Quality of Life and Sleep Assessments in Children with Developmental and Epileptic Encephalopathies Treated With ZYN002 (CBD) Transdermal Gel: BELIEVE (ZYN2-CL-025)

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BACKGROUND

- Developmental and epileptic encephalopathies (DEEs) are a severe group of neurodevelopmental disorders characterized by seizures and abnormal electroencephalogram activity that negatively impact development[1]
- DEEs include, but are not limited to, West syndrome, Lennox-Gastaut syndrome (LGS), and Dravet syndrome[2]; DEEs with onset ≤18 months have an incidence of 1 in 2000 live births[3]
- Children with DEEs are medically fragile and have multiple comorbidities including motor and cognitive impairments, autism spectrum disorder, and sleep disturbance[4-6]
- Seizures are generally refractory to standard antiseizure medications (ASMs)[7] and oral administration of ASMs can be difficult due to behavioral and cognitive impairments
- Quality of life (QoL) of children with drug-resistant epilepsy declines with greater number of ASMs, greater seizure frequency, and lower IQ,[8] further underscoring a need for new therapies
- ZYN002 is a pharmaceutically manufactured transdermal cannabidiol (CBD) gel currently in clinical development for the reduction of seizures in patients with DEEs
- We present the QoL and sleep assessment results of the phase 2 BELIEVE study of ZYN002 in children with DEEs; efficacy and safety are presented in another poster at this meeting[9]

OBJECTIVE

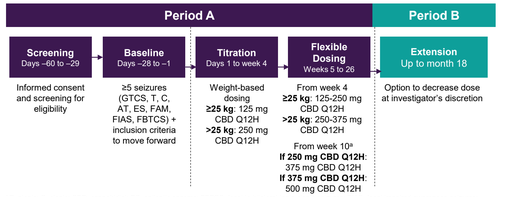
- To evaluate the effects of ZYN002 transdermal CBD gel on QoL, sleep, and caregiver qualitative assessment in child and adolescent patients with DEEs

METHODS

STUDY DESIGN AND TREATMENT

- ZYN2-CL-025 (BELIEVE) was an open-label, multicenter, multiple-dose, phase 2 study 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 up to 46-week extension (Period B)
- Results for the first 26 weeks (Period A) are presented here

Figure 1. BELIEVE Study 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 that was maintained from the baseline period throughout the entire study
  - History of regression, slowing, or plateau in at least one developmental domain after seizure onset
- Key exclusion criteria
  - Use of tetrahydrocannabinol or CBD product ≤12 weeks before screening
  - Treatment with a strong inhibitor/inducer of CYP3A4
  - Change in ASM regimen or epilepsy dietary therapy within the previous 4 weeks
  - Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels ≥3x the upper limit of normal (ULN)

QOL ASSESSMENTS

- QoL assessments were caregiver-rated and included the ELDQOL scale,[10] a daily "good day/bad day" assessment, and qualitative feedback (**Table 1** and **Figure 2**)

Presented at the 2020 American Epilepsy Society (AES) Annual Meeting; December 2020.

Table 1. QoL Assessments

Assessment	Description
ELDQOL[10,a]	• Scale measuring QoL over the prior 4 weeks • Subscales include seizure severity, behavior, and mood • Higher subscale scores indicate poorer QoL
Daily good day/bad day assessment	• Daily assessment of a patient's QoL, in which parents were asked to provide an overall daily score, considering factors such as seizure frequency, alertness, behavior, mood, etc. • Scoring is described in **Figure 2**
Qualitative caregiver feedback	• Investigators asked the following questions of caregivers at week 26: – Has anything improved for "X" and your family since "X" has been using the gel? – Has anything got worse for "X" and your family since "X" has been using the gel? – Let me just ask about a few specific things: Daily activities, eg, school attendance? If so how? Alertness? If so how? • Two independent evaluators working separately coded caregiver statements using ATLAS.ti and classified statements into domains

ELDQOL, Epilepsy and Learning Disabilities Quality of Life; QoL, quality of life.
[a]The ELDQOL was modified with written permission from the developers; modifications did not impact the validity of the questionnaire.

Figure 2. Good Day/Bad Day Assessment

SLEEP ASSESSMENT

- Sleep assessment was conducted by caregivers using the Sleep Disturbance Scale for Children (SDSC)[11] (**Table 2**)

Table 2. Sleep Assessment

Assessment	Description
Sleep Disturbance Scale for Children (SDSC)[11]	• A 26-item, Likert-type scale (5 possible answers per item) • The items are organized into 6 categories: disorders of initiating or maintaining sleep (DIMS, 7 items), sleep breathing disorders (SBD, 3 items), disorder of arousal/nightmares (DA, 3 items), sleep wake transition disorder (SWTD, 6 items), disorders of excessive somnolence (DOES, 5 items), and sleep hyperhidrosis (SHY, 2 items) • The total score is also calculated

