# Post Hoc Analysis—An Open-Label Study of Transdermal Cannabidiol (ZYN002) for the Treatment of Fragile X Syndrome in Children and Adolescents: Estimating Health State Utility Scores

### BACKGROUND

- Fragile X syndrome (FXS) is a rare genetic condition characterized by a range of developmental, neuropsychiatric, and behavioral symptoms<sup>1,2</sup> Approximate prevalence rates of FXS are 1 in 3600-4000 (males) and
- 1 in 4000-6000 (females)<sup>3</sup> • The spectrum and severity of FXS symptoms result in a high clinical, humanistic, and economic burden on patients and caregivers<sup>4-6</sup>
- Compared with matched non-FXS patients/families, patients with FXS and their caregivers experience significantly greater health care resource utilization and associated costs<sup>6</sup>
- FXS is often comorbid with other conditions such as autism spectrum disorder and attention-deficit hyperactivity disorder that further increase patient and family burden<sup>6,7</sup>
- ZYN002 cannabidiol (CBD) transdermal gel is an emerging potential therapeutic for FXS symptoms as the endocannabinoid system, an important modulator of emotion and social interaction, is impaired in preclinical models of FXS<sup>8,9</sup>
- ZYN002 is a pharmaceutically manufactured CBD transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS<sup>10</sup>
- Safety, tolerability, and efficacy of ZYN002 were evaluated in a 12-week, phase 2 open-label study (ZYN2-CL-009) in patients aged 6-17 years with FXS<sup>10</sup>
- ZYN002 treatment resulted in statistically significant improvements from screening at week 12 in mean Anxiety, Depression, and Mood Scale (ADAMS) total score (primary efficacy end point; t = -5.74, P < 0.001, d = 1.36) and in all ADAMS subscale scores except for depressed mood
- Statistically significant improvements from screening at week 12 were also observed for all 6 subscale scores of the Aberrant Behavior Checklist–Community for FXS (ABC- $C_{FYS}$ ; P < 0.05 for all; secondary end point)
- No serious adverse events (AEs) were reported, and while treatmentemergent AEs were reported by 85% of patients, most were mild (70%) and considered unrelated to treatment
- Health state utility indices are commonly employed in clinical and economic analyses of therapies with potential impact on health-related quality of life (HRQoL) and enable comparison of HRQoL across conditions<sup>11,1</sup>
- Health state utility is measured on a 0-1 scale in which 0 represents death and 1 represents complete health
- The Aberrant Behavior Checklist–Community Utility Index (ABC-UI)—a utility index specific to FXS—was derived from the ABC-C<sub>EVS</sub> to measure the HRQoL benefit of treatments for FXS<sup>13</sup>

