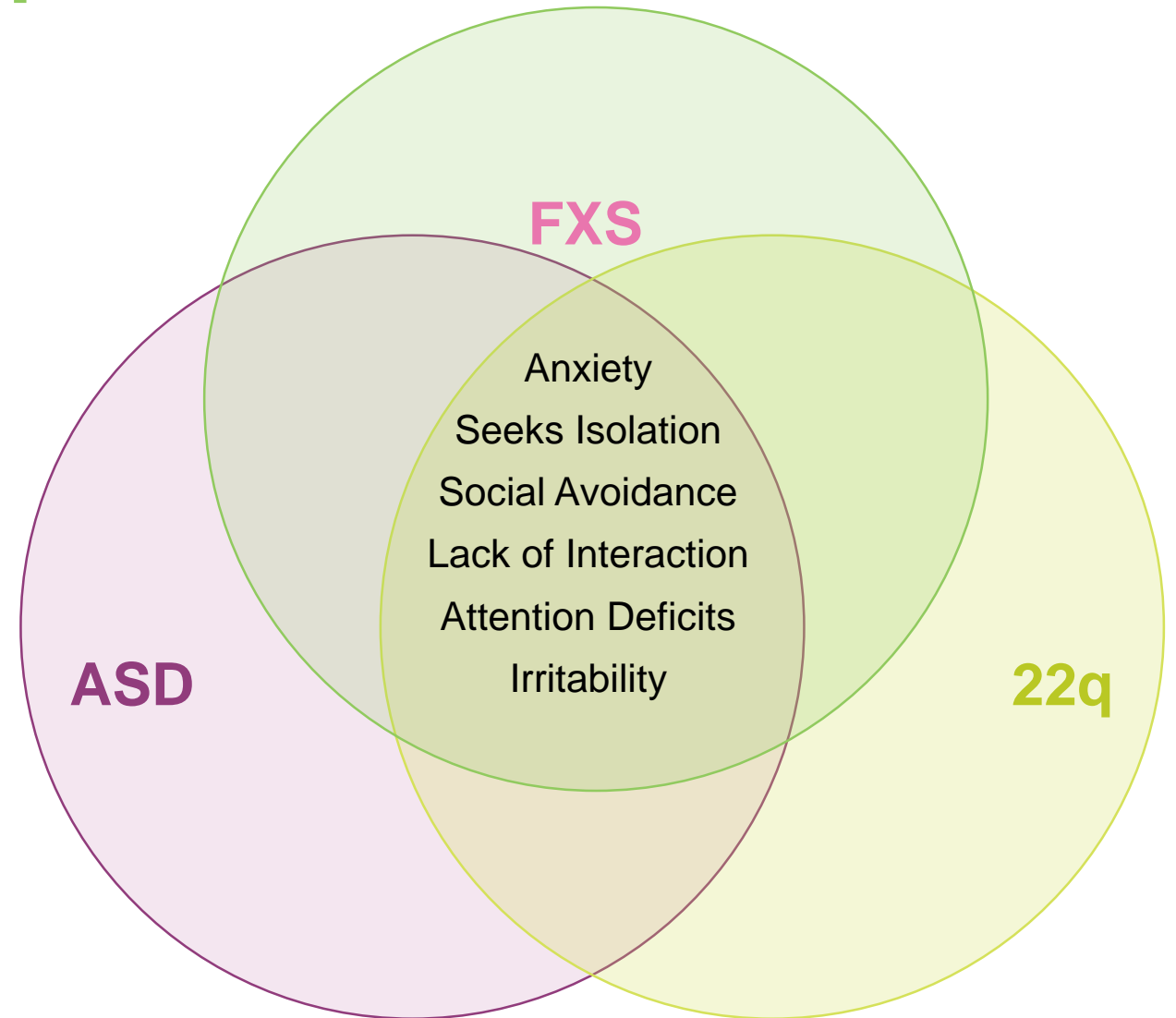
1. Cheung KAK, et al. *Front Psychiatry*. 2021;12:643442.  
2. Laprairie RB, et al. *Br J Pharmacol*. 2015;172(20):4790-4805.  
3. Russo EB, et al. *Neurochem Res*. 2005;30(8):1037-1043.

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.