END POINTS

- QoL efficacy end points
  - Change from baseline to the end of Period A in the ELDQOL
  - Change from baseline in "good day/bad day" assessment
- Sleep efficacy end points
  - Change from baseline to the end of Period A in the SDSC
- Qualitative caregiver end points
  - Qualitative statements of parents and caregivers at the end of Period A
- Safety Assessments: Physical and neurologic examinations, vital signs, electrocardiogram (ECG), skin check examination (investigator) and diary (parent/caregiver), and laboratory tests

STATISTICAL METHODS

- Analysis populations
  - Safety analysis set: All patients who received ≥1 dose of study drug
  - Modified intent-to-treat (mITT) population: All patients who received ≥80 days of study drug and completed ≥80% of seizure diaries
- For the ELDQOL, changes from baseline in mean subscale score at the end of Period A were compared using a paired *t* test; *P* values are nominal
- SDSC raw scores were converted into *t*-scores before comparison of means
- Good day/bad day assessments were averaged over monthly periods, and descriptive statistics are presented
- Descriptive statistics are presented for coded qualitative caregiver feedback
- Statistics were analyzed using SAS version 9.4 (SAS Institute)

RESULTS

BASELINE CHARACTERISTICS

- 48 patients were enrolled in BELIEVE and included in the safety analysis set; the mean age was 10.5 years (**Table 3**)
  - One quarter of patients had LGS or Dravet syndrome
- Clinically important comorbid conditions were present in all patients and included gait and movement disorders (45.8%), sleep disturbances (39.6%), chronic respiratory conditions/infections (37.5%), ASD (29.2%) and percutaneous endoscopic gastrostomy (14.6%)
- The mITT population comprised 46 patients

Table 3. 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)
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)
Syndrome, n (%) Dravet Syndrome Lennox-Gastaut syndrome Epilepsy with myoclonic-atonic seizures West Syndrome Other[c]	 8 (16.7) 5 (10.4) 6 (12.5) 3 (6.3) 26 (54.2)
Monthly frequency of focal impaired awareness and/or tonic-clonic seizures,[a] median (range)	8.2 (0, 713)
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)

ASM, antiseizure medication.
[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 one seizure type.
[c]Includes generalized epileptic encephalopathy, focal DEE, Multifocal DEE, DEE unclassified.

ELDQOL

- Statistically significant reductions from baseline in mean ELDQOL subscale scores for seizure severity, behavior, and mood were observed at week 26 (**Table 4**)

Table 4. Change From Baseline in Mean ELDQOL Subscale Scores, mITT Population (N = 40)[a]

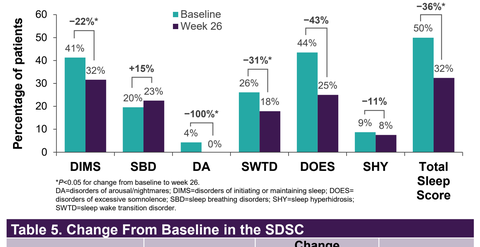
	Mean (SD)	Change[b]	*P* value
ELDQOL subscale			
Seizure severity Baseline (n = 40) Week 26 (n = 40)	 26 (54.2) 22 (45.8)	 −0.19	 **0.008**
Behavior Baseline (n = 40) Week 26 (n = 40)	 8 (16.7) 5 (10.4)	 −0.21	 **0.001**
Mood Baseline (n = 40) Week 26 (n = 40)	 26 (54.2) 21 (43.8)	 −0.15	 **0.001**

[a]Table 4 includes patients who completed both baseline and week 26 ELDQOL assessments; 6 patients completed the baseline assessment but did not complete the week 26 assessment.
[b]Negative change from baseline reflects an improvement.

SLEEP SCORES

- **Figure 3** shows the percentage of patients with a threshold *t*-score >70 at Baseline and Week 26, corresponding to clinically significant sleep problems[12,13]
- Statistically significant improvements from baseline in sleep scores were observed in the total score, Disorders of Initiating or Maintaining Sleep (DIMS), Disorder of Arousal/Nightmares (DA), and Sleep Wake Transition Disorder (SWTD) (**Table 5**)

Figure 3. The Sleep Disturbance Scale for Children (SDSC)–Percentage of Patients Above Threshold for Clinically Significant Sleep Problems at Baseline and Week 26



*P<0.05 for change from baseline to week 26.
DA=disorders of arousal/nightmares; DIMS=disorders of initiating or maintaining sleep; DOES= disorders of excessive somnolence; SBD=sleep breathing disorders; SHY=sleep hyperhidrosis; SWTD=sleep wake transition disorder.