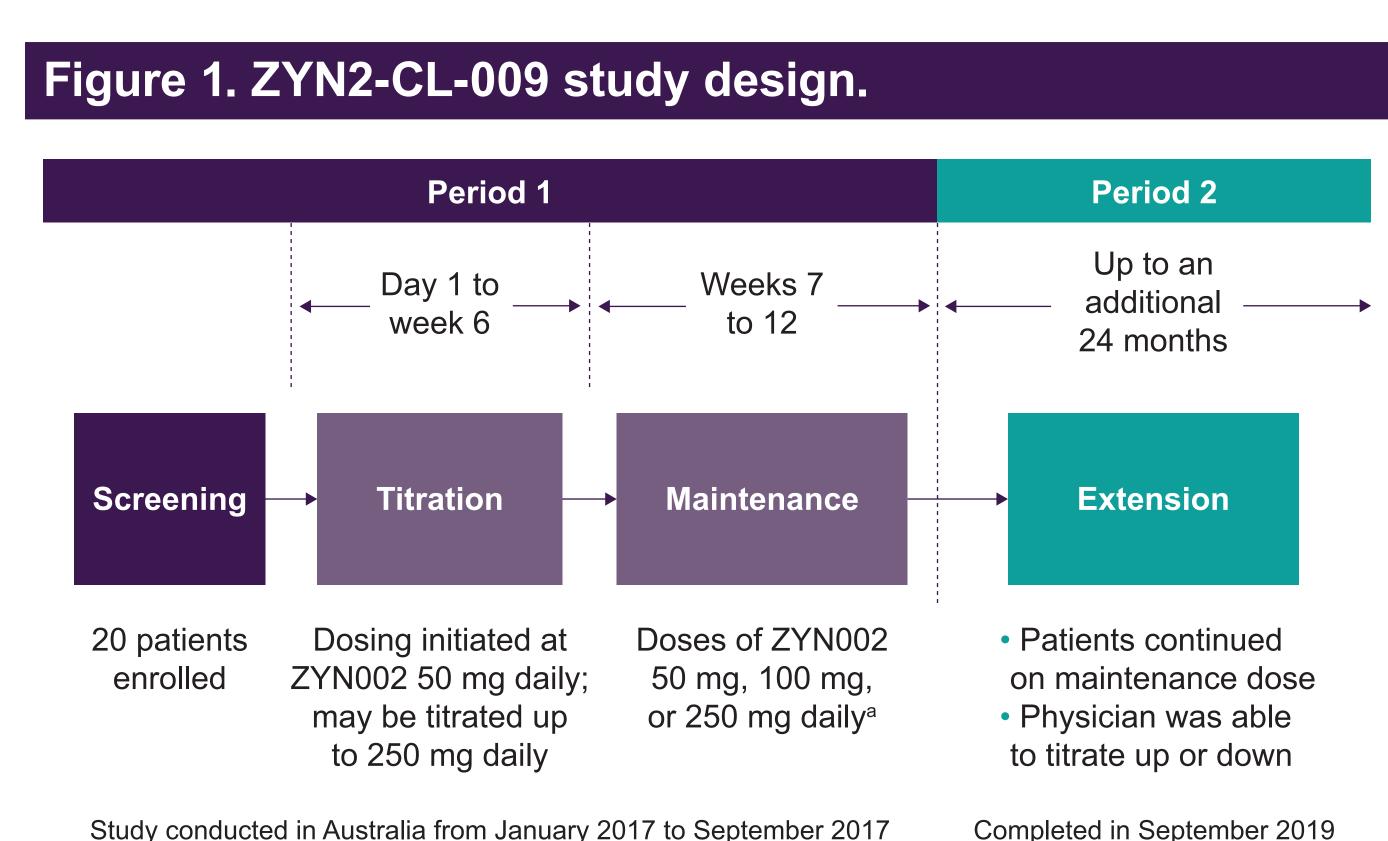
### OBJECTIVE

• To evaluate the potential benefit of ZYN002 on ABC-UI in pediatric and adolescent patients with FXS through post hoc analysis of ZYN2-CL-009

### METHODS

### **STUDY DESIGN AND TREATMENT**

• ZYN2-CL-009 was a multicenter, open-label, phase 2 study to evaluate the safety, tolerability, and efficacy of ZYN002 in pediatric and adolescent patients with FXS (Figure 1)



<sup>a</sup>Total daily dose, administered twice daily.

#### PATIENTS

- Key inclusion criteria
- Male and female patients aged 6-17 years
- Documented FXS diagnosis with full FMR1 mutation Pediatric Anxiety Rating Scale–Revised score (PARS-R) ≥11 Clinical Global Impression—Severity (CGI-S) score ≥3
- Key exclusion criteria
- Acute or progressive neurologic disorder other than FXS
- before screening

#### ASSESSMENTS

- Primary efficacy end point Change from baseline in Anxiety, Depression, and Mood Scale (ADAMS) at weeks 2, 4, 6, 8, 10, and 12
- Key secondary efficacy end points
- Change from baseline in ABC-C<sub>EYS</sub> at weeks 4, 8, and 12

#### **POST HOC ANALYSIS**

- Individual patient-level data from ZYN2-CL-009 were mapped to the ABC-UI algorithm to generate a utility index score for each patient
- items pertaining to the core symptom domains of FXS<sup>13</sup>:
- Irritability: ABC-C:4, "Aggressive to other children or adults (verbally
- or physically)" and ABC-C:36, "Mood changes quickly" Socially unresponsive/lethargic: ABC-C:58, "Shows few social reactions to others"
- or adults"
- Inappropriate speech: ABC-C:22, "Repetitive speech"
- ABC-UI score and change from screening are summarized by the 1-sample *t* test
- The correlation between ABC-UI and CGI-S scores at screening is summarized by Pearson correlation coefficient
- extremely ill" (score = 7)<sup>14</sup>

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- Use of more than 1 antipsychotic and 1 anti-anxiety medication Use of tetrahydrocannabinol or CBD-containing product ≤4 weeks

