Cannabidiol Transdermal Gel for the Treatment of Fragile X Syndrome: Post Hoc Analysis of FAB-C and Pattern of Efficacy on Domains of the Aberrant Behavior Checklist-Community for FXS (ABC-C_{FXS}) Through 116 Weeks of Treatment

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BACKGROUND

- Fragile X syndrome (FXS) is a rare genetic condition involving a range of developmental, neuropsychiatric, and behavioral symptoms that are insufficiently managed by the current standard of care (including behavioral and educational interventions, dietary modifications, and off-label prescription therapies)[1-5]
- Cannabidiol (CBD), the main nonеuphoric component of the *Cannabis* plant, may provide therapeutic benefit in FXS through its effects on the endocannabinoid system, which is dysregulated in animal models of FXS[4]
- ZYN002 is a pharmaceutically manufactured CBD transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS[5]
- In a 12-week, phase 2 open-label study (ZYN2-CL-009, FAB-C) in patients aged 6-17 years with FXS, ZYN002 was well-tolerated and demonstrated efficacy in measures of behavioral symptoms and anxiety[5]
- The ABC-C_{FXS} was developed as an outcome measure for clinical trials in FXS and measures core behavioral symptoms across 6 subscales (social avoidance, irritability, socially unresponsive/lethargic, hyperactivity, stereotypy, and inappropriate speech)[6]
  - An improvement of at least 25% in individual domains of the ABC-C_{FXS} is considered an important criterion in defining responder status in contemporary studies[7]

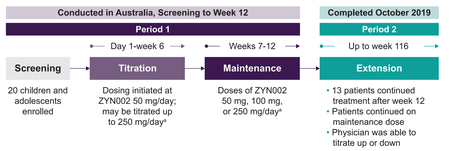
OBJECTIVE

- To evaluate the pattern of clinical efficacy of ZYN002 in the treatment of FXS across ABC-C_{FXS} domains through post hoc analysis of ZYN2-CL-009 (FAB-C) through 116 weeks

METHODS

- ZYN2-CL-009 (FAB-C) was a multicenter, open-label, phase 2 study to assess the safety, tolerability, and efficacy of ZYN002 in children and adolescents with FXS through 116 weeks (**Figure 1**)

Figure 1. ZYN2-CL-009 (FAB-C) Study Design and Treatment



[a]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-S) ≥11
  - Clinical Global Impression–Severity (CGI-S) score ≥3
  - Treatment with ≤2 anti-epileptic drugs
  - Nonpharmacologic educational, behavioral, and dietary therapies stable ≥2 months before screening
- Key exclusion criteria:
  - Acute or progressive neurologic disorder other than FXS
  - Use of more than 1 antipsychotic and 1 anti-anxiety medication
  - Use of tetrahydrocannabinol or CBD-containing product ≤4 weeks before screening

ASSESSMENTS

- Primary efficacy end points:
  - Period 1: Change from screening in ADAMS total score at weeks 2, 4, 6, 8, 10, and 12
  - Period 2: Change from screening in the ABC-C_{FXS} social avoidance subscale score at weeks 25, 38, 51, 64, 77, 90, 103, and 116
- Key secondary efficacy end points:
  - Period 1: Change from screening in ABC-C_{FXS} at weeks 4, 8, and 12
  - Period 2: Change from screening in the ABC-C_{FXS} stereotypy, socially unresponsive/lethargic, irritability, inappropriate speech, and hyperactivity subscale scores at weeks 25, 38, 51, 64, 77, 90, 103, and 116
- Safety assessments included collection of AEs and serious AEs

POST HOC ANALYSES

- Post hoc responder analyses by study visit were conducted for patients who completed period 1 (week 12) and for patients who enrolled in period 2 (up to week 116), with responder thresholds defined as ≥25% and ≥50% improvement from baseline
  - Patients with missing data were considered nonresponders
- Radar charts were created to visualize the proportional effect of ZYN002 across all 6 domains of the ABC-C_{FXS} in patients who enrolled in period 2
  - Group mean ABC-C_{FXS} domain scores at screening and weeks 12 (end of period 1) and 116 (end of period 2) were normalized to the maximum possible score for each domain
  - Each domain of the ABC-C_{FXS} is represented on an individual axis of the radar plot

RESULTS

PATIENT DISPOSITION

- Of the 20 patients who enrolled in ZYN2-CL-009, 18 patients completed period 1 and 13 entered period 2 (**Table 1**)

Table 1. Patient Disposition in ZYN2-CL-009

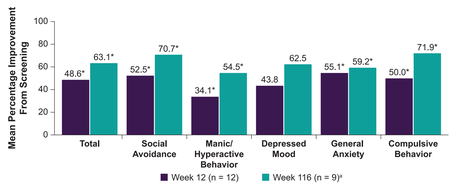
Status	No. of patients
Enrolled	20
Completed period 1 (12 weeks)	18
Entered period 2 at week 12	13
Withdrew consent at ~12.5 weeks[a]	1
Withdrew consent at ~60 weeks	1
Withdrew consent at ~91 weeks	1
Rolled over to an open-label extension trial at week 116	10

[a]This patient was not included in efficacy analyses for period 2.

