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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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 symptoms of ASD are restricted to behavioral therapies and a limited number of approved pharmacologic treatments, which have been associated with serious potential adverse effects[2]
- There is therefore substantial unmet need for novel therapies in this population
- The endocannabinoid system (ECS) is found in diverse species, indicating that it is highly evolutionarily conserved, and may play central roles in physiology and pathophysiology[3]
- Evidence indicates that the ECS has an important role in the central nervous system (CNS) and appears to regulate neuronal development and function, particularly synaptic homeostasis and plasticity[4-6] and may be a key modulator of emotion and social behavior that is dysregulated in ASD[7]
- It is therefore reasonable to explore the question of whether cannabidiol may have broader effects on multiple behavioral target symptoms in ASD; however, the efficacy and safety of cannabidiol in patients with ASD have not been well established[7]
- BRIGHT (ZYN2-CL-030) is an exploratory, single-center, open-label, phase 2 trial evaluating the safety, tolerability, and efficacy of ZYN002 in children and adolescents with ASD who are aged 3 to <18 years old[8]
- ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel

METHODS

- The trial 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 index (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

OBJECTIVE

- To examine longer-term safety, tolerability, and efficacy of ZYN002 in BRIGHT treatment responders through 38 weeks

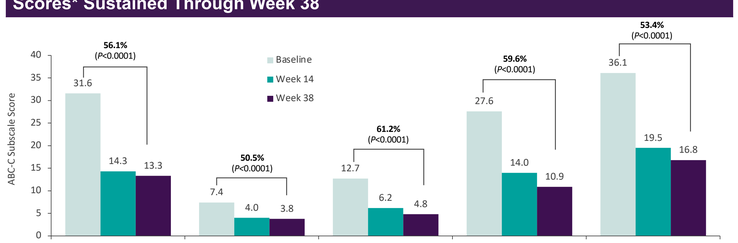
RESULTS

- The baseline demographics were similar between the overall population in Period 1 and patients who entered Period 2 (**Table 1**)
- At week 38, improvements were demonstrated in the ABC-C subscale scores (50% to 61% across domains; *P*<0.0001; **Figure 1**), the PRAS-ASD (42%; *P*<0.0001), APSI (40%; *P*<0.0001) (**Figure 2**) and the AIM (19% to 36% across domains; *P*≤0.0008; **Figure 3**).

Table 1. Baseline Demographics

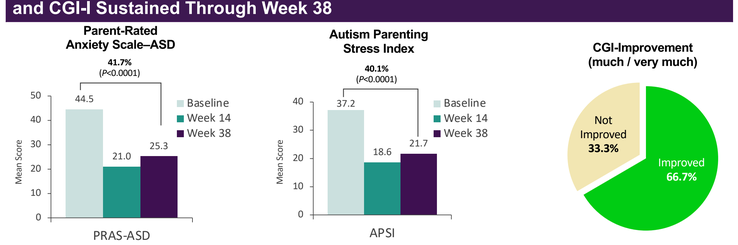
Characteristic	BRIGHT Period 1 (N = 37)	BRIGHT Period 2 (n = 18)
Age, mean years (range)	9.2 (3-16)	9.2 (3-16)
Sex, n (%)		
Male	34 (91.9)	16 (89)
Female	3 (8.1)	2 (11)
Race, %		
White	75.7	77.8
Indigenous Australian	5.4	0
Asian	8.1	5.6
Other	10.8	16.7

Figure 1. Statistically Significant Improvements From Baseline in all ABC-C Subscale Scores* Sustained Through Week 38



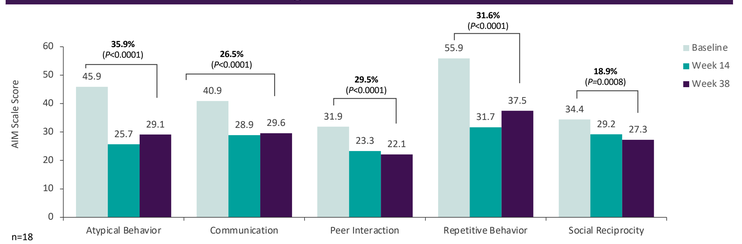
*Lower values reflect improvement in each Aberrant Behavior Checklist-Community (ABC-C) subscale.

Figure 2. Statistically Significant Improvements From Baseline in PRAS-ASD, APSI, and CGI-I Sustained Through Week 38



APSI=Autism Parenting Stress Index; ASD=Autism Spectrum Disorder; CGI=Clinical Global Impression; PASD=Patient-Rated Anxiety Scale.

Figure 3. Statistically Significant Improvements From Baseline in Autism Impact Measure Scores Sustained Through Week 38



OVERALL SAFETY/TOLERABILITY

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

SUMMARY AND CONCLUSIONS

- The BRIGHT trial 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

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

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