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

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Background

- ZYN002 is a pharmaceutically manufactured CBD transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS.

- 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.

- Health state utility indices are commonly employed in clinical and economic analyses of therapies with potential impact on HRQoL and enable comparison of HRQoL across conditions.
  - Health state utility is measured on a 0-1 scale in which 0 represents death and 1 represents complete health.
  - The ABC-UI—a utility index specific to FXS—was derived from the ABC-CFXS to measure the HRQoL benefit of treatments for FXS.

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.
**ZYN2-CL-009 Study Design & Post Hoc Analysis**

- **ZYN-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.

  **Key Inclusion Criteria**
  - Male or female patients aged 6-17 years
  - Documented FXS diagnosis with full *FMR1* mutation
  - PARS-R score ≥11
  - CGI-S score ≥3

**Post Hoc Analysis**
- Individual patient-level data from ZYN-CL-009 were mapped to the ABC-UI algorithm to generate a utility index score for each patient.
- **ABC-C<sub>FXS</sub>** items included in the ABC-UI algorithm:\(^1\)

  **Social avoidance**
  - ABC-C:30, “Isolates him/herself from other children or adults”

  **Irritability**
  - ABC-C:4, “Aggressive to other children or adults (verbally or physically)”
  - ABC-C:36, “Mood changes quickly”

  **Socially unresponsive/lethargic**
  - ABC-C:58, “Shows few social reactions to others”

  **Inappropriate speech**
  - ABC-C:22 “Repetitive speech”

  **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”
  - ABC-C:44, “Being easily distractible”

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\(^1\)Total daily dose, administered twice daily. ABC-C<sub>FXS</sub>, Aberrant Behavior Checklist–Community for FXS; ABC-UI, Aberrant Behavior Checklist–Community Utility Index; CGI-S, Clinical Global Impression–Severity; FMR1, Fragile X Mental Retardation; FXS, fragile X syndrome; PARS-R, Pediatric Anxiety Rating Scale–Revised.

ABC-UI Score at Screening and Reference to Other Conditions

- 20 patients enrolled in the study, received treatment, and were included in the post hoc analysis
- The mean age was 10.4 (SD, 3.88) and most patients were male (75.0%) and white (90.0%)
- The mean ABC-UI score at screening was 0.57 (SD, 0.16)

Mean ABC-UI score of 0.57 in patients with FXS enrolled in ZYN2-CL-009 appears to reflect a poor baseline level of HRQoL, despite standard of care.

ABC-UI Score at Screening With Reference to Literature

Describing HUI in Other Childhood Conditions

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ABC-UI, Aberrant Behavior Checklist–Community Utility Index; ALL, acute lymphoblastic leukemia; CNS, central nervous system; FXS, fragile X syndrome; SD, standard deviation; T1DM, type 1 diabetes mellitus.

Significant improvement with treatment in ABC-UI was observed at the first postscreening assessment and was maintained through week 12 (mean ABC-UI at week 12, 0.71; SD, 0.18).

ABC-UI score at screening was significantly correlated with CGI-S score, suggesting that the ABC-UI is a meaningful measure in FXS.
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

• 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

• The estimated 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