IMPROVEMENTS FROM SCREENING IN ADAMS TOTAL AND SUBSCALE SCORES IN PATIENTS WHO ENTERED PERIOD 2

- The mean ADAMS total score at screening in patients who entered period 2 was 33.3 (SD 13.48)
- Mean (SD) ADAMS subscale scores at screening for these patients were: social avoidance, 9.9 (4.83); manic/hyperactive behavior, 8.8 (4.43); depressed mood, 3.2 (3.66); general anxiety, 9.8 (4.54); and compulsive behavior, 3.2 (2.52)
- Statistically significant improvements from screening in ADAMS total score (primary efficacy end point) and all ADAMS subscale scores except depressed mood were observed at week 12 and persisted to week 116 (**Figure 2**)

Figure 2. Mean Percentage Improvements From Screening in ADAMS Total and Subscale Scores, Patients Who Entered Period 2

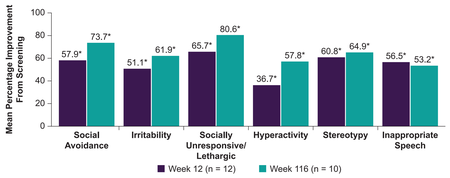


[a]The ADAMS assessment was not completed for 1 patient at week 116.
ADAMS, Anxiety, Depression, and Mood Scale.
*$P < 0.05$ for mean change from screening in total or subscale score.
P values were calculated by within group *t* test (null hypothesis: no change from baseline).

IMPROVEMENTS FROM SCREENING IN ABC-C_{FXS} SUBSCALE SCORES IN PATIENTS WHO ENTERED PERIOD 2

- Mean (SD) ABC-C_{FXS} subscale scores at screening in patients who entered period 2 were: social avoidance, 5.7 (3.58); irritability, 22.3 (10.52); socially unresponsive/lethargic, 10.8 (6.62); hyperactivity, 16.6 (9.77); stereotypy, 9.7 (5.97); and inappropriate speech, 6.2 (1.70)
- Statistically significant improvements from screening were observed across all ABC-C_{FXS} domains at week 12 and persisted to week 116 (**Figure 3**)

Figure 3. Mean Percentage Improvements From Screening in ABC-C_{FXS} Subscale Scores, Patients Who Entered Period 2

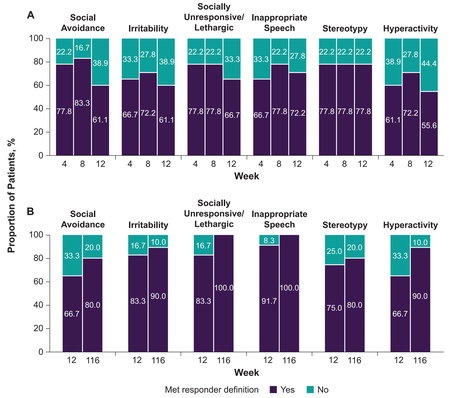


ABC-C_{FXS}, Aberrant Behavior Checklist-Community for FXS.
*$P < 0.05$ for mean change from screening in subscale score.
P values were calculated by within group *t* test (null hypothesis: no change from baseline).

ABC-C_{FXS} RESPONDER ANALYSIS: IMPROVEMENT FROM SCREENING OF ≥25%

- Responses attained by week 4 were generally maintained or improved upon through week 12, with maximal 25% responder rates per individual domain at any time point ranging from 61.1% to 83.3% (**Figure 4A**)
- For patients who entered period 2, similarly, the 25% responder rate established at week 12 was maintained or augmented, with maximal responses per individual domain at any time point observed to range from 80.0% to 100.0% (**Figure 4B**)

Figure 4A and 4B. Proportion of Patients With ≥25% Improvement From Screening in ABC-C_{FXS} Domains for (A) Patients Who Completed Period 1 and (B) Patients Who Entered Period 2

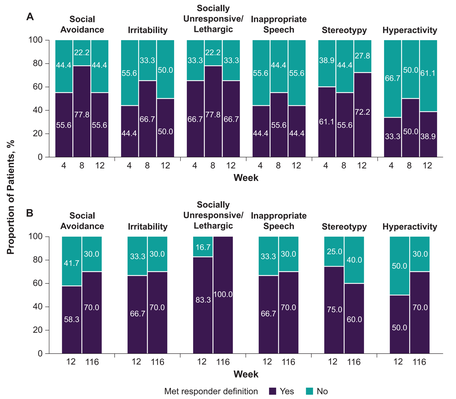


ABC-C_{FXS}, Aberrant Behavior Checklist-Community for FXS.
N = 18 for weeks 4, 8, and 12 (patients who completed period 1).
N = 12 for patients who were evaluated in period 2.
N = 10 for week 116.

