Impact of ZYN002 Cannabidiol Transdermal Gel on Sleep in Children and Adolescents With Developmental and Epileptic Encephalopathies and Comorbid Autism Spectrum Disorder

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BACKGROUND

- Epilepsy and sleep disorders have a bidirectional relationship and co-occur in individuals with autism spectrum disorder (ASD)
- Developmental and epileptic encephalopathies (DEEs) are a group of severe neurodevelopmental disorders, characterized by seizures and abnormal encephalographic activity, that negatively impact development[1]
- DEEs include, but are not limited to, West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome[2]; DEEs with onset ≤18 months have an incidence of 1 in 2000 live births[3]
- Seizures are generally refractory to antiseizure medications (ASMs),[4] and oral administration of ASMs can be difficult due to behavioral and cognitive impairments
- Children with DEEs are medically fragile and have multiple comorbidities, including motor and cognitive impairments, ASD, and sleep disturbance, which further increase disability[3,5,6]
- Improvements in sleep may result in better seizure control and behavior
- ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel in development for DEEs, ASD, and fragile X syndrome
- In an open-label trial with ZYN002, patients with DEEs showed reduced seizure frequency and improved sleep

OBJECTIVES

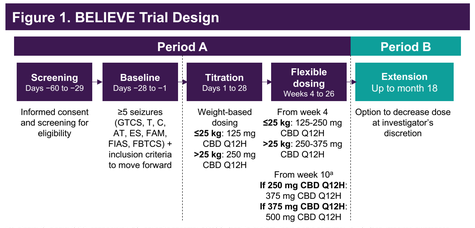
- To compare the impact of ZYN002 on sleep disorders in patients with DEEs, with and without ASD

METHODS

TRIAL DESIGN AND TREATMENT

- ZYN2-CL-025 (BELIEVE) was an open-label, 2-center, multiple-dose, phase 2 trial to assess the safety, tolerability, and efficacy of ZYN002 in patients aged 3 to <18 years with DEEs (**Figure 1**)
- ZYN002 was administered in total daily doses of 250 mg to 1000 mg over an initial 26-week treatment period (Period A) followed by an extension of up to 18 months (Period B)
- Efficacy results for sleep assessments and general safety results for Period A, as well serious adverse events through 72 weeks, are presented here

Figure 1. BELIEVE Trial Design



AT, atonic; C, clonic; CBD, cannabidiol; ES, epileptic spasms; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; FAM, focal aware motor seizures; GTCS, generalized tonic-clonic seizures; Q12H, every 12 hours; T, tonic.
[a]Doses were adjusted at the investigator's discretion.

PATIENTS

- Key inclusion criteria
  - Male and female patients aged 3 to <18 years
  - Diagnosis of DEE as defined by International League Against Epilepsy classification
  - Stable regimen of 1 to 4 ASMs maintained from the baseline period throughout the entire trial
  - History of regression, slowing, or plateau in ≥1 developmental domains after seizure onset
- Key exclusion criteria
  - Use of any tetrahydrocannabinol- or cannabidiol-containing product ≤12 weeks before screening
  - Treatment with a strong inhibitor/inducer of cytochrome P450 3A4
  - Experienced a change in ASM regimen or epilepsy dietary therapy within the previous 4 weeks
  - Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels ≥3 times the upper limit of normal (ULN)

END POINTS

- Safety assessments – Physical and neurologic examinations; vital signs; electrocardiogram (ECG); skin check examination (investigator) and diary (parent/caregiver); and laboratory tests
- Primary efficacy end point – Median percentage change from baseline in 28-day seizure frequency (SF28), captured via the daily seizure diary, for the following types: focal impaired awareness seizures (FIAS) and tonic-clonic seizures (TCS, including generalized TCS and focal to bilateral TCS)
- Sleep efficacy end point: change from baseline to the end of Period A in the Sleep Disturbance Scale for Children (SDSC)

SLEEP ASSESSMENT

- Sleep assessment was conducted by caregivers using the SDSC[7] (**Table 1**)

Table 1. Sleep Assessment

Assessment	Description
Sleep Disturbance Scale for Children[7]	• A 26-item, Likert-type scale (5 possible answers per item) • The items are organized into 6 categories: disorders of initiating or maintaining sleep (7 items), sleep breathing disorders (3 items), disorder of arousal/nightmares (3 items), sleep-wake transition disorder (6 items), disorders of excessive somnolence (5 items), and sleep hyperhidrosis (2 items) • The total score is also calculated

