ZYN002 Cannabidiol Transdermal Gel: Efficacy and Safety Findings in Children and Adolescents With Autism Spectrum Disorder (ASD) and Related Disorders

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BACKGROUND

- There is shared underlying neuropathophysiology among autism spectrum disorder (ASD), seizure disorders, and fragile X syndrome (FXS), which may include neuronal disinhibition and alterations in synaptic plasticity and brain anatomical architecture (**Figure 1**)[1-9]
- FXS is the most common monogenic cause of ASD[10]
- Cannabinoid receptors are found in a variety of diverse organisms,[11] indicating that the endocannabinoid system (ECS) is highly evolutionarily conserved and may play central roles in physiology and pathophysiology[12]
- In addition, evidence indicates that the ECS has an important role in the CNS and appears to regulate neuronal development and function, particularly synaptic homeostasis and plasticity[13-15] and may be dysfunctional in ASD and FXS[1,16]
- ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel in development for ASD, FXS, 22q deletion syndrome, and developmental epileptic encephalopathies (DEE)

OBJECTIVE

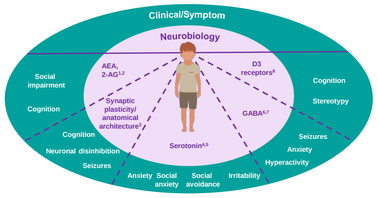
- Select efficacy assessments and safety of ZYN002 in patients aged 3-17 years are presented from 2 open-label trials (BRIGHT [ASD] and BELIEVE [DEE]) and a double-blind, placebo-controlled trial (CONNECT-FX [FXS])

METHODS

- **BRIGHT (ASD)** was an open-label, Phase 2 trial in children and adolescents with ASD (N=37) (**Table 1**)
- **BELIEVE (DEE)** was an open-label, Phase 2 trial in children and adolescents with DEE (N=48) (**Table 1**)
  - Analyses of key endpoints were conducted in 14 (29%) patients with comorbid ASD
- **CONNECT-FX (FXS)** was a randomized, double-blind, placebo-controlled, Phase 3 trial in children and adolescents with FXS (N=212) with a full *FMR1* gene mutation (**Table 1**)
  - Primary endpoint was change in Social Avoidance (SA) as measured by the SA subscale of the Aberrant Behavior Checklist–Community FXS (ABC-C_{FXS})
  - ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set
  - A pre-planned ad hoc analysis of patients having at least 90% methylation of the *FMR1* gene[a] was performed. Patients with complete/near complete methylation are believed to be most likely to have silencing of the *FMR1* gene and may be a different biologic population than the patients without silencing[17,18]

[a]*FMR1* methylation status was determined using Southern blot analysis.

Figure 1. Postulated Shared Neurobiology of ASD, FXS, and Seizures



RESULTS

Table 1. Numbers of Patients With ASD in Each Clinical Trial

Trial	Population	Total Number of Patients	Patients With ASD, n (%)	Patients With Moderate-Severe ASD[a] n (%)
BRIGHT (ZYN2-CL-030)	ASD	37	37 (100%)	34 (92%)
BELIEVE (ZYN2-CL-025)	DEE	48	14 (29%)	NA[b]
CONNECT-FX (ZYN2-CL-016)	FXS	212	180 (85%)	158 (75%)
≥90% *FMR1* methylation group	FXS	169	146 (86%)	127 (75%)

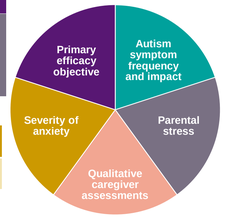
[a]Severity of ASD-related symptoms as defined by Autism Diagnostic Observation Schedule®-2 (ADOS®-2) comparison scores
[b]NA=not available; ASD severity not assessed.

Figure 2. Results of the BRIGHT Phase 2 Trial in ASD (N=37)

Statistically Significant Results at Week 14 Compared to Baseline

Aberrant Behavior Checklist-Community (ABC-C) subscales % improvement

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)



Autism Impact Measure (AIM) % improvement

Atypical behavior: 34.1% (p<0.001)
Communication: 19.7% (p<0.001)
Peer interaction: 19.8% (p<0.001)
Repetitive behavior: 32.1% (p<0.0001)
Social reciprocity: 10.7% (p=0.0053)

Parent-Rated Anxiety Scale for ASD (PRAS-ASD)

Mean improvement of 46% (p<0.0001)

Autism Parenting Stress Index

Mean improvement of 38.9% (p<0.0001)

Qualitative Caregiver Behavioral Problems Survey % Improvements

Behavioral: 69% improved
Social: 63% improved
Emotional: 72% improved

Safety

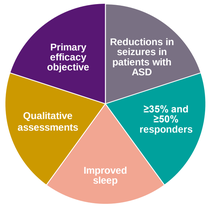
- All treatment-emergent adverse events (TEAEs; any event, whether unrelated or related to study drug) were mild (75%) or moderate (25%) and reported in 49% of patients
- Treatment-related TEAEs were reported in 14% of patients
  - Most were mild and transient
- 1 patient discontinued due to an AE of application site reaction. Dermatologic testing revealed a positive reaction to both active and placebo study gel
- No serious or severe AEs or clinically significant changes in laboratory tests or electrocardiograms (ECGs) were reported

Figure 3. Seizure and Sleep Results of the BELIEVE Phase 2 Trial in DEE (N=48)