ABC-C_{FXS} RESPONDER ANALYSIS: IMPROVEMENT FROM BASELINE OF ≥50%

- Responses attained by week 4 were maintained or improved upon through week 12, with maximal responses per individual domain ranging from 50.0% to 77.8% (**Figure 5A**)
- For patients who entered period 2, similarly, improvement established at week 12 was maintained or further improved, with maximal responses per individual domain observed to range from 70.0% to 100.0% (**Figure 5B**)

Figure 5A and 5B. Proportion of Patients With ≥50% Improvement From Screening in ABC-C_{FXS} Domains for (A) Patients Who Completed Period 1 and (B) Patients Who Entered Period 2

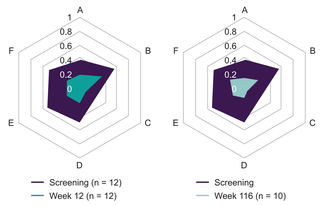


ABC-C_{FXS}, Aberrant Behavior Checklist-Community for FXS.
N = 18 for weeks 4, 8, and 12 (patients who completed period 1).
N = 12 for patients who were evaluated in period 2.
N = 10 for week 116.

VISUALIZATION OF OVERALL SEVERITY ACROSS ABC-C_{FXS} DOMAINS

- Radar charts visualizing the severity of aberrant behavior at screening and weeks 12 and 116 across domains of the ABC-C_{FXS} suggest a global reduction in severity with ZYN002 treatment in patients who entered period 2 (**Figure 6**)

Figure 6. Radar Plots Showing Normalized Group Mean ABC-C_{FXS} Domain Scores for Subjects Who Entered Period 2



A. Irritability
B. Hyperactivity
C. Socially Unresponsive/Lethargic
D. Social Avoidance
E. Stereotypy
F. Inappropriate Speech

ABC-C_{FXS}, Aberrant Behavior Checklist-Community for FXS.

SAFETY

- A total of 66 TEAEs were reported in 19 patients (95%) through week 116
  - All TEAEs were mild (56/66) or moderate (10/66) in severity
  - Most TEAEs were considered unrelated to study treatment (60/66)
- Treatment-related TEAEs were reported in 6 patients (**Table 2**)
- One serious adverse event was reported (constipation) and was not related to treatment

Table 2. Treatment-Emergent Treatment-Related AEs Through Week 116[a]

	N = 20
≥1 treatment-related AE, n (%)	6 (30.0)
Vomiting	1 (5.0)
Application site dryness	1 (5.0)
Eosinophil count abnormal	1 (5.0)
Psychomotor hyperactivity	1 (5.0)
Nightmare	1 (5.0)
Rash, pruritic[b]	1 (5.0)

AE, adverse event; Q12H, every 12 hours; QD, once daily.
[a]Per Figure 1, ZYN002 was flexibly dosed per investigator discretion from 50 mg/day to a total daily dose of 250 mg/day. Nineteen patients received final doses of 250 mg/day. One patient received a final daily dose of 125 mg/day.
[b]Rash, possibly related, alternate etiology allergic reaction to antibiotic.

CONCLUSIONS

- In this post hoc analysis, the majority of patients who completed period 1 met important criteria for therapeutic response (≥25% or ≥50% improvement from baseline in ABC-C_{FXS} domains) at weeks 4, 8, and 12; this response was maintained or continued to improve through week 116 in patients who entered period 2
- Simultaneous visualization of change across all ABC-C_{FXS} domains through radar charts provided additional evidence for global, multi-domain reduction in behavioral symptom burden in patients who entered period 2
- ZYN002 was well tolerated through week 116; most TEAEs were mild and were considered unrelated to treatment
- These data may suggest evidence of the clinical efficacy and favorable safety and tolerability of ZYN002 CBD transdermal gel in children and adolescents with FXS when added to stable standard of care therapies. A double-blind, placebo-controlled study of ZYN002 in FXS is currently in progress and will extend the knowledge gained in this phase 2 study

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