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

OBJECTIVE

- 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[a]

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 (Autism Parenting Stress Index [APSI]), 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)

RESULTS

BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

- Of the 37 patients (mean age: 9.2 years) enrolled, 94% had moderate-to-severe symptoms per Autism Diagnostic Observation Schedule 2nd edition criteria (**Table 1**)
- The mean baseline ABC-C Irritability score was 30.3 (**Table 1**)

Table 1. Baseline demographics and disease characteristics

Characteristic	BRIGHT Participants N=37
Age, mean years (range)	9.2 (3-16)
Sex, n (%) Male Female	 34 (91.9) 3 (8.1)
Race, % White Indigenous Australian Asian Other	 75.7 5.4 8.1 10.8
Time since diagnosis, n Mean years (range)	37 5.4 (0.07-15.7)
ABC-C Irritability subscale score, n Mean (range)	36[a] 30.3 (18-43)
PRAS-ASD score, n Mean (range) >52, n (%)	36[a] 40.8 (21-68) 9 (24.3)
AIM domain scores, n Atypical behavior, mean (range) Communication, mean (range) Peer interaction, mean (range) Repetitive behavior, mean (range) Social reciprocity, mean (range)	36[a] 44.0 (16-56) 39.3 (17-60) 31.2 (13-40) 54.0 (24-80) 33.9 (14-48)
DSM-5 severity level[b] Level 1 (mild), n (%) Level 2 (moderate), n (%) Level 3 (severe), n (%)	 3 (8.1) 15 (40.5) 19 (51.4)
ADOS®-2 comparison score, n <5, n (%) 5-7, n (%) 8-10, n (%)	36[a] 2 (5.6) 19 (52.8) 15 (41.7)

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

[a]One patient had missing data.
[b]DSM-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).[4]

[a]One 3-year-old participant was enrolled.
ABC-C=Aberrant Behavior Checklist-Community; ADOS®-2=Autism Diagnostic Observation Schedule®, 2nd edition; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PRAS-ASD=Parent Rated Anxiety Scale—Autism Spectrum Disorder.

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EFFICACY RESULTS

- At week 14, significant improvement was observed for each ABC-C subscale (**Figure 1**)
- Significant improvements were also seen in PRAS-ASD, APSI, CGI-I, and AIM scales (**Figures 2 and 3**)
- Most caregivers indicated improvements in behavioral, emotional, and social problems (**Figure 4**)

Figure 1. Statistically Significant Improvements in All ABC-C Subscale Scores

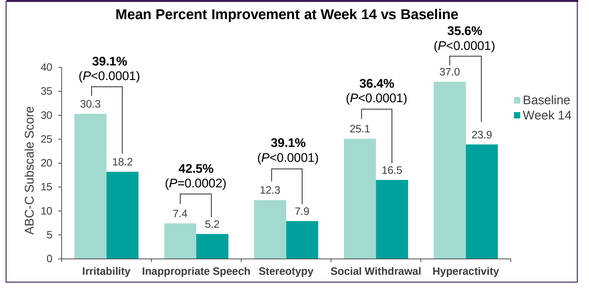


Figure 2. Statistically Significant Improvements in PRAS-ASD, APSI, and CGI-I

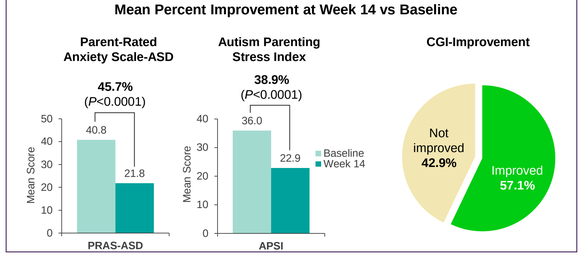


Figure 3. Statistically Significant Improvements in Autism Impact Measure Scores

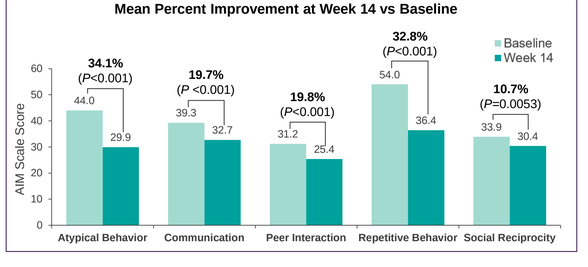
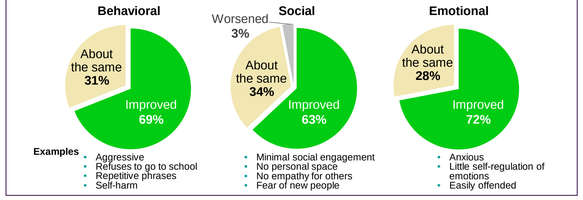


Figure 4. Notable Improvements in the Qualitative Caregiver Behavioral Problems Survey at Week 14



SAFETY RESULTS

- All AEs were mild (75%) or moderate (25%) and reported in 49% of patients (**Table 2**)
- Treatment-related AEs 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

Table 2. TEAEs experienced by ≥2 patients through 14 weeks

Description	Number of Participants N=37	Number of AEs
Patients with at least 1 TEAE	18 (48.6%)	24
Application site pain	2 (5.4%)	2
Application site pruritus	2 (5.4%)	3
Ear infection	2 (5.4%)	2
Nasopharyngitis	2 (5.4%)	2

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

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