BACKGROUND

- There is shared underlying neuropathophysiology among autism spectrum disorder (ASD), seizure disorders, and fragile X syndrome (FXS), which may include neuronal disinhibition and alterations in synaptic plasticity and brain anatomical architecture (Figure 1).1-4
- FXS is the most common monogenic cause of ASD.5-8
- Cannabinoid receptors are found in a variety of diverse organisms,9 indicating that the endocannabinoid system (ECS) is highly evolutionarily conserved and may play central roles in physiology and pathophysiology.10
- In addition, evidence indicates that the ECS has an important role in the CNS and appears to regulate neuronal development and function, particularly synaptogenesis and plasticity,10,11 and may be dysfunctional in ASD and FXS.12,13

ZYN002 is a pharmaceutical-manufactured transdermal cannabidiol gel in development for ASD, FXS, 22q deletion syndrome, and developmental epileptic encephalopathies (DEE).

OBJECTIVE

- Select efficacy assessments and safety of ZYN002 in patients aged 3-17 years are presented from 2 open-label trials (BRIGHT [ASD] and BELIEVE [DEE]) and a double-blind, placebo-controlled trial (CONNECT-FX [FXS]).

METHODS

- **BRIGHT (ASD)** was an open-label, Phase 2 trial in children and adolescents with ASD (N=37) (Table 1)

- **BELIEVE (DEE)** was an open-label, Phase 2 trial in children and adolescents with DEE (N=94), (Table 1)

- Analyses of key endpoints were conducted in 14% of patients with comorbid ASD

- **CONNECT-FX (FXS)** was randomized, double-blind, placebo-controlled, Phase 3 trial in children and adolescents with FXS (N=121) with a full FMR1 gene mutation (Table 1)

RESULTS

Table 1: Numbers of Patients With ASD in Each Clinical Trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Total Number of Patients</th>
<th>Patients With ASD (N=37)</th>
<th>Patients With Moderate-to-Severe ASD (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIGHT (ZYN-CGI-026)</td>
<td>37</td>
<td>37 (100%)</td>
<td>34 (92%)</td>
<td></td>
</tr>
<tr>
<td>BELEIVE (ZYN-CGI-026)</td>
<td>48</td>
<td>48 (100%)</td>
<td>24 (50%)</td>
<td></td>
</tr>
<tr>
<td>CONNECT-FX (ZYN-CGI-016)</td>
<td>212</td>
<td>212 (100%)</td>
<td>150 (71%)</td>
<td></td>
</tr>
<tr>
<td>±50% FMR1 methylation group</td>
<td>169</td>
<td>169 (100%)</td>
<td>127 (75%)</td>
<td></td>
</tr>
</tbody>
</table>

- ZYN002 appeared to demonstrate a positive benefit-risk profile across a spectrum of endpoints including behavior, seizure reduction and sleep, when added to standard of care in children and adolescents with ASD and DEE (open-label), as well as in FXS patients with ≥90% methylation of the FMR1 gene.

- **BRIGHT (ASD)**: Provides support for a positive benefit-risk profile for ZYN002 when administered in addition to standard of care in children and adolescents with moderate-to-severe ASD. ZYN002 (open label) showed improvement in all ASD measures (Table 1).

- **BELIEVE (DEE)**: Meanings reductions from baseline in seizures (FIAS and TCS) with ZYN002 treatment (CL), which were maintained through 12 months. In the subgroup of patients with ASD (N=14), ZYN002 demonstrated meaningful reductions from baseline in seizures (FIAS and TCS) with ZYN002 treatment (CL), which were maintained through 12 months. In the subgroup of patients with ASD (N=14), ZYN002 demonstrated meaningful reductions from baseline in FIAS and TCS and improvement in symptoms of sleep disorders as determined from the SIDSC.

- **CONNECT-FX (FXS)**: ZYN002 was superior to placebo in multiple analyses in the group of patients with ≥90% methylation of their FMR1 gene (80% of the full analysis set), of which 80% had symptoms of ASD. ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set.

- Further trials are warranted to confirm these findings in ASD and ASOR-related disorders

DISCUSSION

- The ECS is an evolutionarily conserved control system that plays a foundational role in the CNS

- ZYN002 appeared to demonstrate a positive benefit-risk profile across a spectrum of endpoints including behavior, seizure reduction and sleep, when added to standard of care in children and adolescents with ASD and DEE (open-label), as well as in FXS patients with ≥90% methylation of the FMR1 gene.

REFERENCES


ACKNOWLEDGEMENTS

- *For more detailed information on these clinical trials, please click this link: https://zynerba.com/publications*