# Why Study ZYN002 in 22q?

- Anxiety and a constellation of behavioral symptoms are similar between 22q, FXS, and ASD<sup>1</sup>
- ZYN002 has been shown to have potential benefit in FXS<sup>2</sup> and ASD<sup>3</sup>
- Dysfunction in the ECS may be present in all 3 disorders<sup>4</sup>
- ZYN002 does not contain THC, which may increase the risk for schizophrenia,<sup>5</sup> and should be avoided in individuals with 22q, who are at increased risk of schizophrenia<sup>6</sup>



1. Heussler H, et al. 22nd SSBP International Research Symposium, September 4-6, 2019.

2. Heussler H, et al. *J Neurodev Disord*. 2019;11(1):16.

3. Heussler H, et al. 23rd SSBP International Research Symposium, September 9-10, 2021.

4. Cheung KAK, et al. *Front Psychiatry*. 2021;12:643442.

5. Vaucher, J, et al. *Mol Psychiatry* 2018. 23, 1287–1292.

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



# 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  $\geq 4$  at Screening and Visit 2 (Day 1)
  - Pediatric Anxiety Rating Scale-Revised (PARS-R) score of  $\geq 10$  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  $\leq 35$  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  $\leq 35$  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)

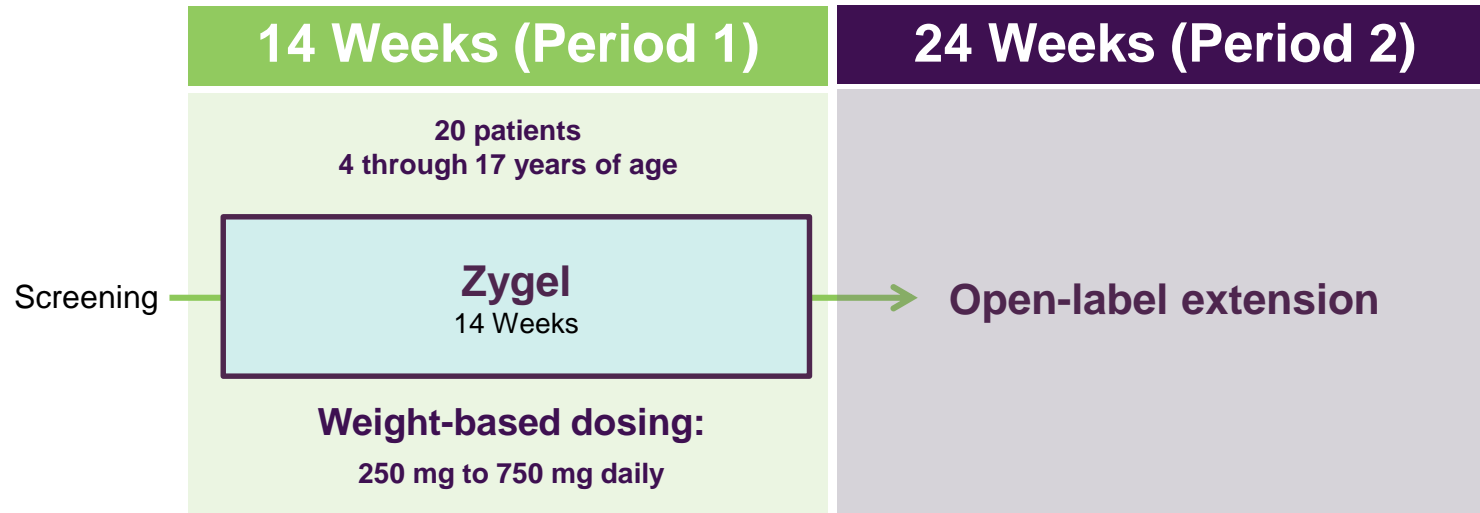




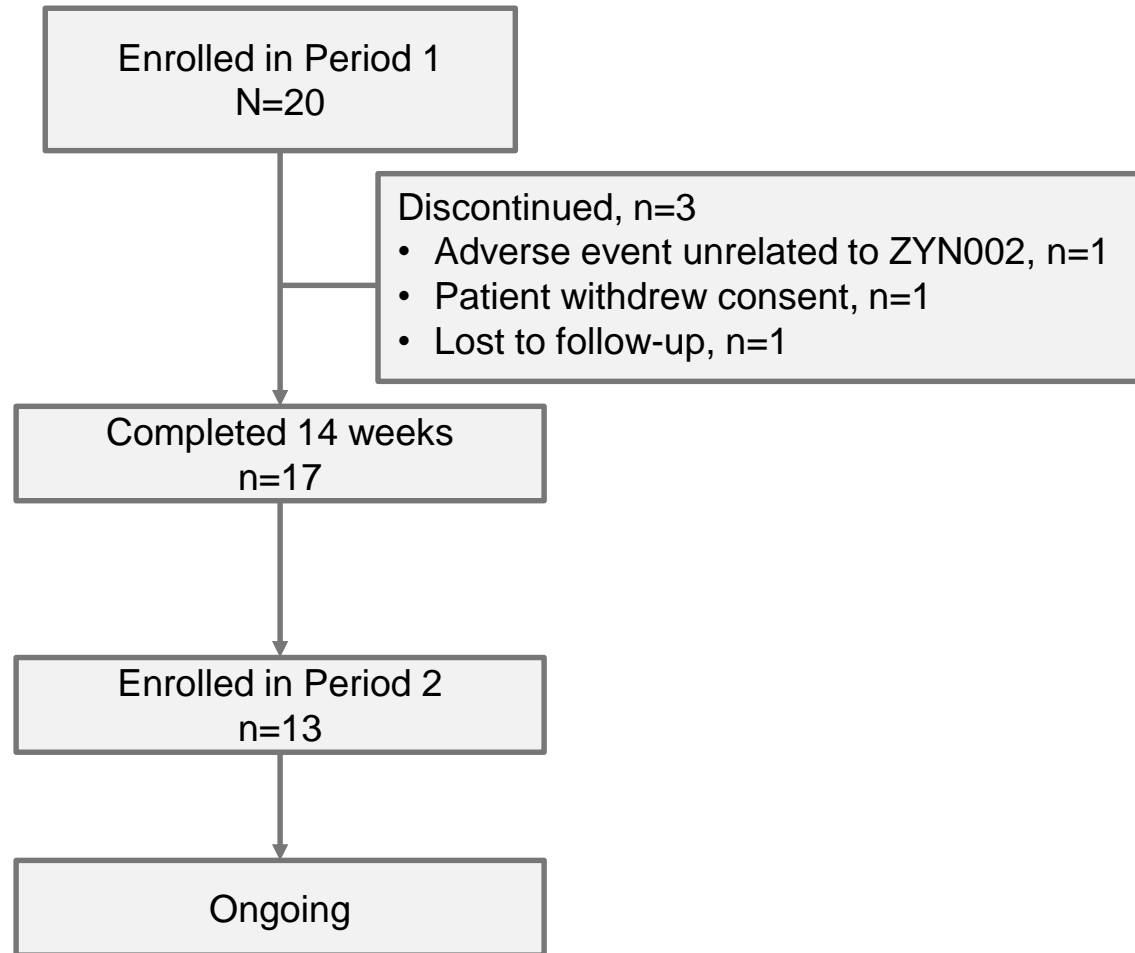
# INSPIRE Phase 2 Trial Design

Assessing the Impact of Zygel (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 <sup>2</sup> )	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 (%)
<b>Congenital Disorders</b> (eg aberrant aortic arch, cleft palate)	<b>9 (45)</b>
<b>Ear and Labyrinth Disorder</b> (eg conductive deafness)	<b>8 (40)</b>
<b>Nervous System</b>	<b>12 (60)</b>
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)
<b>Psychiatric</b>	<b>16 (80)</b>
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: Period 1

