Longer Term Tolerability and Efficacy of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents with Autism Spectrum Disorder (ASD): An Open-Label Phase 2 Study (BRIGHT [ZYN2-CL-030])

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Disclosures: TH, CO, DG, and JP are employees of Zynerba Pharmaceuticals. HH and MD have received research support from Zynerba Pharmaceuticals. The study was funded by Zynerba Pharmaceuticals.
• This presentation is intended to communicate scientific and medical information about data from clinical trials involving ZYN002. ZYN002 is an experimental treatment which has not been approved by any government regulatory bodies, including the United States Food and Drug Administration (FDA), and has not been determined by the FDA to be a safe or effective treatment for any disease or condition. This presentation is not designed or intended to promote the use of ZYN002 or any other Company product in order to impact prescribing.

• This slide presentation is based on an abstract submitted and accepted for presentation at the 2021 annual meeting of the American Academy of Child and Adolescent Psychiatry.
Background

• Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by difficulties with behaviors, communication, and reciprocal social interaction\(^1,2\)

• Current management options for ASD symptoms are restricted to cognitive behavioral therapy and a limited number of approved pharmacologic treatments, highlighting the substantial unmet need for novel therapies in this population\(^2\)

• The endocannabinoid system is a key modulator of emotion and social behavior and is dysregulated in ASD\(^3\)

• It is therefore possible that cannabidiol may provide therapeutic benefit in ASD; however, the efficacy and safety of cannabidiol in patients with ASD have not been well established\(^3\)

• BRIGHT (ZYN2-CL-030) is an exploratory, single-center, open-label, Phase 2 study evaluating the safety and tolerability and efficacy of ZYN002 in children and adolescents with ASD who are 3 to <18 years old

• ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel

Methods

The study enrolled patients with an Aberrant Behavior Checklist-Community (ABC-C) Irritability score ≥18 and a Clinical Global Impression (CGI)–Severity score ≥4 (moderate or greater)

Primary objective: To evaluate the safety and tolerability of ZYN002 for up to 38 weeks (14-week treatment period [Period 1] and a 24-week extension period [Period 2])

- Safety assessments included adverse events (AEs), skin assessments, laboratory tests, and electrocardiograms (ECGs)

The primary efficacy assessments included ABC-C and CGI

Secondary objectives comprised evaluation of the efficacy of ZYN002 in the treatment of symptoms of ASD, including measuring parental/caregiver stress (APSI†), Parent Rated Anxiety Scale (PRAS), Autism Impact Measure (AIM), and qualitative caregiver-reported behavioral problems, assisting us to appreciate the voice of the patient and family

Patients received ZYN002 250 mg or 500 mg (weight-based dose) daily for up to 38 weeks in addition to stable standard of care medications (including antipsychotic agents, when prescribed)

Patients demonstrating ≥35% improvement in the ABC-C irritability subscale at week 14 were allowed to continue treatment for an additional 24 weeks

The focus of this presentation is data from patients who entered Period 2 and completed 38 weeks of treatment

†APSI=Autism Parenting Stress Index.
Baseline Demographics and Patient Disposition

Demographics were similar for patients in Period 1 and Period 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRIGHT Participants</th>
<th>BRIGHT Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1 N=37</td>
<td>Period 2 n=18</td>
</tr>
<tr>
<td>Age, mean years (range)</td>
<td>9.2 (3-16)</td>
<td>9.2 (3-16)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 34 (91.9)</td>
<td>Female 16 (89)</td>
</tr>
<tr>
<td></td>
<td>Male 3 (8.1)</td>
<td>Female 2 (11)</td>
</tr>
<tr>
<td>Race, %</td>
<td>White 75.7</td>
<td>Asian 77.8</td>
</tr>
<tr>
<td></td>
<td>Indigenous Australian 5.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asian 8.1</td>
<td>Other 5.6</td>
</tr>
<tr>
<td></td>
<td>Other 10.8</td>
<td></td>
</tr>
</tbody>
</table>

Demographics were similar for patients in Period 1 and Period 2

Enrolled in Period 1
N=37 (Safety Analysis Population)
- Discontinued, n=9
  - Adverse event, n=1
  - Patient withdrew consent, n=2
  - Caregiver withdrew consent, n=3
  - Lost to follow-up, n=3

Enrolled in Period 2
n=18
- Not eligible, n=10
  - Did not meet ABC-C Irritability criteria

Completed 14 weeks
n=28

Completed 38 weeks
n=17
Efficacy: Statistically Significant Improvements From Baseline in all ABC-C Subscale Scores* Sustained Through Week 38

Mean Scores and Percent Improvement Period 1
(n=28 [n=26 for Inappropriate Speech])

