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

Joseph M Pamboukian 1, Natalie Silove 2, Jonathan Cohen 3, Carol O'Neill 3, Nancy Tich 3, Wei Du 4, Helen Heussley 5

1Synthesa Pharmaceuticals, Devon, PA, USA; 2The Children's Hospital at Westmead, Sydney, NSW, Australia; 3Fragile X Alliance, North Caulfield, VIC, Australia; 4Clinical Statistics Consulting, Blue Bell, PA, USA; 5Centre for Clinical Trials in Rare Neurodevelopmental Disorders (CTRND), Children's Health Queensland, Brisbane, QLD, Australia; 6Centre for Child Health Research, University of Queensland, Brisbane, QLD, Australia

BACKGROUND
Fragile X Syndrome (FXS) is a rare genetic condition involving a range of developmental, neurobehavioral, and behavioral symptoms that are significantly associated with aging, cognitive deficits, motor and learning difficulties, sleep disturbances, anxiety, stereotypical behaviors, and seizures. The efficacy and safety of cannabidiol (CBD) in FXS have been demonstrated in clinical trials in young children to adolescents. ZYN2-CL-009 (FAB-C) is a gel-formulation of CBD for the treatment of FXS in children and adolescents aged 6-17 years, approved by the FDA in November 2020. This study aimed to evaluate the pattern of clinical efficacy of ZYN002 in the treatment of FXS to provide therapeutic benefit in FXS through its effects on the endocannabinoid system.

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

- It is a 13 week, phase 2, open-label study: ZYN2-CL-009 (FAB-C) in patients aged 6-17 years with FXS. ZYN002 was evaluated in terms of safety, tolerability, and efficacy.
- It was a 3-period, multi-dose, placebo-controlled study.
- Key inclusion criteria:
  - Male and female patients aged 6-17 years
  - Nonpharmacologic educational, behavioral, and dietary therapies stable
  - Clinical Global Impression–Severity (CGI-S) score ≥3
  - ABC-CFXS (Aberrant Behavior Checklist-Clinician for FXS) total score ≥50%

- Key exclusion criteria:
  - Use of tetrahydrocannabinol or CBD-containing product ≤4 weeks before screening
  - Use of more than 1 antipsychotic and 1 anti-anxiety medication
  - Male and female patients aged 6-17 years
  - Male and female patients aged 6-17 years

RESULTS
Of the 20 patients who enrolled in ZYN2-CL-009, 18 patients completed period 1 and (B) Patients Who Entered Period 2

IMPROVEMENTS FROM SCREENING IN ABC-CFXS SUBSCALE SCORES IN PATIENTS WHO ENTERED PERIOD 2

- **Response obtained by week 4 were generally maintained or improved upon through week 12, with minimal responses per individual domain ranging from 51.0% to 77.8% (Figure 5A)**
- For patients who entered period 2, the 250 mg/day dose was maintained or further improved, with maximal responses per individual domain observed to range from 33.3% to 100.0% (Figure 5B).

Table 1: Patient Disposition in ZYN2-CL-009

<table>
<thead>
<tr>
<th>Period</th>
<th>Status</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed period 1</td>
<td>12 weeks</td>
<td>10</td>
</tr>
<tr>
<td>Completed period 2</td>
<td>12 weeks</td>
<td>10</td>
</tr>
<tr>
<td>Withdraw consent</td>
<td>≤3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Withdraw consent</td>
<td>≥4 months</td>
<td>1</td>
</tr>
<tr>
<td>Withdraw consent</td>
<td>≥5%</td>
<td>1</td>
</tr>
<tr>
<td>TotalNumber of patients at week 116</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

PATIENTS
- Age and gender criteria:
  - Male and female patients aged 6-17 years
- Documented FXS diagnosis with 47, XXY karyotype
- Pediatric Anxiety Rating Scale-Revised score (PARS-R) ≤11
- Clinical Global Impression–Severity (CGI-S) score ≤4
- Treatment with SSRI and antipsychotic drugs
- Nonpharmacological educational, behavioral, and dietary therapies stable
- No use of any other psychotropic medication before screening
- No response to baseline in ABC-CFXS

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

- **ABC-CFXS RESPONDER ANALYSIS: IMPROVEMENT FROM SCREENING OF ≥25%**
- **ABC-CFXS RESPONDER ANALYSIS: IMPROVEMENT FROM BASELINE OF ≥25%**

Table 5: Mean Percentage Improvements From Screening in ABC-CFXS Subscales, Patients Who Entered Period 1

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate speech, socially verbal, socially inappropriate speech, and hyperactivity sub scores at weeks 25, 38, 51, 64, 77, 90, 103, and 116</td>
<td>50.0%</td>
<td>77.8%</td>
</tr>
<tr>
<td>Socially avoidant, socially irritable, socially stereotypy, socially socially avoidant, and socially irritable sub scores at weeks 25, 38, 51, 64, 77, 90, 103, and 116</td>
<td>50.0%</td>
<td>77.8%</td>
</tr>
</tbody>
</table>

CONCLUSIONS
- These data suggest evidence of the clinical efficacy and favorable safety, tolerability, and treatment benefit of ZYN2002 in children and adolescents with FXS when added to standard care of patients. A change in this current study was the addition of the ABC-CFXS domain at week 12 and persisted to week 16 (Figure 2).

SAFETY
- A total of 66 TEAEs were reported in 15 patients (55%) through week 116.
- All TEAEs were mild (58%) or moderate (18%) in severity.
- Most TEAEs were considered unrelated to study treatment (66%).
- Treatment-related TEAEs were reported in 6 patients (Table 5).

Table 2: Treatment-Emergent Treatment-Related AEs Through Week 116

<table>
<thead>
<tr>
<th>AE</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, possibly related, alternate etiology allergic reaction to antibiotic</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Rash, poison</td>
<td>1 (5.0)</td>
</tr>
</tbody>
</table>

REFERENCES