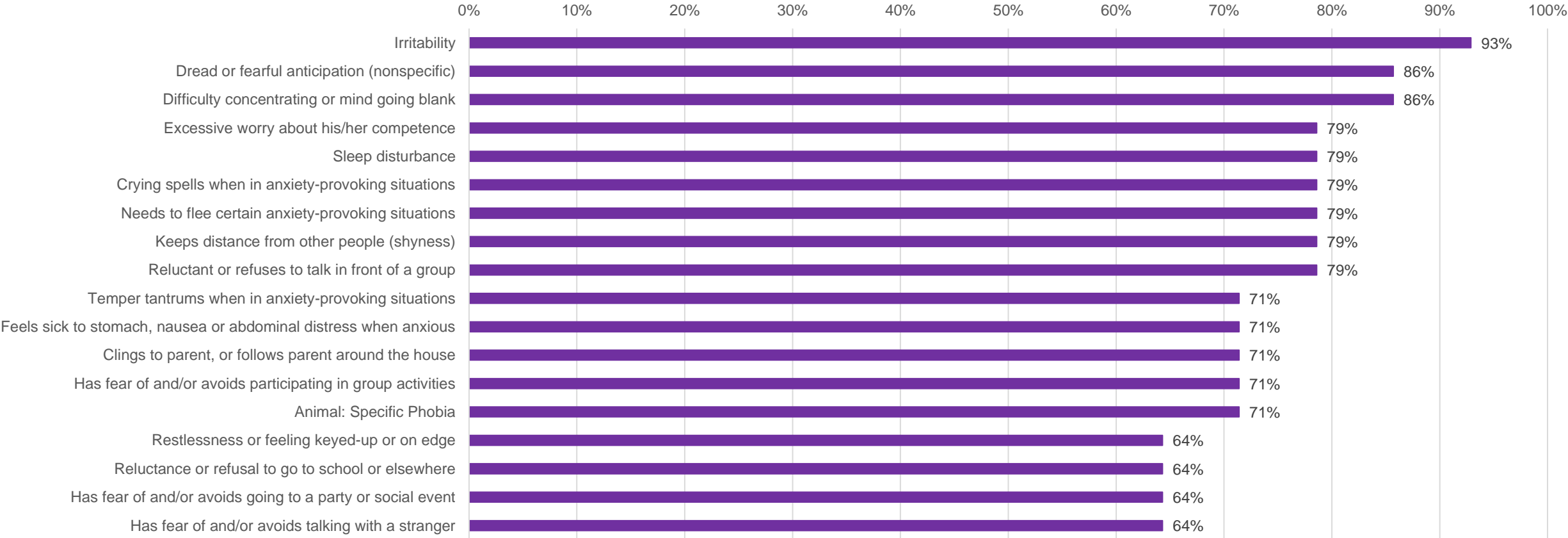
Adverse Event Type	Patients (n=20) % Patients (n patients or events)
<b>Treatment Emergent Adverse Events (TEAEs)</b>	35% (7 patients; 13 events)
Mild in severity	100%
<b>Treatment-Related TEAEs</b>	15% (3 patients; 3 events)
Application site pain	10% (2 patients; 2 events)
Application site itching	5% (1 patient; 1 event)
<i>Both were mild and transient</i>	
<b>Discontinuations due to TEAEs unrelated to ZYN002</b>	1 patient

- No clinically significant laboratory, vital signs, or ECG findings



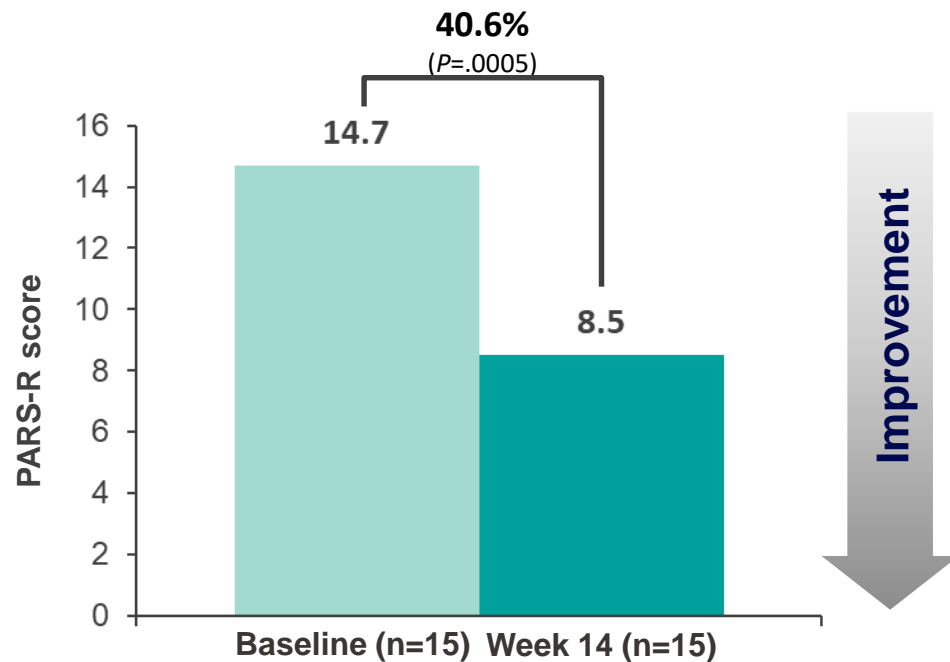
# Anxiety Symptoms at Baseline in 2/3 of Patients PARS-R Clinical Rater