- Clinical Global Impression–Severity score at weeks 2, 4, 8, and 12

The ABC-UI algorithm calculates utility index score based on ABC-C<sub>EVS</sub>

 Stereotypy: ABC-C:35, "Repetitive hand, body, or head movements" Hyperactivity: ABC-C:13, "Impulsive (acts without thinking)"; ABC-C:15, "Restless, unable to sit still"; and ABC-C:44, "Being easily distractible" - Social avoidance: ABC-C:30, "Isolates him/herself from other children

descriptive statistics (mean and standard deviation), and the statistical significance of the change from screening at each visit was tested using

- CGI-S scores range from "normal" (score = 1) to "among the most

- To help contextualize the utility score in this rare genetic disease, utility scores (primarily Health Utility Index 2 [HUI2] and HUI3) reported in select published literature in other pediatric conditions were referenced
- HUI2 is a classification system consisting of 7 attributes including sensation, mobility, emotion, cognition, self-care, pain, and fertility (fertility is not currently used in the HUI2 questionnaire)<sup>15</sup>
- HUI3 is a classification system consisting of 8 attributes including vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain<sup>16</sup>

### RESULTS

#### PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS

 20 patients enrolled in the study, received treatment, and were included in the post hoc analysis (**Table 1**)

Table 1. Demographic and Disease Characteristics				
Demographic or Disease Characteristic	ZYN002-Treated Patients N = 20			
Age, years				
Mean (SD)	10.4 (3.88)			
Sex, n (%)				
Male	15 (75.0)			
Female	5 (25.0)			
Race, n (%)				
White	18 (90.0)			
Other	2 (10.0)			
CGI-S score				
n	19			
Mean (SD)	5.2 (1.38)			
PARS-R total severity score				
n	20			
Mean (SD)	21.4 (5.27)			
ADAMS total score				
n	20			
Mean (SD)	33.4 (14.18)			
ABC-C <sub>FXS</sub> score by factor, mean (SD)				
n	20			
Social avoidance	5.1 (3.29)			
Irritability	18.2 (12.12)			
Socially unresponsive/lethargic	8.7 (6.27)			
Inappropriate speech	6.1 (2.24)			
Stereotypy	7.9 (5.72)			
Hyperactivity	14.5 (8.96)			

ABC-C<sub>EVS</sub>, Aberrant Behavior Checklist–Community for FXS; ADAMS, Anxiety, Depression, and Mood Scale: CGI-S. Clinical Global Impression–Severity; PARS-R, Pediatric Anxiety Rating Scale Revised.

#### **ABC-UI SCORE AT SCREENING WITH REFERENCE TO LITERATURE DESCRIBING HUI IN OTHER CHILDHOOD CONDITIONS**

- The mean ABC-UI score at screening in patients enrolled in ZYN-CL-009 was 0.57 (SD, 0.16)
- Mean ABC-UI of 0.57 in patients with FXS enrolled in ZYN-CL-009 appears to reflect a poor baseline level of HRQoL, despite standard of care (Table 2, Figure 2)