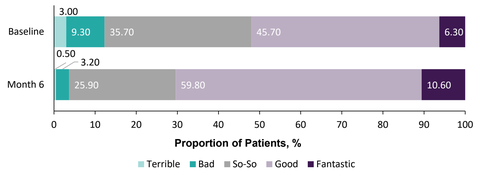
Table 5. Change From Baseline in the SDSC

SDSC Factors	*t*-Score Mean (SD)	Change (negative number is improvement)	*P* value
Total Score			
Baseline (n=46)	71.6 (12.68)		
Week 26 (n=37)	63.9 (13.40)	−5.1	**0.012**
Disorders of Initiating and Maintaining Sleep (DIMS)			
Baseline (n=46)	69.6 (14.67)		
Week 26 (n=38)	63.2 (15.76)	−5.1	**0.006**
Sleep Breathing Disorders (SBD)			
Baseline (n=46)	60.6 (15.46)		
Week 26 (n=40)	58.9 (15.08)	0.40	0.797
Disorders of Arousal/Nightmares (DA)			
Baseline (n=46)	51.5 (9.91)		
Week 26 (n=39)	49.0 (5.07)	−1.7	**0.031**
Sleep Wake Transition Disorder (SWTD)			
Baseline (n=46)	65.0 (13.09)		
Week 26 (n=39)	60.2 (13.78)	−4.6	**0.030**
Disorders of Excessive Somnolence (DOES)			
Baseline (n=46)	68.5 (16.76)		
Week 26 (n=40)	63.1 (13.82)	−3.6	0.100
Sleep Hyperhidrosis (SHY)			
Baseline (n=46)	52.7 (12.28)		
Week 26 (n=40)	50.6 (9.95)	−2.8	0.154

GOOD DAY/BAD DAY ASSESSMENT

- In comparing baseline to Month 6, the combined proportion of "good day" and "fantastic day" reports increased from 52.0% at baseline to 70.4%, and the combined proportion of "terrible day" and "bad day" reports decreased from 12.3% at baseline to 3.7% (**Figure 4**)

Figure 4. Distribution of Good Day/Bad Day Ratings at Baseline and Month 6[a]



QUALITATIVE CAREGIVER FEEDBACK

- The qualitative caregiver assessment was administered to parents/caregivers for 43 of the 46 patients in the mITT population
- 84% (n = 36) of parents/caregivers provided ≥1 statement about improvement and 60% (n = 26) provided ≥1 statement about worsening (**Table 6**)
- Improvement in summary measures of qualitative assessments was observed in most patients for most measures
  - Any improvement: 84% (n = 36)
  - Improved vitality: 58% (n = 25)
  - Improvement in seizures: 51% (n = 22)
  - Improved cognition/concentration: 47% (n = 20)
  - Improved socially avoidant behaviors: 44% (n = 19)
  - Improvement in irritability: 33% (n = 14)
  - School improvement: 28% (n = 12)
  - Medical improvement: 14% (n = 6)

Table 6. Most Frequent Positive and Negative Qualitative Statements (n ≥ 8) Made by Parents and Caregivers During Period A, mITT Population (N = 43)

Improvement/Positive Statement	n (%)
Behavior, Cognition, Mood	
Improved alertness	17 (40)
Improved engagement/participation	15 (35)
Improved cognition	14 (33)
Attending school on time/more often	12 (28)
More energy/less fatigue	12 (28)
Improved concentration	10 (23)
Improved behavior	9 (21)
Improved mood	8 (19)
Seizures	
Reduced seizure frequency	16 (37)
Reduced seizure amplitude/intensity	9 (21)
Reduced seizure duration	9 (21)
Worsening/Negative Statement	n (%)
Other	
Difficulty in applying gel	11 (26)
Redness, dry skin, or sensitive skin at gel application site	8 (19)

SAFETY

- ZYN002 was well tolerated in BELIEVE
- Most treatment-emergent adverse events (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 72-week treatment period, of which two (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

Conclusions

- Treatment with ZYN002 may be associated with clinically meaningful improvements in:
  - Seizure severity, behavior, and mood
  - Initiating and maintaining sleep, disorders of arousal/nightmares, sleep wake transition, and overall sleep
  - Vitality, cognition/concentration, and socially avoidant behavior
- ZYN002 was well tolerated over 72 weeks of treatment in this patient population of children and adolescents with DEEs

REFERENCES

1. Scheffer IE et al. *Epilepsia*. 2017;58(4):512-521.
2. Aaberg KM et al. *Epilepsia*. 2017;58(11):1880-1891.
3. Howell KB et al. *Epilepsia*. 2018;59:1177-1187.
4. Skluzacek JV et al. *Epilepsia*. 2011;52(suppl 2):95-101.
5. Turner SJ et al. *Neurology*. 2017;88(8):743-749.
6. Rodda JM et al. *Arch Neurol*. 2012;69:873-878.
7. Vigevano F et al. *Epilepsia*. 2013;54(suppl 8):45-50.
8. Conway L et al. *Epilepsia*. 2016;57(8):1256-1264.
9. Scheffer I et al. ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Developmental and Epileptic Encephalopathies: An Open-Label Clinical Trial [BELIEVE (ZYN2-CL-025)]. Presented at the 2020 American Epilepsy Society (AES) Annual Meeting; December 2020.
10. Buck, D, et al. *Epilepsy Behav*. 2007;10(1):38-43.
11. Bruni, O, et al. *J Sleep Res*. 1996;5(4):251-261.
12. Marriner, AM, et al. *J Sleep Res*. 2017;26(5):587-594.
13. Licheni, SH, et al. *Dev Med Child Neurol*. 2018;60(2):192-198.

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