PARS-R - Anxiety Symptoms at Baseline in Over 2/3 of Patients (by Clinical Rater)



# Efficacy: Significant Improvement in Anxiety as Measured by the PARS-R

## Mean PARS-R Scores and Percentage Improvement



- The PARS-R is a clinical interview that assesses symptoms of anxiety and generates a composite score for:
  - Overall frequency of anxiety symptoms
  - Overall severity of anxiety feelings
  - Overall avoidance of anxiety-provoking situations
  - Interference with family relationships and/or performance at home
  - Interference with peer and adult relationships and/or performance outside of home
- At Baseline, patients had **clinically significant moderate anxiety** on average (PARS-R=15)
- At Week 14, patients had improved to **minimal to mild anxiety** on average (PARS-R=5-10)

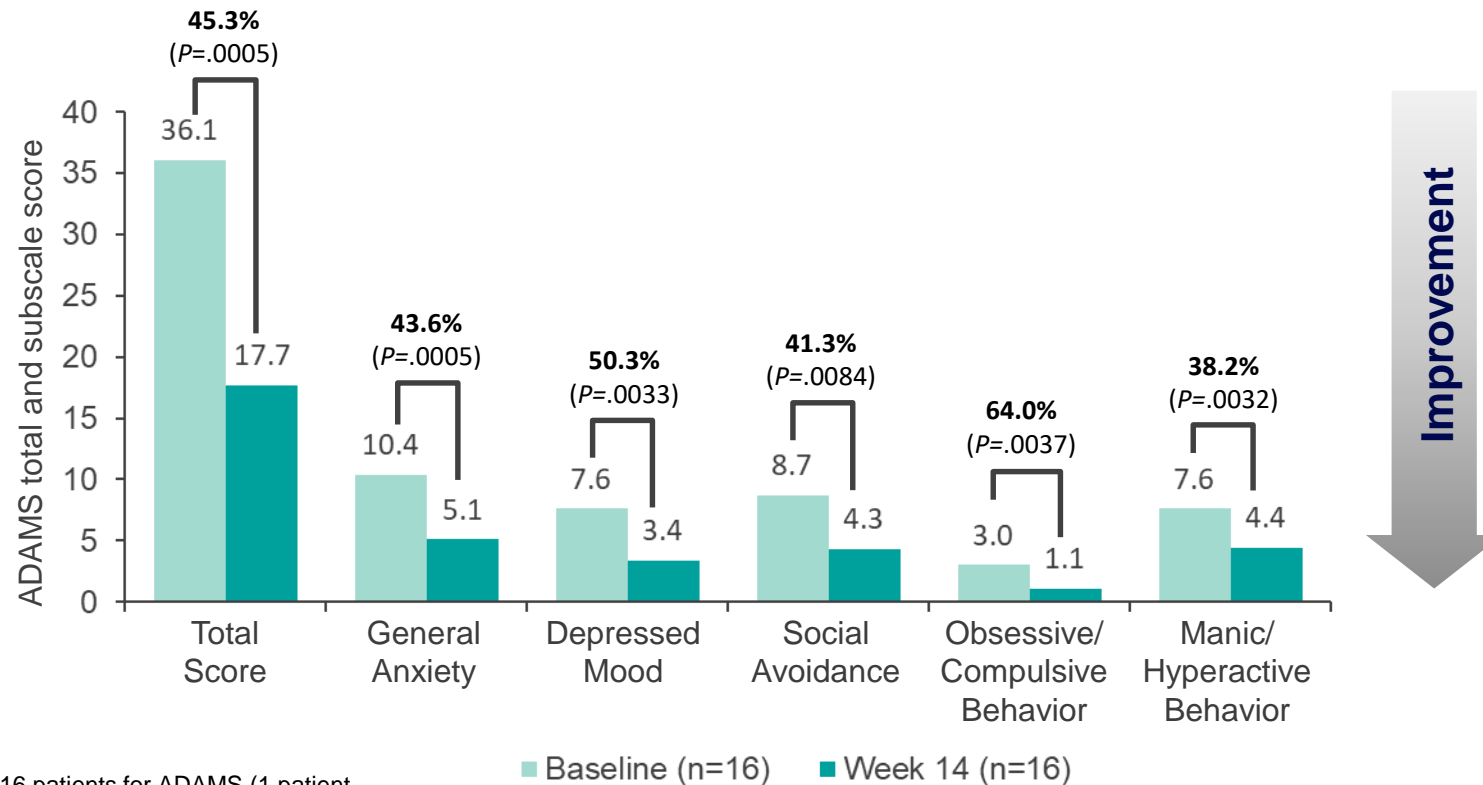
The efficacy analysis included 15 patients for PARS-R (2 patients did not have valid assessments at week 14).

