BACKGROUND

- Epilepsy and sleep disorders have a bidirectional relationship and occur in individuals with autism spectrum disorder (ASD).
- Developmental and epileptic encephalopathies (DEEs) are a group of severe neurodevelopmental disorders, characterized by seizures and abnormal neurophysiologic activity, that negatively impact development.
- DEEs include, but are not limited to, West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome.
- DEEs with onset ≤18 months have an incidence of 1 in 2000 live births.

OBJECTIVES

- To compare the impact of ZYN002 on sleep disorders in patients with DEEs, with and without ASD.
- To evaluate the safety of ZYN002 in patients aged 3 to <18 years with DEEs (phase 2).

METHODS

TRIAL DESIGN AND TREATMENT

- ZYN-CL-G255 (BELIEVE) was an open-label, 0-3-month, multiple-dose, phase 2 trial to assess the safety, tolerability, and efficacy of ZYN002 in patients aged 3 to 16 years with DEEs (Figure 1).
- ZYN002 was administered in blinded, randomized, phase 2 trials at a dose of 500 mg CBD Q12H for 26 consecutive weeks.
- In an open-label trial with ZYN002, patients with DEEs showed reduced seizure frequency and improved sleep.

SLEEP ASSESSMENT

- Sleep assessment was conducted by caregivers using the SDSC (Table 1).

Table 1. Sleep Assessment

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Week 26 (n = 26)</th>
<th>Week 26 (n = 12)</th>
<th>Baseline (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported Sleep Scale for Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficacy end point: change from baseline to the end of Period A</td>
<td>−6.5 (−10.8, −2.1)</td>
<td>−8.7 (−15.9, −1.5)</td>
<td>−6.8 (−12.9, −0.7)</td>
</tr>
<tr>
<td>Sleep efficacy end point: change from Period A to Period B</td>
<td>1.8 (−3.0, 6.5)</td>
<td>6.1 (−1.2, 13.4)</td>
<td>5.9 (−1.9, 13.7)</td>
</tr>
<tr>
<td>Sleep efficacy end point: change from Baseline to Period B</td>
<td>5.7 (−2.0, 13.4)</td>
<td>6.9 (−1.2, 15.8)</td>
<td>6.8 (−1.9, 15.6)</td>
</tr>
<tr>
<td>Sleep efficacy end point: change from Baseline to Week 26</td>
<td>8.2 (−0.7, 16.7)</td>
<td>5.7 (−2.0, 13.4)</td>
<td>5.9 (−1.9, 13.7)</td>
</tr>
</tbody>
</table>

SLEEP SCORES

- Of 25 children with DEEs and clinically significant sleep disturbances, 16 (64%) met the SDSC in full at week 26.
- 11 children with DEEs without ASD had clinically significant sleep disturbances.
- In patients without ASD, improvements in mean t-score at week 26 (t-score < 70) was seen in initiating and maintaining sleep (−8.7; 95% CI: −15.3, −2.1).
- In patients with ASD, improvements in mean t-scores at week 26 were observed in sleep breathing (−6.7; 95% CI: −12.1, −1.2).

RESULTS

BASILINE CHARACTERISTICS

- A total of 46 patients were enrolled in BELIEVE and were included in the safety analysis set: the mean age was 12 years (Table 2).
- 26 of 46 children with DEEs (52%) had clinically significant sleep disturbances at baseline as defined by a SDSC t-score ≥70.

Table 2. Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographic or Disease Characteristic</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>10.5 (2.7)</td>
<td>10.0 (9.0)</td>
<td>5-18</td>
</tr>
<tr>
<td>Sex, n (%): Male/Female</td>
<td>22/24</td>
<td>11/15</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.0 (4.2)</td>
<td>20.0 (3.0)</td>
<td>12-30</td>
</tr>
</tbody>
</table>

PATIENTS

- Key inclusion criteria:
  - Male and female patients aged 3 to <18 years.
  - Diagnosis of DEE as defined by International League Against Epilepsy classification.

- Key exclusion criteria:
  - Use of any cannabinoid-containing product within 30 days before screening.

- Period A, as well as in patients aged 3 to <18 years with DEEs (phase 2).

- ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel in development for DEEs, ASD, and fragile X syndrome.

- Improvements in sleep may result in better seizure control and improved general health.

SAFETY

- ZYN002 was well tolerated in BELIEVE.
- The DEE with ASD cohort showed more wide-range changes in sleep-related biomarkers compared to patients without ASD.

CONCLUSIONS

- BELIEVE was an open-label, parallel-group, randomized controlled trial of ZYN002 in children and adolescents with DEEs.

REFERENCES