Cannabidiol Transdermal Gel in Children and Adolescents With Developmental and Epileptic Encephalopathies: 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 have an incidence of 1 in 2000 live births (onset ≤18 months)[3] and are associated with increased risk for mortality:other DEEs start later[4]
- Seizure activity is generally refractory to antiseizure medications (ASMs),[5] and oral administration of therapies can be challenging in children with behavioral and cognitive problems
- Patients are medically fragile and often have comorbidities including motor and speech impairments, autism spectrum disorder, and sleep disturbance, which further increase disability[3,6,7]
- Cannabidiol (CBD) is the main noneuphoric component of the *Cannabis* plant, and an oral formulation reduces seizures in DEE syndromes including LGS and Dravet syndrome[8-10]
- ZYN002 is a pharmaceutically manufactured transdermal CBD gel currently in clinical development for reduction of seizures in patients with DEEs

OBJECTIVE

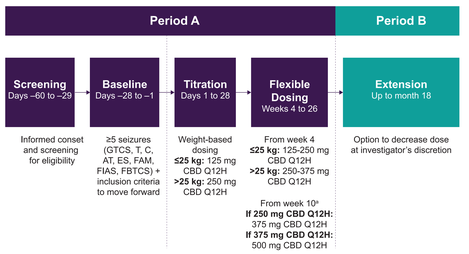
- To evaluate the safety, tolerability, and efficacy of ZYN002 in children and adolescent patients with DEEs

METHODS

STUDY DESIGN AND TREATMENT

- ZYN2-CL-025 (BELIEVE) was an open-label, two-center, 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)

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 during Period A for the following types in total: focal impaired awareness seizures (FIAS) and tonic-clonic seizures (TCS, including generalized tonic-clonic seizures [GTCS] and focal to bilateral tonic-clonic seizures [BTCS])
- Number of patients meeting 35% and 50% reduction in FIAS and TCS

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
- Statistics were analyzed using SAS version 9.4 (SAS Institute)

RESULTS

BASELINE DEMOGRAPHICS, DISEASE CHARACTERISTICS, AND SEIZURE FREQUENCY

- 48 patients were enrolled in BELIEVE and included in the safety analysis set; the mean age was 10.5 years (**Table 1**)
  - 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; 33 patients in the mITT population had FIAS and/or TCS at baseline and constituted the population in which the primary efficacy end point was measured

Table 1. Baseline Demographics and Disease Characteristics, Safety Analysis Set

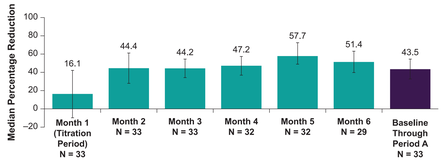
Demographic or Disease Characteristic	Safety Analysis Set (N = 48)
Age, years	
Mean (range)	10.5 (3, 16)
Sex, n (%)	
Male	26 (54.2)
Female	22 (45.8)
Body mass index, kg/m^2	
Mean (SD)	19.2 (4.91)
Diagnosis, n (%)	
Dravet Syndrome	8 (16.7)
Lennox-Gastaut syndrome	5 (10.4)
West Syndrome	3 (6.3)
Other	32 (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.

EFFICACY

- Over the initial treatment period (Period A), the median percentage reduction from baseline in monthly frequency of FIAS and TCS was 43.5% (primary efficacy end point; range, −152.2 to 100.0; **Figure 2**)
  - Reduction from baseline in 28-day seizure frequency was ≥44% from month 2 onward
  - When analyzed by seizure type, median (range) reductions from baseline at month 6 for FIAS, GTCS, and BTCS were 45.3% (−1000.0, 100.0), 59.5% (−141.1, 100.0), and 58.7% (−79.0, 100.0), respectively

Figure 2. Median Percentage Reduction From Baseline in 28-Day Frequency of FIAS and TCS by Time Point During Period A, mITT Population With FIAS and/or TCS at Baseline (N = 33)



FIAS, focal impaired awareness seizures; mITT, modified intent-to-treat; TCS, tonic-clonic seizures.
Bars represent median ± standard error (calculation: [range/4]/square root[N]). Median values are shown above each bar.
Month = SF28

- The percentage of patients meeting ≥35% and ≥50% reduction in FIAS and TCS at months 3 and 6 were 57.6% and 62.1%, and 45.5% and 55.2%, respectively (**Figure 3**)

Figure 3. Percentage of Patients With 35% and 50% Reduction in FIAS and TCS by Time Point, mITT Population With FIAS and/or TCS at Baseline (N = 33)

FIAS, focal impaired awareness seizures; mITT, modified intent-to-treat; TCS, tonic-clonic seizures.
Month = SF28

SAFETY

- Most patients (n=46, 95.8%) experienced ≥1 adverse event (AE) during Period A (**Table 2**)
  - Most AEs were mild (77.1%) or moderate (19.3%)
- Sixty percent of patients (n=29) experienced ≥1 treatment-related AE
  - The most common treatment-related AEs were application site dryness, application site pain, and somnolence
  - All 4 patients with treatment-related somnolence were taking concomitant clobazam
  - Only 1 (2.1%) treatment-related gastrointestinal AE (diarrhea)
- One patient, with a history of keratosis pillaris, 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
- 10 patients (20.8%) reported a serious AE (SAE); most were infection-related
  - Two SAEs (nonconvulsive status epilepticus and lower respiratory tract infection) were considered possibly related to treatment
  - All SAEs resolved and did not require dose alteration
- 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

Table 2. Summary of Adverse Events Reported During 26-Week Period A, Safety Analysis Set

No. (%) of patients	Safety Analysis Set (N = 48)
AE	46 (95.8)
Treatment-related AE	29 (60.4)
Most common treatment-related AEs	
Application site dryness	4 (8.3)
Application site pain	4 (8.3)
Somnolence	4 (8.3)
Application site reaction	2 (4.2)
Fatigue	2 (4.2)
Decreased appetite	2 (4.2)
SAE	10 (20.8)
AE leading to discontinuation	1 (2.1)

AE, adverse event; SAE, serious adverse event.

CONCLUSIONS

- BELIEVE is the first clinical trial of ZYN002 (transdermal CBD) in DEEs
- These data suggest meaningful reductions in FIAS and TCS with ZYN002 treatment beginning as early as month 2 and sustained through 26 weeks
- ZYN002 was well tolerated over 26 weeks of treatment in a medically fragile patient population of children and adolescents with DEEs
- The positive benefit/risk profile of ZYN002 in this trial supports further study in patients with DEEs and FIAS and TCS

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