Scheffer IE, Hulihan J, Messenheimer J, et al. Safety and tolerability of transdermal cannabidiol gel in children with developmental and epileptic encephalopathies: a nonrandomized controlled trial. *JAMA Netw Open.* 2021;4(9):e2123930. doi:10.1001/jamanetworkopen.2021.23930

ZYN002 Cannabidiol (CBD)

ZYN2-CL-025

Open Label Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Children and Adolescents (3 to <18 years) with Developmental and Epileptic Encephalopathy (BELIEVE 1)

Protocol Number:	ZYN2-CL-025
Original Protocol Date:	February 2, 2018
Protocol Amendment .01 Date:	May 3, 2018
Protocol Amendment .02 Date:	October 19, 2018
Protocol Amendment .03 Date:	June 4, 2019
Protocol Amendment .04 Date:	October 08, 2019
Phase:	2A
PIND Number:	[redacted]
Sponsor:	Zynerba Pharmaceuticals Pty. Ltd. 2 Riverside Quay Southbank, VIC 3006
Medical Monitor:	[redacted]

1. INVESTIGATOR'S AGREEMENT

I have received and read the [redacted].
I have read the ZYN2-CL-025 Protocol Amendment .04 dated 08 October 2019, and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator and Site Number

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Email and Telephone Number
Responsible Physician	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company: Zynerba Pharmaceuticals Pty. Ltd.	
Name of Investigational Product: ZYN002	
Name of Active Ingredient: Cannabidiol (CBD)	
Title of Study: Open Label Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Children and Adolescents (3 to <18 years) with Developmental and Epileptic Encephalopathy (BELIEVE 1)	
Study center(s): Australia, New Zealand	
Principal Investigators: Professor Ingrid Scheffer, AO MBBS PhD FRACP FAA; Lynette Sadleir MB ChB MD DipPaed FRACP	
Studied period (years): Estimated date first patient enrolled: [redacted] Estimated date last patient completed: [redacted]	**Phase of Development:** 2A

Objectives:

Primary:

To evaluate the safety and tolerability of ZYN002 in child and adolescent epilepsy patients with developmental and epileptic encephalopathies (DEE) for up to 72 weeks.

Secondary:

- To evaluate the efficacy of ZYN002 in terms of seizure frequency, caregiver stress, quality of life, sleep disturbances, adaptive behavior among epilepsy patients and an overall daily assessment ("good day / bad day").
- To evaluate the pharmacokinetics of CBD following administration of ZYN002 in child and adolescent epilepsy patients with DEE.

Exploratory:

The identification of CBD metabolite(s) from collected plasma and urine may be conducted.

Methodology:

This is a sequential, multi-stage, open-label, multi-national, multiple-center, multiple-dose study to assess the long-term safety and tolerability of ZYN002 (transdermal CBD gel) in child and adolescent epilepsy patients 3 to <18 years of age having seizures associated with developmental and epileptic encephalopathies (DEE) according to the International League Against Epilepsy (ILAE) classification (Scheffer et al. 2017). In Period A, patients will undergo a baseline period of 4-weeks, followed by a 4-week titration period, and a 22-week flexible dosing maintenance period. Patients will be treated for a total of 26 weeks in Period A.

In Period B, patients will continue to receive ZYN002 for up to an additional 46 weeks at the same maintenance dose they were receiving at Week 26 (e.g. end of Period A).

Period A: Baseline Period

During the 4-week Baseline period, parents and/or caregivers will record the number of seizures of the following types in a seizure diary:

- Generalized tonic-clonic ("primary generalized tonic-clonic') seizures
- Focal impaired awareness seizures
- Focal to bilateral tonic-clonic seizures
- Focal aware seizures with motor signs
- Tonic seizures
- Clonic seizures
- Atonic seizures
- Epileptic spasms (A cluster of epileptic spasms should be counted as a single seizure.)

Seizures of the following types will be captured in the daily diary at the same time and for the same duration every day, as determined by the investigator (e.g. 6:00 PM for 30 minutes):

- Myoclonic seizures
- Absence seizures
- Focal aware seizures without motor signs (e.g. focal sensory seizures)

In addition, caregivers will rate their impression of absence, myoclonic and focal sensory seizures daily using a 3-point Likert-type scale of 0= no seizures, 1=some seizures and 2 = lots of seizures as directed by the Investigator.