#### Table 2. ABC-UI Score and Selected Published Utility Index Scores for Children and Adolescents by Condition

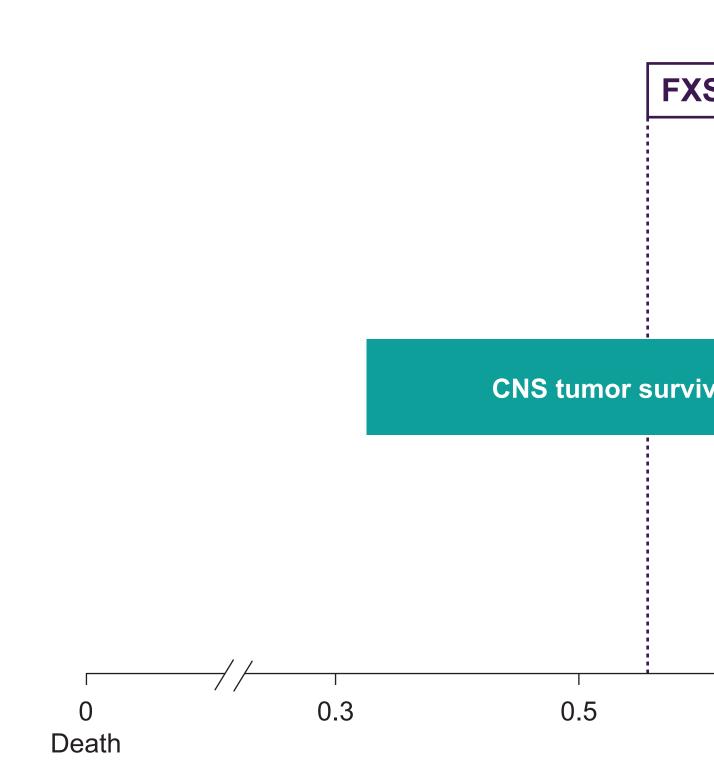
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Condition	Patient Age, mean, years	Utility Index	Source of QoL Information	Utility Index Score <sup>a</sup>
FXS	10.4	ABC-UI	Caregiver	Mean: 0.57
CNS tumor survivors ≥1 year from treatment completion <sup>17</sup>	10.5	HUI2 HUI3	<section-header></section-header>	HUI2 (mean) Patient: 0.78 Parent: 0.82 Physiotherapist: 0.85 Physician: 0.89 HUI3 (mean) Patient: 0.66 Parent: 0.72 Physiotherapist: 0.76 Physician: 0.83
CNS tumor survivors <0.1 to 8.6 years from treatment completion by disease status (no, residual, or recurrent disease) <sup>18</sup>	9.5	HUI2 HUI3		HUI2 (mean) No detectable disease: 0.89 Residual: 0.81 Recurrent: 0.56 HUI3 (mean) No detectable disease: 0.78 Residual: 0.56 Recurrent: 0.32
ALL survivors ≥1 year from treatment completion <sup>19</sup>	12.1	HUI3	Parent	Mean: 0.86
Type 1 diabetes with severe hypoglycemic event in past 12 months <sup>20</sup>	11.8	EuroQoL- 5D	Patient (adolescents) or parent (young children)	Median: 0.85
Children/adolescents receiving inpatient chemotherapy or outpatient care from rheumatology, hemophilia, or bone marrow transplantation clinics <sup>21</sup>	13.7	HUI2b HUI3b	Patient, parent	HUI2 (mean) Patient: 0.95 Parent: 0.82 HUI3 (mean) Patient: 0.92 Parent: 0.79

ABC-UI, Aberrant Behavior Checklist-Community Utility Index; ALL, acute lymphoblastic leukemia; CNS, central nervous system FXS, fragile X syndrome; HUI, health utility index

<sup>a</sup>Designation of patient, parent, pediatrician, physician, or physiotherapist in this column pertains to the rater of QoL.

<sup>b</sup>Utility indices based on the Standard Gamble. Visual Analogue Scale, and Time Trade-Off assessments were also reported. For comparative purposes, only data for HUI2 and HUI3 are shown.

## Figure 2. ABC-UI score at screening with reference to literature describing HUI in other childhood conditions. Hypoglycemia (0.85)<sup>20</sup> ALL survivors (0.86)<sup>19</sup> FXS (0.57) (0.79 - 0.9)**CNS tumor survivors<sup>18</sup> (0.32-0.89)** CNS tumor survivor (0.66-0.89)