RESULTS

BASELINE CHARACTERISTICS

- A total of 48 patients were enrolled in BELIEVE and were included in the safety analysis set; the mean age was 10.5 years (**Table 2**)
- Of 48 children with DEEs, 25 (52%) had clinically significant sleep disturbance at baseline defined as a SDSC Total t-score >70

Table 2. Baseline Demographics and Disease Characteristics, Safety Analysis Set

Demographic or Disease Characteristic	Safety Analysis Set (N = 48)
Age, years Mean (range)	10.5 (3-16)
Sex, n (%) Male Female	 26 (54.2) 22 (45.8)
Body mass index, kg/m^2 Mean (SD)	19.2 (4.9)
Syndrome, n (%) Dravet syndrome Lennox-Gastaut syndrome West syndrome Other	 8 (16.7) 5 (10.4) 3 (6.3) 32 (66.7)
Seizure type,[a,b] n (%) Focal impaired awareness Tonic-clonic Generalized tonic-clonic Focal to bilateral tonic-clonic	 26 (54.2) 21 (43.8) 14 (29.2) 7 (14.6)
Monthly frequency of focal impaired awareness and/or tonic-clonic seizures,[a] median (range)	8.2 (0-713)
ASD,[c,d] n (%) Seizure type in ASD patients, n (%) Focal impaired awareness Tonic-clonic Generalized tonic-clonic Focal to bilateral tonic-clonic	14 (29.2) 6 (42.9) 8 (57.1) 5 (35.7) 3 (21.4)
Number of concomitant ASMs, mean	2.7
Concomitant ASMs, n (%) Sodium valproate Clobazam Levetiracetam Lamotrigine Topiramate	48 (100) 34 (70.8) 25 (52.1) 17 (35.4) 16 (33.3) 13 (27.1)

ASD, autism spectrum disorder; ASM, antiseizure medication; SD, standard deviation.
[a]During the 4-week baseline period.
[b]For seizure type, N = 33. Thirty-three patients with focal impaired awareness and/or tonic-clonic seizures; patients could have more than 1 seizure type.
[c]ASD diagnosis per investigator.
[d]For seizure type, N = 11. Eleven patients with focal impaired awareness and/or tonic-clonic seizures; patients could have more than 1 seizure type.

SLEEP SCORES

- Of 25 children with DEEs and clinically significant sleep disturbances, 16 completed the SDSC in full at week 26
  - 11 DEE patients without ASD
  - 5 DEE patients with ASD
- In patients without ASD, an improvement in mean t-score at week 26 was seen in initiating and maintaining sleep (−8.7; *P* = .033) (**Table 3**)
- **Figure 2** shows the percentage of patients without ASD with a threshold t-score >70 at Baseline and Week 26, corresponding to clinically significant sleep problems[8-9]
- In patients with ASD, improvements in mean t-scores at week 26 were observed in (**Table 4**):
  - Sleep breathing (−6.7; *P* = .018)
  - Sleep-wake transition (−15.8; *P* = .006)
  - Total SDSC score (−10.4; *P* = .024)
- **Figure 3** shows the percentage of patients with ASD with a threshold t-score >70 at Baseline and Week 26, corresponding to clinically significant sleep problems

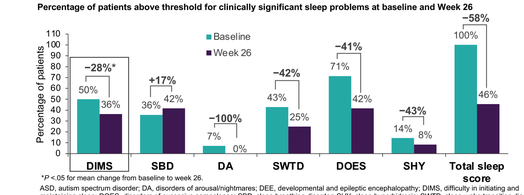
Table 3. Change From Baseline in the SDSC in DEE Patients Without ASD and >70 Total t-Score (Clinically Significant Sleep Disorder) at Baseline

SDSC factors	*t*-score Mean (SD)	Change (negative number is improvement)	*P* value
Total score			
Baseline (n = 11)	78.5 (5.82)		
Week 26 (n = 11)	70.2 (10.18)	−8.3	0.082
Disorders of initiating and maintaining sleep			
Baseline (n = 11)	69.5 (11.6)		
Week 26 (n = 11)	60.8 (14.02)	−8.7	**0.033**
Sleep breathing disorders			
Baseline (n = 12)	62.0 (17.9)		
Week 26 (n = 12)	65.9 (17.91)	3.9	0.122
Disorders of arousal/nightmares			
Baseline (n = 12)	53.6 (10.4)		
Week 26 (n = 12)	50.8 (7.40)	−2.8	0.186
Sleep-wake transition disorder			
Baseline (n = 12)	73.1 (10.77)		
Week 26 (n = 12)	67.3 (15.11)	−5.8	0.245
Disorders of excessive somnolence			
Baseline (n = 12)	74.5 (12.77)		
Week 26 (n = 12)	70.3 (12.44)	−4.3	0.321
Sleep hyperhidrosis			
Baseline (n = 12)	60.8 (17.08)		
Week 26 (n = 12)	52.9 (11.02)	−7.9	0.131

ASD, autism spectrum disorder; DEE, developmental and epileptic encephalopathy; SDSC, Sleep Disturbance Scale for Children.