PARS-R, Pediatric Anxiety Rating Scale-Revised.



# Efficacy: Significant Improvements in ADAMS Total and All Subscale Scores

Mean Scores and Percentage Improvement



The efficacy analysis included 16 patients for ADAMS (1 patient did not have a valid assessment at week 14).

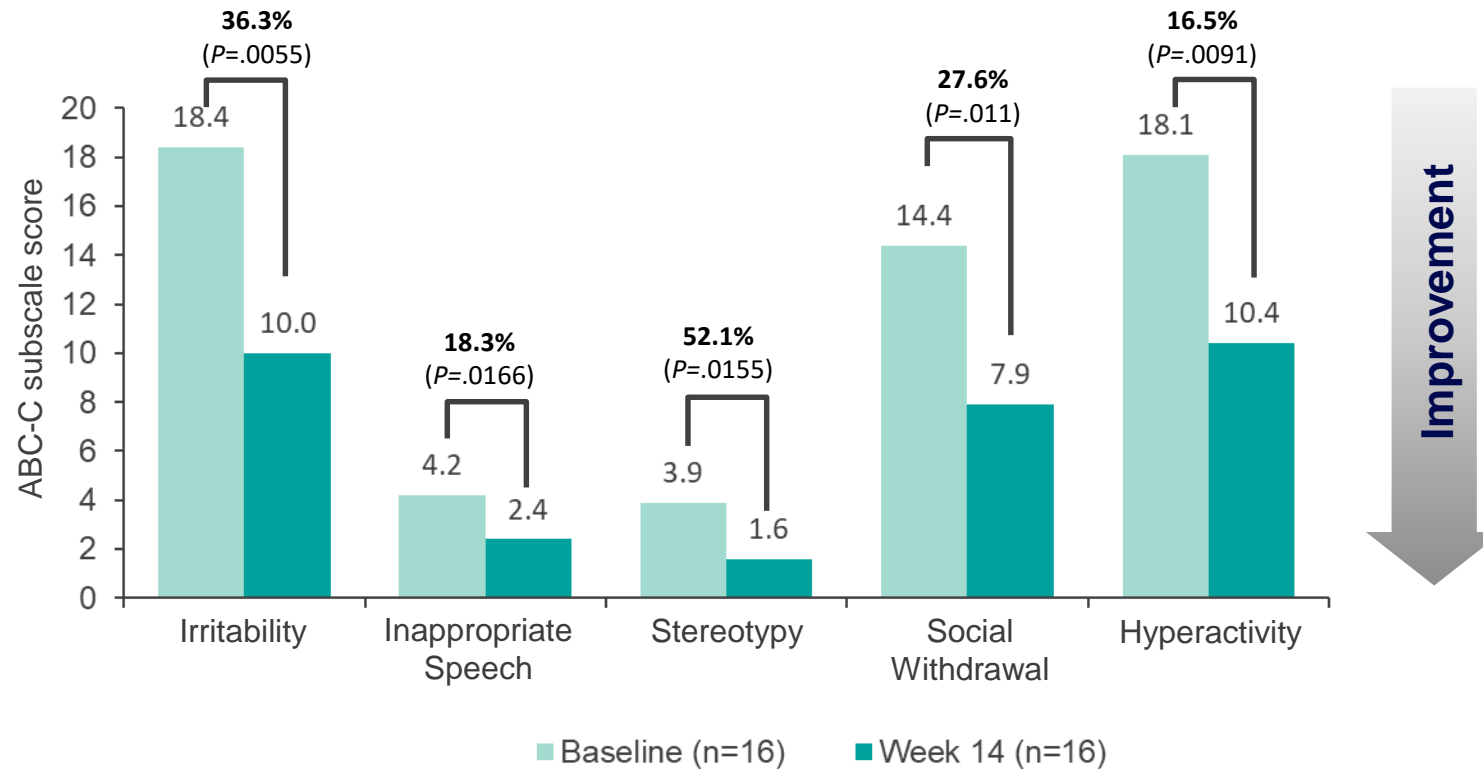
ADAMS, Anxiety, Depression, and Mood Scale.





