ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Developmental and Epileptic Encephalopathies: An Open-Label Clinical Trial [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]
- 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, autism spectrum disorder (ASD), and sleep disturbance, which further increase disability[3,5,6]
- Cannabidiol (CBD) is the main noneuphoric cannabinoid of the *Cannabis* plant, and an oral formulation is approved to reduce seizures in DEE syndromes of LGS and Dravet syndrome[7-9]
- ZYN002 is a pharmaceutically manufactured transdermal CBD gel currently in clinical development for reduction of seizures in patients with DEEs, and improvement in behavioral symptoms in patients with ASD and Fragile X Syndrome (FXS)

OBJECTIVES

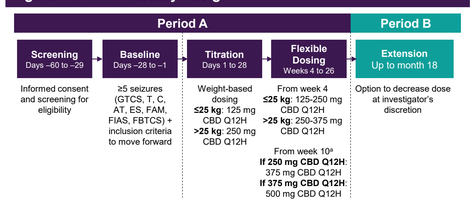
- To evaluate the efficacy of ZYN002 in children and adolescent patients with DEEs
- To evaluate the safety and tolerability of ZYN002 in children and adolescent patients with DEEs
- An exploratory analysis to evaluate efficacy of ZYN002 in DEE patients with ASD

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)
- Efficacy results for Period A and through Month 12 of Period B and safety results through 72 weeks 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 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 ≥3 × 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 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 [FBTCS])
- Number of patients meeting 35% and 50% reduction in FIAS and TCS

PATIENT POPULATION

- Safety analysis set included all patients who received ≥1 dose of study drug
- Patients who received ≥80 days of study drug and completed ≥80% of seizure diaries were included in the efficacy analyses

RESULTS

PATIENT DISPOSITION

- Of the 48 patients who enrolled in ZYN2-CL-025, 40 patients completed Period A and 28 completed through Month 12 of Period B (**Table 1**)

Table 1. Patient Disposition in ZYN2-CL-025

Status	No. of patients
Entered Period A	48
Recorded FIAS and or TCS in Baseline	33
Completed Period A	40
Entered Period B	29
Recorded FIAS and/or TCS in Baseline	19
Withdrew consent at Week 42	1
Completed 12 months	28

BASELINE 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 2**)
  - 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 efficacy study population comprised 46 patients (2 patients were excluded from efficacy analysis because they did not complete 80% of diaries or use study medication for 80 days); 33 patients had FIAS and/or TCS at baseline and constituted the population in which the primary efficacy end point was measured

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

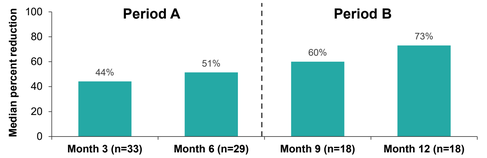
Demographic or Disease Characteristic	Safety Analysis Set (N = 48)
Age, years Mean (range)	10.5 (3, 16)
Sex, n (%) Male Female	26 (54.2) 22 (45.8)
Body mass index, kg/m^2 Mean (SD)	19.2 (4.9)
Syndrome, n (%) Dravet Syndrome Lennox-Gastaut syndrome West Syndrome Other	8 (16.7) 5 (10.4) 3 (6.3) 32 (66.7)
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)
Autism spectrum disorder,[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.
[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]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 one seizure type

EFFICACY

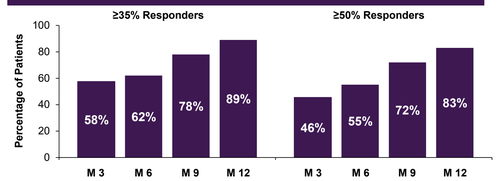
- Over the 12-month treatment period, the median percentage reduction from baseline in monthly frequency of FIAS and TCS ranged from 44% at Month 3 to 73% at Month 12 (**Figure 2**)
- When analyzed by seizure type, median reductions from baseline at Month 6 for FIAS, GTCS, and FBTCS were 45%, 60%, and 59%, respectively. At Month 12, the median reductions for FIAS, GTCS and FBTCS were 100%, 83% and 59% respectively

Figure 2. Median Percentage Reduction From Baseline in 28-Day Frequency of FIAS and TCS by Time Point, Patients With FIAS and/or TCS at Baseline



- A substantial percentage of patients achieved ≥35% and ≥50% reduction in FIAS and TCS by Month 3 that continued through Month 12 (**Figure 3**)

Figure 3. Percentage of Patients With 35% and 50% Reduction in FIAS and TCS by Time Point, Patients With FIAS and/or TCS at Baseline



- In patients with co-morbid ASD:
  - Median percentage reductions from baseline in monthly frequency of FIAS and TCS are shown in **Figure 4**
  - The ≥35% responders and ≥50% responders for Periods A and B are shown in **Figure 5**
  - 8/9 parents/caregivers provided a statement about improvement and 1/9 stated no benefit. Caregivers reported improvements in concentration, engagement, alertness and less sleepiness at school (see QoL assessment poster at this meeting)[10]

Figure 4. Median Percentage Reduction From Baseline in 28-Day Frequency of FIAS and TCS by Time Point, Patients With Co-morbid ASD at Baseline

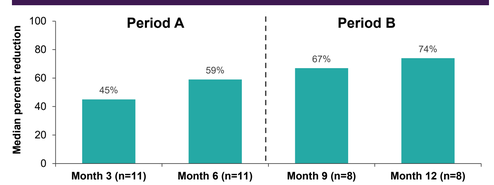
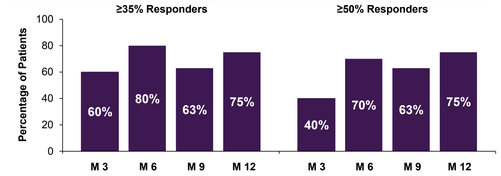


Figure 5. Percentage of Patients With 35% and 50% Reduction in FIAS and TCS by Time Point, Patients With Co-morbid ASD at Baseline



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

- BELIEVE is the first clinical trial of ZYN002 (transdermal CBD) in DEEs
- These data suggest meaningful reductions in FIAS and TCS with ZYN002 treatment which is maintained through to 12 months
- In the subgroup of patients with ASD, ZYN002 demonstrated meaningful reductions in FIAS and TCS seizures, with most children reaching the 35% or 50% responder threshold by Month 3 and Month 6 respectively
- ZYN002 was well tolerated over 18 months 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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