Clinically Meaningful Improvements in FIAS/TCS and Sleep vs Baseline

Median % Reductions in Seizures[a]: All Patients

Month 3 (n=33): 44%
Month 6 (n=29): 51%
Month 9 (n=18): 60%
Month 12 (n=18): 73%



Median % Reductions in Seizures[a]: Comorbid ASD

Month 3 (n=10): 45%
Month 6 (n=10): 59%
Month 9 (n=8): 67%
Month 12 (n=8): 74%

ELDQOL All Patients

Statistically significant reductions in subscale scores for seizure severity, behavior, and mood (p<0.001)

Caregiver Feedback All Patients

Verbatim feedback included improved vitality, concentration and cognition, and school improvement

% of patients with ≥35% and ≥50% Reductions in FIAS and TCS All Patients / Comorbid ASD

≥35% reductions	≥50% reductions
Month 3: 58% / 60%	Month 3: 46% / 40%
Month 6: 62% / 80%	Month 6: 55% / 70%
Month 12: 89% / 75%	Month 12: 83% / 75%

All Patients Sleep Disturbance Scale for Children (SDSC)[b] Improvement in mean *t*-scores; % improvement in patients with significant disorder

Statistically significant improvements observed in

Disorders of Initiating & Maintaining Sleep −7.3 (p=0.018); 18%
Sleep Wake Transition −9.2 (p=0.018); 50%
Sleep Hyperhidrosis −7.2 (p=0.04); 35%
Total SDSC score −8.9 (p=0.01); 62%
Baseline vs week 26

Patients with Comorbid ASD Sleep Disturbance Scale for Children (SDSC)[b] Improvement in mean *t*-scores; % improvement in patients with significant disorder

Statistically significant improvements observed in

Sleep Breathing −6.7 (p=0.018); 58%
Sleep Wake Transition −15.8 (p=0.006); 61%
Total SDSC score −10.4 (p=0.02); 80%
Baseline vs week 26

Safety

- ZYN002 was well tolerated in BELIEVE
- Most TEAEs (any event, whether unrelated or related to study drug) were mild or moderate
- There were 30 serious adverse events reported by 14 patients over the 18-month treatment period, of which 2 (lower respiratory tract infection and status epilepticus) were considered possibly drug related
- One patient, with a history of keratosis pilaris, discontinued study medication due to an AE (intense application site erythema); dermatologic patch testing showed this was not caused by allergic contact dermatitis from ZYN002 and was likely irritant contact dermatitis complicated by a secondary bacterial infection
- There were no clinically significant changes in vital signs, ECGs, or laboratory findings except for 1 patient with a transient, benign, isolated elevation of alkaline phosphatase at week 26 (1.69 × ULN) that was not considered related to study medication

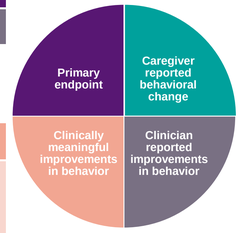
[a]FIAS=focal impaired awareness seizures; TCS=tonic clonic seizures.
[b]In patients with an SDSC Total *t*-score >70 at baseline.

Figure 4. CONNECT-FX Results and Safety: ≥90% *FMR1* Methylation in FXS (N=169)

Consistent Improvements Observed With ZYN002 vs Placebo

ABC-C_{FXS} Social Avoidance subscale

40% median percent improvement in socially avoidant behaviors (p=0.020)



Caregiver Global Impression of Change

Any Improvement
ZYN002 vs placebo

Social interaction
66% vs 41% (p=0.002)

Irritable/Disruptive Behaviors
53% vs 35% (p=0.028)

Social Avoidance/Isolation
60% vs 43% (p=0.038)

Overall behavior
63% vs 48% (p=0.052)

Clinically meaningful improvement

Significantly more patients achieved a clinically meaningful change
ZYN002 vs placebo

Social Avoidance (≥3 points)
58% vs 41% OR=2.04 (p=0.031)

Irritability (≥9 points)
40% vs 24% OR=2.17 (p=0.036)

Clinical Global Impression of Improvement (anchored)[a]

Any Improvement
ZYN002 vs placebo
51% vs 36%
Trend toward statistical significance (p=0.056)

Safety

- ZYN002 was very well tolerated in CONNECT-FX
- There were no serious or severe adverse events reported during the trial
- TEAEs (any event, whether unrelated or related to study drug) were mild or moderate
  - The most common treatment-related TEAE was application site pain (ZYN002: 6.4%; placebo: 1.0%)
- Laboratory values for chemistry and hematology, and ECG parameters were comparable between the placebo and ZYN002 treatment groups, and there were no clinically relevant abnormalities in either group
  - There were no clinically significant changes to liver function tests

[a]Not specific to Social Avoidance. OR=odds ratio.

DISCUSSION

- The ECS is an evolutionarily conserved control system that plays a foundational role in the CNS
- ZYN002 appeared to demonstrate a positive benefit-risk profile across a spectrum of endpoints including behavior, seizure reduction and sleep, when added to standard of care in children and adolescents with ASD and DEE (open-label), as well as in FXS patients with ≥90% methylation of the *FMR1* gene, in an ad-hoc analysis of double-blind treatment with ZYN002 versus placebo
  - **BRIGHT (ASD):** Provides support for 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 (open label) showed improvement in all ASD measures
  - **BELIEVE (DEE):** Meaningful reductions from baseline observed in seizures (FIAS and TCS) with ZYN002 treatment (OL), which were maintained through 12 months. In the subgroup of patients with ASD (n=14), ZYN002 demonstrated meaningful reductions from baseline in FIAS and TCS and improvement in symptoms of sleep disorders as determined from the SDSC
  - **CONNECT-FX (FXS):** ZYN002 was superior to placebo in multiple analyses in the group of patients with ≥90% methylation of their *FMR1* gene (80% of the full analysis set), of which 86% had symptoms of ASD. ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set
- Further trials are warranted to confirm these findings in ASD and ASD-related disorders

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

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