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

Mean Scores and Percentage Improvement



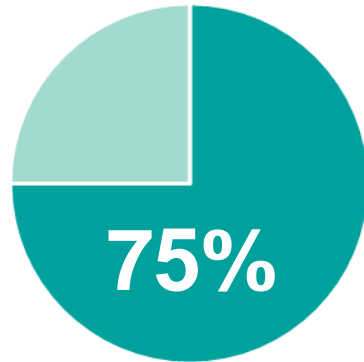
The efficacy analysis included 16 patients for ABC-C (1 patient did not have a valid assessment at week 14).

ABC-C, Aberrant Behavior Checklist-Community.

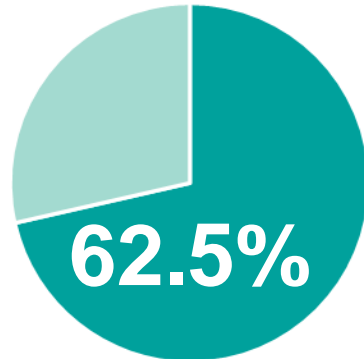


# Efficacy: Clinically Meaningful Improvements in CGI-I

## Clinician CGI-I Rating of Patients at Week 14 (n=16)



**Improved / Much Improved / Very Much Improved**  
Percentage of patients rated by clinicians as  
“improved,” “much improved,” or “very much improved”



