BACKGROUND

- Fragile X syndrome (FXS) is the most common monogenic cause of autism spectrum disorder (ASD)
- Disruption in the endocannabinoid system is one of the proposed mechanisms for the loss of synaptic plasticity and the deficits in emotional responsibility observed in FXS

- Cannabinoid acts as a negative allosteric modulator at presynaptic CB, receptors, a 
SHT, agonist, and a D2 partial agonist

- ZYN002 is a pharmacologically produced cannabidiol transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS, ASD, and IQN1-2 liver disease

- The Aberrant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObRO) measure that has been validated in individuals with intellectual disabilities

- An FXS-specific domain structure of the ABC-C (hereafter the ABC-CFXS), which is more representative of the FXS phenotype, has been established and has been used to assess changes in behaviors in trials assessing ZYN002

- ZYN002 was superior to placebo in a pre-specified ad hoc analyses in patients with either ≤90% methylation or complete methylation (100%) of their FMR1 gene in ZYN002-CL-016 (CONNECT-FX) (NCT03814683), suggesting that methylation impact response to ZYN002

- ZYN2-CL-003, RECONNECT, an ongoing Phase 3, randomized, double-blind, placebo-controlled confirmatory trial evaluating the efficacy and safety of ZYN002 over 16 weeks (NCT0497986)

OBJECTIVES

- To determine the long-term safety and efficacy of ZYN002 in patients with FXS

- Here, we report interim analyses of data of an ongoing, open-label extension trial (OLE): ZYN2-CL-017 (NCT03802799), through February 3, 2022

METHODS

- Patients ages 3 through 17 years entered the trial from 1 completed and 1 ongoing controlled, trial evaluating the efficacy and safety of ZYN002 for 116 weeks prior to entering ZYN2-CL-009

- ZYN2-CL-017: (OLE), ZYN2-CL-017 (NCT03802799), through February 2, 2022

SAFETY RESULTS

- ZYN002 was safe and well tolerated in patients with FXS

- Over 90% of patients had no erythema during any month of exposure. Only 2 patients had ≥3% of patients had intense erythema with or without edema; and 4=intense erythema with 3=intense erythema with or without edema; and 4=intense erythema with

RESULTS

- Baseline characteristics are shown in Table 1

Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Race, n (%)</th>
<th>White 193 (76.3)</th>
<th>Black or African American 9 (3.5)</th>
<th>Hispanic 31 (12.9)</th>
<th>Other 16 (6.7)</th>
<th>Native Hawaiian or Other Pacific Islander 1 (0.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Female 57 (23.8)</td>
<td>Male 183 (76.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, Range</td>
<td>14.6, 91.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SAFETY REASONS

- Mild-to-moderate AEs 97.6% (events)

- Upper respiratory infection 15.8%

- Cough 3.3%

- Ear infection 4.2%

- Anxiety 3.8%

- Fatigue 2.6%

- Depression 2.1%

- Asthenia 2.1%

- Incontinence 2.1%

- Otitis media 1.4%

- Influenza 1.4%

- Rash 1.4%

- Upper respiratory other 1.4%

- Vomiting 1.4%

-10% or more in any month of exposure. Only 2 patients had ≥3% of patients had intense erythema with or without edema; and 4=intense erythema with

-1.0, 1.2, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0, 21.0, 22.0, 23.0, 24.0, 25.0, 26.0, 27.0, 28.0, 29.0, 30.0, 31.0, 32.0, 33.0, 34.0, 35.0, 36.0, 37.0, 38.0, 39.0, 40.0, 41.0, 42.0, 43.0, 44.0, 45.0, 46.0, 47.0, 48.0, 49.0, 50.0, 51.0, 52.0, 53.0, 54.0, 55.0, 56.0, 57.0, 58.0, 59.0, 60.0, 61.0, 62.0, 63.0, 64.0, 65.0, 66.0, 67.0, 68.0, 69.0, 70.0, 71.0, 72.0, 73.0, 74.0, 75.0, 76.0, 77.0, 78.0, 79.0, 80.0, 81.0, 82.0, 83.0, 84.0, 85.0, 86.0, 87.0, 88.0, 89.0, 90.0, 91.0, 92.0, 93.0, 94.0, 95.0, 96.0, 97.0, 98.0, 99.0, 100.0

CONCLUSIONS

- ZYN002 is safe and well tolerated during long-term administration

- ZYN002 led to improvements in ABC-CFXS Social Avoidance in the full population, with the greatest improvements being seen in patients with complete methylation of their FMR1 gene

- Patients with complete methylation, who match the primary efficacy population in the ongoing confirmatory trial, RECONNECT, achieved and maintained clinically meaningful change in Social Avoidance, supporting design enhancements for RECONNECT

- The interim results from this open-label extension trial support the long-term safety and effectiveness of ZYN002 in children and adolescents with Fragile X syndrome, with the greatest improvements seen in those with complete methylation of their FMR1 gene

REFERENCES