Figure 2. Improvement in Sleep Disturbance in DEE Patients Without ASD and With Clinically Significant Sleep Disorder at Baseline by Total Sleep Score (n=11)

Percentage of patients above threshold for clinically significant sleep problems at baseline and Week 26



*P <.05 for mean change from baseline to week 26.
ASD, autism spectrum disorder; DA, disorders of arousal/nightmares; DEE, developmental and epileptic encephalopathy; DIMS, difficulty in initiating and maintaining sleep; DOES, disorders of excessive somnolence; SBD, sleep breathing disorder; SHY, sleep hyperhidrosis; SWTD, sleep-wake transition disorders.

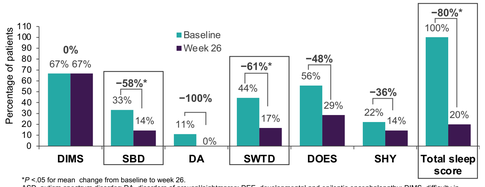
Table 4. Change From Baseline in the SDSC in DEE Patients With ASD and >70 Total t-Score at Baseline

SDSC factors	*t*-score Mean (SD)	Change (negative number is improvement)	*P* value
Total score			
Baseline (n = 5)	81.0 (11.31)		
Week 26 (n = 5)	70.6 (16.76)	−10.4	**0.024**
Disorders of initiating and maintaining sleep			
Baseline (n = 6)	84.2 (19.17)		
Week 26 (n = 6)	79.5 (16.18)	−4.7	0.37
Sleep breathing disorders			
Baseline (n = 7)	66.1 (17.14)		
Week 26 (n = 7)	59.4 (15.55)	−6.7	**0.018**
Disorders of arousal/nightmares			
Baseline (n = 6)	48.4 (4.49)		
Week 26 (n = 6)	48.8 (4.49)	0.0	NA
Sleep-wake transition disorders			
Baseline (n = 6)	73.2 (13.32)		
Week 26 (n = 6)	57.3 (12.83)	−15.8	**0.006**
Disorders of excessive somnolence			
Baseline (n = 7)	71.7 (20.36)		
Week 26 (n = 7)	68.3 (15.10)	−3.4	0.544
Sleep hyperhidrosis			
Baseline (n = 7)	57.6 (14.83)		
Week 26 (n = 7)	51.7 (10.84)	−5.9	0.130

ASD, autism spectrum disorder; DEE, developmental and epileptic encephalopathy; SD, standard deviation; SDSC, Sleep Disturbance Scale for Children.

Figure 3. Improvement in Sleep Disturbance in DEE Patients With ASD and With Clinically Significant Sleep Disorder at Baseline by Total Sleep Score (n=5)

Percentage of patients above threshold for clinically significant sleep problems at baseline and week 26



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ASD, autism spectrum disorder; DA, disorders of arousal/nightmares; DEE, developmental and epileptic encephalopathy; DIMS, difficulty in initiating and maintaining sleep; DOES, disorders of excessive somnolence; SBD, sleep breathing disorder; SHY, sleep hyperhidrosis; SWTD, sleep-wake transition disorders.

SAFETY

- ZYN002 was well tolerated in BELIEVE
- Most treatment-emergent adverse events (any event, whether unrelated or related to study drug) were mild or moderate
  - 60% of participants had ≥1 related adverse event over 26 weeks; 93% were mild/moderate severity
- A total of 30 serious adverse events were reported by 14 patients over the 72-week 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 adverse event (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

Conclusions

- BELIEVE was an open-label trial of transdermal cannabidiol added on top of standard of care for the primary treatment of DEEs
- In patients with DEEs, ZYN002 was associated with improved sleep in children with or without ASD
- The DEE with ASD cohort showed more wide-ranging benefits of improved sleep
- Interestingly, the improvements were in different aspects of sleep in the patients with and without ASD
- ZYN002 was well tolerated in this patient population of children and adolescents with DEEs
- Although the sample size with complete sleep data was limited, the overall direction and magnitude of changes appear to be of potential clinical importance and may be worthy of future prospective confirmation

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