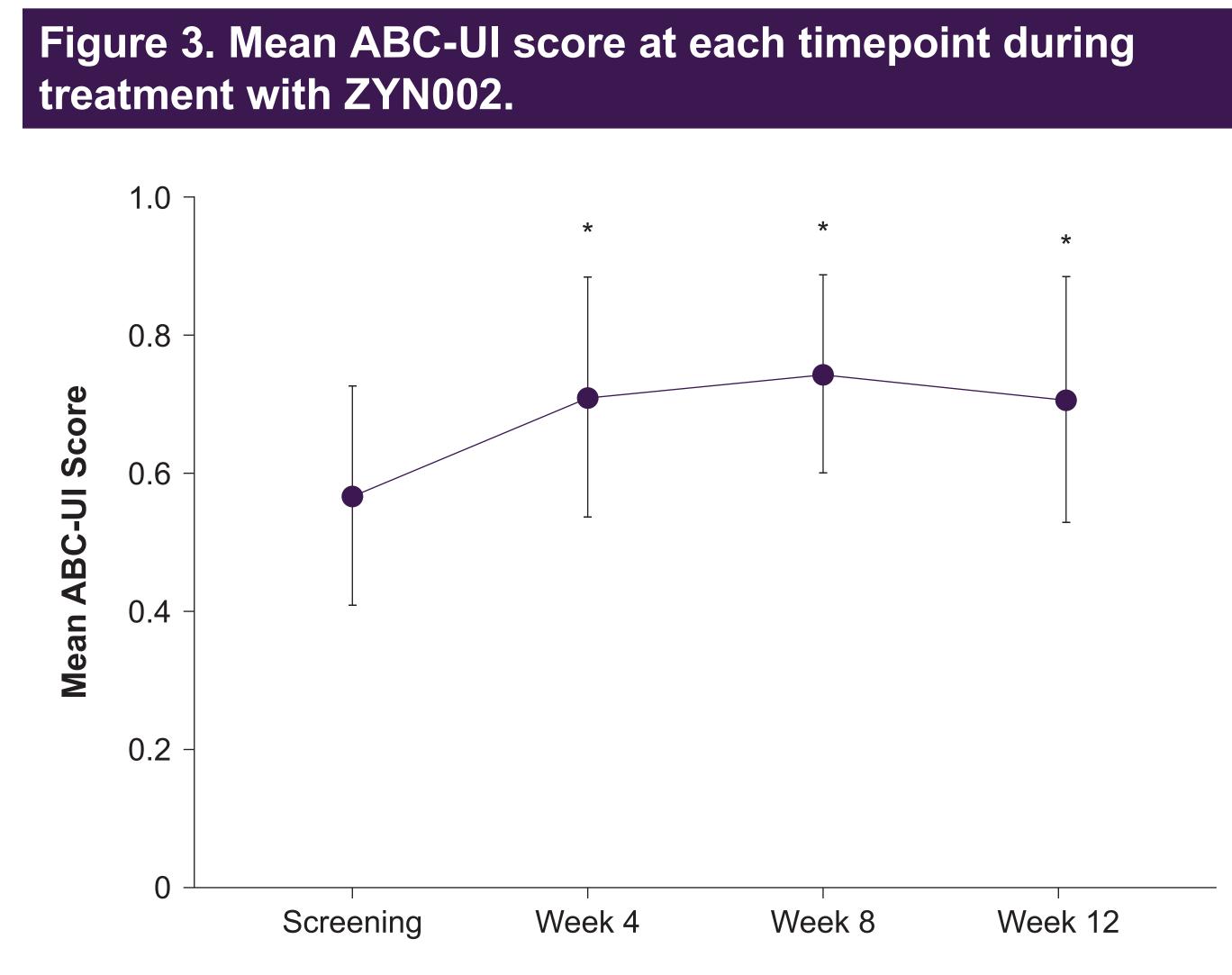


BC-UI, Aberrant Behavior Checklist–Community Utility Index; ALL, acute lymphoblastic leukemia; CNS, central nervous system; -XS, fragile X syndrome; HUI, health utility index; T1DM, type 1 diabetes mellitus. Jutpatient care was received from rheumatology, hemophilia, or bone marrow transplantation clinics

#### **IMPROVEMENT IN ABC-UI SCORE WITH ZYN002** TREATMENT

- Significant improvement from screening in mean ABC-UI with ZYN002 treatment was observed beginning at the first postscreening measurement (week 4, 0.14; SD, 0.13; *P* < 0.0001) and was maintained through weeks 8 (0.18; SD, 0.12; *P* < 0.0001) and 12 (0.14; SD, 0.17; *P* < 0.01) (**Figure 3**)
- Mean ABC-UI at week 12 was 0.71 (SD, 0.18)