- **Irritability**: Baseline 30.3, Week 14 18.2
- **Inappropriate Speech**: Baseline 7.4, Week 14 5.2
- **Stereotypy**: Baseline 12.3, Week 14 7.9
- **Social Withdrawal**: Baseline 25.1, Week 14 16.5
- **Hyperactivity**: Baseline 37.0, Week 14 23.9

- **Irritability**: 39.1% (P<0.0001)
- **Inappropriate Speech**: 42.5% (P=0.0002)
- **Stereotypy**: 39.1% (P<0.0001)
- **Social Withdrawal**: 36.4% (P<0.0001)
- **Hyperactivity**: 35.6% (P<0.0001)

Mean Scores and Percent Improvement Period 2
(n=18)

- **Irritability**: Baseline 31.6, Week 14 14.3, Week 38 13.3
- **Inappropriate Speech**: Baseline 7.4, Week 14 4.0, Week 38 3.8
- **Stereotypy**: Baseline 12.7, Week 14 6.2, Week 38 4.8
- **Social Withdrawal**: Baseline 27.6, Week 14 14.0, Week 38 10.9
- **Hyperactivity**: Baseline 36.1, Week 14 19.5, Week 38 16.8

- **Irritability**: 56.1% (P<0.0001)
- **Inappropriate Speech**: 50.5% (P<0.0001)
- **Stereotypy**: 53.4% (P<0.0001)

*Lower values reflect improvement in each ABC-C subscale.
Efficacy: Statistically Significant Improvements From Baseline in Autism Impact Measure Scores\textsuperscript{a} Sustained Through 38 weeks

\textbf{Mean Scores and Percent Improvement Period 1} \\
(n=28)

\begin{tabular}{lcc}
  & Mean Scores & Percent Improvement \\
  & (n=28) & \\
  & Baseline & Week 14 & \\
  Irritability & 44.0 & 34.1\% (P<0.001) & \\
  Inappropriate Speech & 39.3 & 19.7\% (P<0.001) & \\
  Stereotypy & 31.2 & 19.8\% (P<0.001) & \\
  Social Withdrawal & 36.4 & 10.7\% (P=0.0053) & \\
  Hyperactivity & 33.9 & - & \\
\end{tabular}

\textbf{Mean Scores and Percent Improvement Period 2} \\
(n=18)

\begin{tabular}{lcc}
  & Mean Scores & Percent Improvement \\
  & (n=18) & \\
  & Baseline & Week 14 & Week 38 \\
  Irritability & 45.9 & 35.9\% (P<0.0001) & \\
  Inappropriate Speech & 40.9 & 26.5\% (P<0.0001) & \\
  Stereotypy & 28.9 & 29.5\% (P<0.0001) & \\
  Social Withdrawal & 31.9 & 31.6\% (P<0.0001) & \\
  Hyperactivity & 31.7 & 18.9\% (P=0.0008) & \\
\end{tabular}

\textsuperscript{a}The AIM score has been shown to be sensitive to change as a measure of core ASD symptoms.\textsuperscript{1}

Efficacy: Statistically Significant Improvements From Baseline in PRAS-ASD, APSI, and CGI-I Sustained Through Week 38

Mean Scores and Percent Improvement Through Week 38

Parent-Rated Anxiety Scale–ASD

Autism Parenting Stress Index

CGI-Improvement (any)

Not improved 11.1%

Improved 88.9%

PRAS-ASD

APSI

n=18

ASD=Autism Spectrum Disorder; CGI=Clinical Global Impression.
Summary of Overall Safety/Tolerability

• ZYN002 was generally well tolerated, and the safety profile was consistent with data from previous ZYN002 clinical trials
• During the 38-week study, slightly more than half (54.1%) of patients experienced any adverse event (AE) (whether unrelated or related to study drug)
• Throughout the study, all AEs were mild (80%) or moderate (20%) and transient
• 7 patients (19%) experienced a total of 10 AEs that were deemed to be treatment-related
• Of the 10 treatment-related AEs reported, 7 were application site-related (application site reaction, pruritus, and dryness) and 1 each of sleep disorder, increased appetite, and pollakiuria (frequent urination)
• There were no severe or serious AEs reported during the study
• There were no clinically significant changes in vital signs, laboratories, or electrocardiogram (ECG) parameters
Summary of Results: BRIGHT

• Through 38 weeks of treatment, BRIGHT provides initial evidence suggesting a positive benefit-risk profile for ZYN002 when administered in addition to stable standard of care in children and adolescents with moderate-to-severe ASD

• ZYN002 showed improvement in all ASD efficacy measures (ABC-C, AIM, PRAS-ASD, CGI-I)

• Further controlled studies are warranted in this difficult-to-treat population