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

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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 (CBD) may provide therapeutic benefit in ASD; however, the efficacy and safety of CBD in patients with ASD have not been well established\(^3\)

- ZYN002 is a pharmaceutically manufactured transdermal CBD gel in development for the treatment of ASD

- 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 4 to <18 years old*

- The results suggest that ZYN002 may have potential benefit in ASD and controlled trials are warranted


*One 3-year-old participant was enrolled.*
Methods

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

• Primary objective: to evaluate the safety and tolerability of ZYN002 in patients aged 4 to <18 years,\(^a\) for up to 38 weeks (14-week treatment period and a 6-month extension period)
  • Safety assessments included adverse events (AEs), laboratory tests, and electrocardiograms (ECGs)

• Secondary objectives comprised evaluation of the efficacy of ZYN002 in the treatment of symptoms of ASD, including measuring parental/caregiver stress (APSI\(^b\)), Autism Impact Measure (AIM), and caregiver reported behavioral problems

• Patients received ZYN002 250 mg or 500 mg (weight-based dose) daily for 14 weeks in addition to stable standard of care medications (including antipsychotic agents, when prescribed)

\(^a\)One 3-year-old participant was enrolled.
\(^b\)APSI=Autism Parenting Stress Index.
### Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRIGHT Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=37</td>
</tr>
<tr>
<td>Age, mean years (range)</td>
<td>9.2 (3-16)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (91.9)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>75.7</td>
</tr>
<tr>
<td>Indigenous Australian</td>
<td>5.4</td>
</tr>
<tr>
<td>Asian</td>
<td>8.1</td>
</tr>
<tr>
<td>Other</td>
<td>10.8</td>
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</tbody>
</table>
### Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRIGHT Participants N=37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since diagnosis, n Mean years (range)</td>
<td>37 5.4 (0.07-15.7)</td>
</tr>
<tr>
<td>ABC-C Irritability subscale score, n Mean (range)</td>
<td>36a 30.3 (18-43)</td>
</tr>
<tr>
<td>PRAS-ASD score, n Mean (range)</td>
<td>36a 40.8 (21-68) 9 (24.3)</td>
</tr>
<tr>
<td>AIM domain scores, n Atypical behavior, mean (range)</td>
<td>44.0 (16-56)</td>
</tr>
<tr>
<td>Communication, mean (range)</td>
<td>39.3 (17-60)</td>
</tr>
<tr>
<td>Peer interaction, mean (range)</td>
<td>31.2 (13-40)</td>
</tr>
<tr>
<td>Repetitive behavior, mean (range)</td>
<td>54.0 (24-80)</td>
</tr>
<tr>
<td>Social reciprocity, mean (range)</td>
<td>33.9 (14-48)</td>
</tr>
<tr>
<td>DSM-5 severity levelb</td>
<td></td>
</tr>
<tr>
<td>Level 1 (mild), n (%)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Level 2 (moderate), n (%)</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td>Level 3 (severe), n (%)</td>
<td>19 (51.4)</td>
</tr>
<tr>
<td>ADOS®-2 comparison score, n &lt;5, n (%)</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>5-7, n (%)</td>
<td>19 (52.8)</td>
</tr>
<tr>
<td>8-10, n (%)</td>
<td>15 (41.7)</td>
</tr>
</tbody>
</table>

ABC-C Irritability subscale: Score of 30 confirms severity

PRAS-ASD: 24% of participants had scores >52, indicating possible clinical anxiety

DSM-5: 92% of participants had moderate to severe symptoms of ASD

ADOS-2: 94% of participants had moderate to severe symptoms of ASD

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aOne patient had missing data.
bDSM-5 severity levels are based on degree of social communication impairment and behavioral flexibility. The levels indicate patients “requiring support” (level 1), “requiring substantial support” (level 2), and “requiring very substantial support” (level 3).1

Efficacy: Statistically Significant Improvements in All ABC-C Subscale Scores

Mean Percent Improvement at Week 14 vs Baseline

- 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)

n=28 (n=26 for Inappropriate Speech)
*Lower values reflect improvement in each ABC-C subscale
Efficacy: Statistically Significant Improvements in PRAS-ASD, APSI, and CGI-I

Mean Percent Improvement at Week 14 vs Baseline

**Parent-Rated Anxiety Scale-ASD**

Mean Score

- **Baseline**: 40.8
- **Week 14**: 21.8

**Mean Percent Improvement**: 45.7%

*Statistically significant; \( P < 0.0001 \)

**Autism Parenting Stress Index**

Mean Score

- **Baseline**: 36.0
- **Week 14**: 22.9

**Mean Percent Improvement**: 38.9%

*Statistically significant; \( P < 0.0001 \)

**Not improved**: 42.9%

**Improved**: 57.1%
Efficacy: Statistically Significant Improvements in Autism Impact Measure Scores
Mean Percent Improvement at Week 14 vs Baseline

- Atypical Behavior: 34.1% (P<0.001)
- Communication: 19.7% (P<0.001)
- Peer Interaction: 19.8% (P<0.001)
- Repetitive Behavior: 32.8% (P<0.001)
- Social Reciprocity: 10.7% (P=0.0053)

n=28
Efficacy: Notable Improvements in the **Qualitative Caregiver Behavioral Problems** Survey at Week 14

**Behavioral**
- About the same: 31%
- Improved: 69%

**Social**
- About the same: 34%
- Improved: 63%

**Emotional**
- About the same: 28%
- Improved: 72%

Examples at baseline
- Aggressive
- Refuses to go to school
- Repetitive phrases
- Self-harm

- Minimal social engagement
- No personal space
- No empathy for others
- Fear of new people

- Anxious
- Little self-regulation of emotions
- Easily offended
Safety Assessments and Conclusions Through 14 Weeks

- All TEAEs were mild (75%) or moderate (25%) and reported in 49% of patients
- Treatment-related TEAEs were reported in 14% of patients
  - Most were mild and transient
- No serious or severe AEs or clinically significant changes in laboratory tests or ECGs were reported

### TEAEs experienced by ≥2 patients through 14 weeks

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Patients N=37</th>
<th>Number of AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 TEAE</td>
<td>18 (48.6%)</td>
<td>24</td>
</tr>
<tr>
<td>Application site pain</td>
<td>2 (5.4%)</td>
<td>2</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>2 (5.4%)</td>
<td>3</td>
</tr>
<tr>
<td>Ear infection</td>
<td>2 (5.4%)</td>
<td>2</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (5.4%)</td>
<td>2</td>
</tr>
</tbody>
</table>

**Conclusions**

- Through 14 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 measures (ABC-C, AIM, PRAS-ASD, CGI and Qualitative Caregiver Assessments)
- Further controlled studies are warranted in this difficult-to-treat population

TEAE=treatment-emergent adverse event.