# treatment with ZYN002.



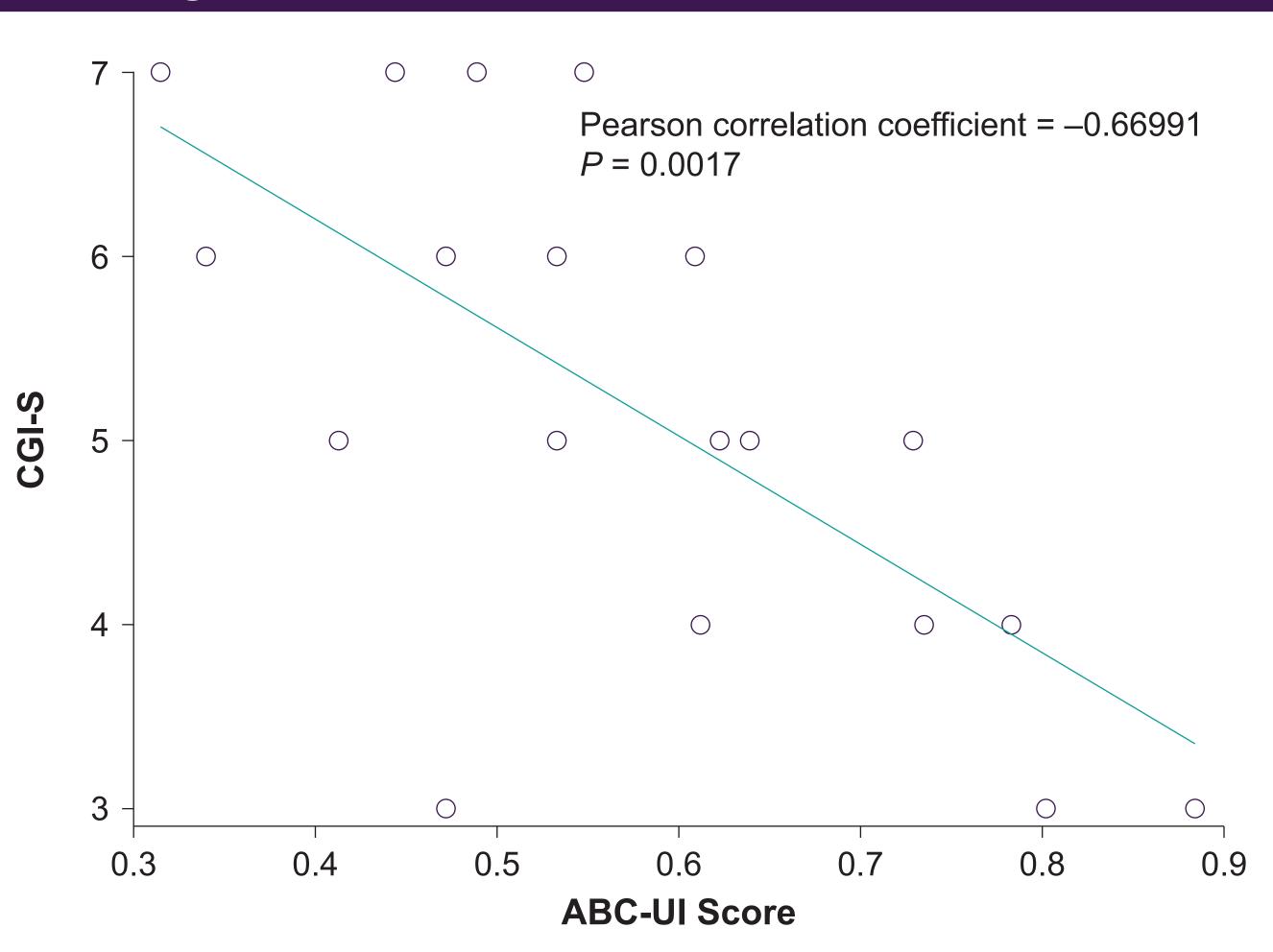
ABC-UI. Aberrant Behavior Checklist–Community Utility Index. \*P < 0.01 Data represent mean ± standard deviation

#### **Correlation of ABC-UI Score With the CGI-S Scale**

 ABC-UI score at screening was significantly correlated with CGI-S score ( $\rho = -0.67$ , P = 0.0017), suggesting that the ABC-UI score is a meaningful measure in FXS (Figure 4)

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#### Figure 4. Scatter plot of ABC-UI score and CGI-S score at screening.



ABC-UI, Aberrant Behavior Checklist–Community Utility Index; CGI-S, Clinical Global Impression–Severity.

### LIMITATIONS

• The ABC-UI, HUI2, and HUI3 may not be directly comparable, and direct comparisons have not been made

### CONCLUSIONS

- In this post hoc analysis, treatment with ZYN002 significantly improved health state utility index scores in pediatric and adolescent patients with FXS, suggesting a potential broad spectrum of activity of ZYN002 in the important domains of the ABC-C<sub>EVS</sub> that were incorporated into the utility index
- The correlation of the ABC-UI scores with CGI-S scores in these patients suggests that the ABC-UI appropriately reflects symptom severity in FXS
- Health state utility index score of 0.57 in patients with FXS enrolled in ZYN2-CL-009 appears to describe a poor baseline level of HRQoL, despite standard of care, highlighting the considerable impact of FXS symptoms on patient HRQoL

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