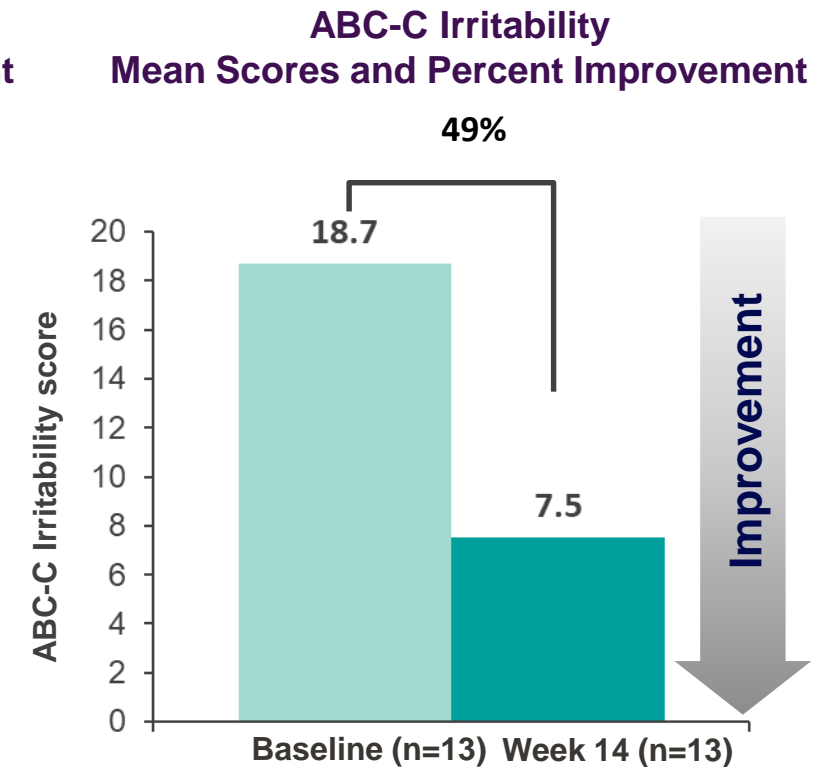
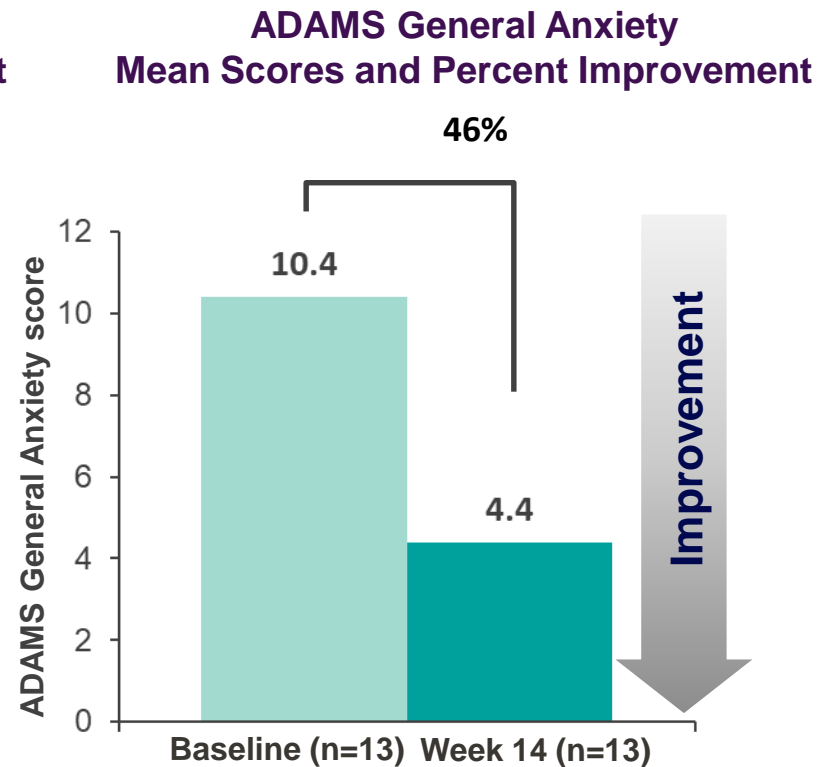
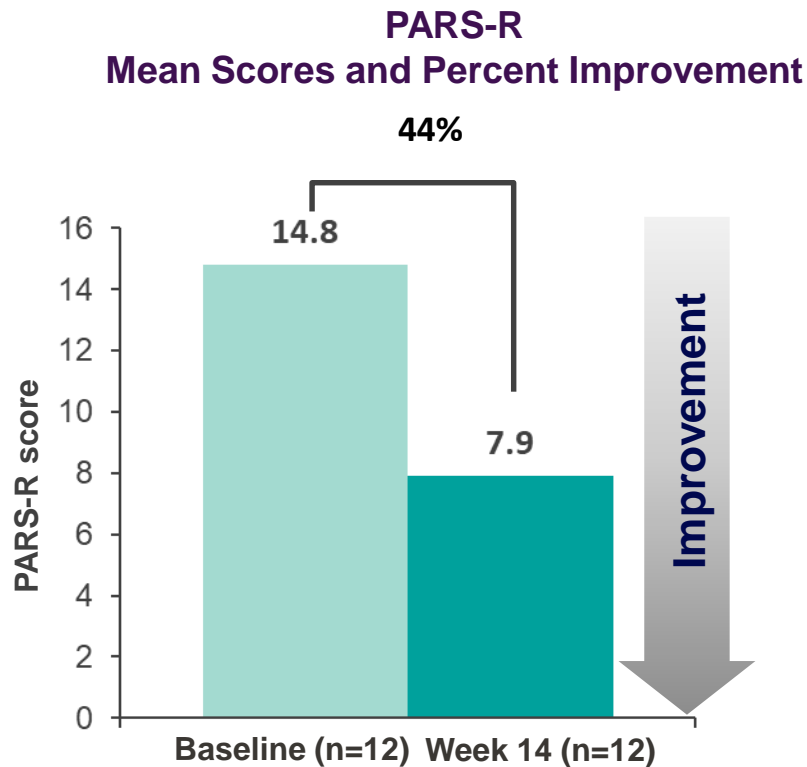
**Much Improved / Very Much Improved**  
Percentage of patients rated by clinicians as  
“much improved” or “very much improved”

The efficacy analysis included 16 patients for CGI-I (1 patient did not have a valid assessment at week 14).

CGI-I, Clinical Global Impression-Improvement.



# Patients Entering Period 2: Improvement in Anxiety as Measured by the PARS-R and ADAMS and Irritability Measured by the ABC-C



ABC-C, Aberrant Behavior Checklist-Community;  
ADAMS, Anxiety, Depression, and Mood Scale  
PARS-R, Pediatric Anxiety Rating Scale-Revised.

13 patients entered Period 2. The efficacy analysis included 12 patients for PARS-R (1 patients did not have valid assessments at week 14)



# Summary and 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
- Statistically significant improvements in:
  - PARS-R
  - Total score and all 5 subscales of ADAMS
  - All 5 subscales of ABC-C
- Clinically meaningful improvements in CGI-I ratings
- Well tolerated with a safety profile consistent with other ZYN002 clinical trials
- These findings warrant further study of ZYN002 in children and adolescents with 22q

