Quality of Life and Qualitative Caregiver Assessments in Children and Adolescents with Developmental and Epileptic Encephalopathies Treated With Cannabidiol Transdermal Gel: An Open-Label Clinical Trial (BELIEVE)

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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 (other DEEs start later) have an incidence of 1 in 2000 live births[3]
- Children with DEEs are medically fragile and often have comorbidities including motor and speech impairments, autism spectrum disorder, and sleep disturbance[4-6]
- Seizure activity is generally refractory to standard antiseizure medications (ASMs)[7] and oral administration of ASMs in children with DEEs is difficult due to behavioral and cognitive impairments
- Quality of life (QoL) of children with refractory epilepsy declines with greater number of antiseizure medications, 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 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]

OBJECTIVES

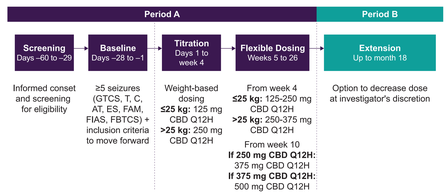
- To evaluate the effects of ZYN002 transdermal CBD gel on QoL and caregiver qualitative assessment in child and adolescent patients with DEEs

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; FBTCS, focal to bilateral tonic-clonic seizures; C, clonic; CBD, cannabidiol; ES, epileptic spasms; 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
  - History of developmental delay with regression, slowing, or plateau in at least one developmental domain after seizure onset
- Key exclusion criteria
  - Use of any tetrahydrocannabinol- or CBD-containing product ≤12 weeks before screening
  - Treatment with a strong inhibitor/inducer of CYP3A4
  - Experienced a 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

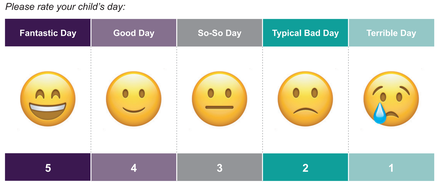
- QoL assessments were caregiver-rated and included the Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale, a daily "good day/bad day" assessment, and qualitative feedback (**Table 1** and **Figure 2**)

Table 1. QoL Assessments

Assessment	Description
ELDQOL[14,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 score for the day, considering factors such as seizure frequency, alertness, behavior, mood, etc. • Scoring was as follows: 1, terrible day; 2, bad day; 3, so-so day; 4, good day; 5, fantastic day
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



END POINTS

- QoL efficacy end points
  - Change from baseline to the end of Period A in the subscale scores of the ELDQOL
  - Change from baseline in "good day/bad day" assessment
- 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
- 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 DEMOGRAPHICS AND DISEASE CHARACTERISTICS

- 48 patients were enrolled in BELIEVE and included in the safety analysis set; the mean age was 10.5 years (**Table 2**)
  - One quarter of patients had LGS or Dravet syndrome
- Clinically important comorbid conditions were present in all patients and included chronic respiratory conditions/infections (37.5%), gait and movement disorders (45.8%), percutaneous endoscopic gastrostomy (14.6%), and sleep disturbances (39.6%)
- The mITT population comprised 46 patients

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	26 (54.2)
Female	22 (45.8)
Diagnosis, n (%)	
Dravet syndrome	8 (16.7)
Lennox-Gastaut syndrome	5 (10.4)
West syndrome	3 (6.3)
Other	32 (66.7)
Seizure type,[a,b] n (%)	
Focal impaired awareness	26 (54.2)
Tonic-clonic	21 (43.8)
Generalized tonic-clonic	14 (29.2)
Focal to bilateral tonic-clonic	7 (14.6)
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 (%)	48 (100)
Sodium valproate	34 (70.8)
Clobazam	25 (52.1)
Levetiracetam	17 (35.4)
Lamotrigine	16 (33.3)
Topiramate	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.

ELDQOL

- Statistically significant reductions from baseline in mean ELDQOL subscale scores for seizure severity, behavior, and mood were observed at week 26 (*P* < 0.01 for all) (**Table 3**)

Table 3. Change from Baseline in Mean ELDQOL Subscale Scores, mITT Population (N = 40)[a]

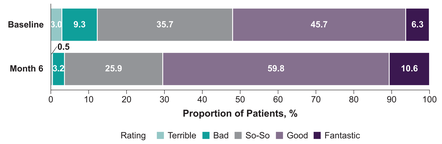
	Mean (SD)	Change[b]	*P* value
ELDQOL subscale			
Seizure severity			
Baseline (n = 40)	1.90 (0.410)		
Week 26 (n = 40)	1.71 (0.476)	−0.19	**0.008**
Behavior			
Baseline (n = 40)	2.19 (0.567)		
Week 26 (n = 40)	1.98 (0.538)	−0.21	**0.001**
Mood			
Baseline (n = 40)	2.05 (0.409)		
Week 26 (n = 40)	1.90 (0.417)	−0.15	**0.001**

[a]Table 3 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.

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 3**)

Figure 3. Distribution of Good Day/Bad Day Ratings at Baseline and Month 6[a]



[a]Modified intent-to-treat (mITT) population, observed cases during the 4 weeks of month 6.

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 (**Tables 4 and 5**)
- 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 4. 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)

Table 5. Example Verbatim Responses For Positive and Negative Qualitative Statements Made by Parents and Caregivers During Period A, mITT Population (N = 43)

Improvement/Positive Statements

Alertness, engagement/participation, cognition:
- *More alert when given simple commands*
- *More of a willingness to learn and do the things he was missing out on*
- *Cognitive shift, better understanding when asked to do something*

School:
- *School—now attending full days for a full week—previously only going half days a few times a week so remarkable improvement*

Energy/concentration:
- *Longer periods of being settled, able to complete an activity he starts*
- *He had a bit more spark and energy*

Behavior/mood:
- *Social improvement, having better days, making friends and not being social (sic) isolated from peers due to his change in his behavior*
- *He is happier, more engaged and able to now wave at people*

Seizures:
- *Yes! Seizures have had a significant reduction, they are less frequent and also shorter*

Worsening/Negative Statements

Difficulty in applying gel:
- *Application of the gel, not fun, time consuming*

Redness, dry skin, or sensitive skin at gel application site:
- *Sensitive skin/skin rashes*

SAFETY

- During Period A, 46 patients (95.8%) experienced ≥1 adverse event (AE), 29 (60.4%) experienced ≥1 treatment-related AE, and 10 (20.8%) experienced ≥1 serious AE
- The most common treatment-related AEs were application site dryness (n = 4, 8.3%), application site pain (n = 4, 8.3%), and somnolence (n = 4, 8.3%)
  - All 4 patients with treatment-related somnolence were taking concomitant clobazam
  - Only 1 (2.1%) treatment-related gastrointestinal AE was reported
- There were no clinically significant changes in vital signs, ECGs, or laboratory findings except for one patient with a benign, isolated elevation of alkaline phosphatase at week 26 (1.69× ULN) that was not considered related to study medication

CONCLUSIONS

- ZYN002 was well tolerated over 26 weeks of treatment in a medically fragile patient population of children and adolescents with DEEs
- Treatment with ZYN002 may be associated with clinically meaningful improvements in social behaviors and cognitive symptoms and increased QoL in children and adolescents with DEEs and their families

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