The Investigator will identify the most disabling seizure type the patient experiences. This is based on the clinical view of the Investigator.

Video electroencephalograms (video-EEGs) of 2, 4, or 24 hours in duration will be performed at the beginning and end of the study. Information to be captured via video-EEG will include characteristics of the waking and sleep EEG background, interictal epileptiform and non-epileptiform abnormalities, and EEG and clinical features of seizuresthat occur during the study. Video-EEG interpretation will be completed by an independent reviewer. Where additional consent is required to transfer EEG data to the central reviewer, the investigator must obtain the consent before the EEG leaves the site. If the subject/caregiver does not provide consent, the EEGs will not be provided for central review.

Patients must continue to meet inclusion/exclusion criteria to proceed to the treatment period.

Period A: Treatment Period

4-Week Titration Period

Prior to the initial dosing on Study Day 1, patients will report to the clinic to have a pre-dose blood sample drawn for plasma levels of CBD and anti-epileptic drugs (AEDs). All concomitant medications (prescription and over-the-counter [OTC]) will be recorded including dose and reason for use. Parents/caregivers will be provided instructions on how to apply the gel and the first dose of study drug will be applied by the patient/caregiver while at this study visit.

The initial dose for patients $\leq$ 25 kg is 125 mg CBD Q12H ($\pm$2 hours), for a total daily dose of 250 mg CBD for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose can remain at 250 mg CBD daily or be increased to 250 mg CBD Q12H ($\pm$2 hours), for a total daily dose of 500 mg CBD (4 sachets) for the remaining 22 weeks of the treatment period.

Patients weighing > 25 kg will receive 250 mg CBD Q12H ($\pm$2 hours), for a total daily dose of 500 mg CBD for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose can remain at 500 mg CBD daily or be increased to 375 mg CBD Q12H ($\pm$2 hours), for a total daily dose 750 mg CBD (6 sachets) for the remaining 22 weeks of the treatment period.

22-Week Maintenance Period

The first dose of study drug will be applied by the patient/caregiver at the clinic visit under the direction of the site. Where feasible, the dose will be administered after the blood sample collection for plasma CBD and AEDs.

No sooner than Week 10, based on the investigator's assessment of seizure frequency, tolerability of study medication and CBD level determinations from Weeks 4 and/or 6, the CBD dose may be increased. Patients with any moderate or severe adverse event that is ongoing after Week 6 must attend an unscheduled visit at Week 10 for an assessment of study drug safety and tolerability before the dose can be increased. At Week 10, patients taking 500 mg CBD daily may be increased to 750 mg CBD daily (6 sachets) and patients taking 750 mg CBD daily may be increased to 1000 mg CBD (8 sachets). There is no requirement for patients to attend an unscheduled visit at Week 10 if they have no moderate or severe ongoing AEs after Week 6. If the CBD level from the blood sample obtained at Week 4 or 6 is $\geq$ 60 ng/ml, the investigator should discuss the planned Week 10 dose increase with the Zynerba Medical Monitor.

The Investigator may decrease the dose as needed based on safety and tolerability after the patient starts the maintenance period. Patients taking CBD 250 mg Q12H (±2 hours); total daily dose 500 mg CBD may have their dose decreased to 125 mg CBD Q12H (±2 hours); total daily dose 250 mg CBD. Patients taking CBD 375 mg Q12H (±2 hours); total daily dose 750 mg CBD dose may have their dose decreased to 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD. Patients taking CBD 500 mg Q12H (±2 hours); total daily dose 1000 mg CBD dose may have their dose decreased to CBD 375 mg Q12H (±2 hours); total daily dose 750 mg or 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD. Patients whose weight changes during the course of the study may have their dose increased or decreased following discussions with the Sponsor Medical Monitor.

A taper period ranging from one to three weeks, depending on the patient's dose at the time of the discontinuation, will be completed. Following taper, patients will also be required to complete a 4-week telephone follow-up period.

The safety evaluations include: physical and neurological exams, vital signs, skin check diary, skin check examination, Columbia Suicidality Severity Rating Scale (C-SSRS) for Children, Marijuana Withdrawal Checklist short form (Behavior Checklist) and AE review. Concomitant medication check (including AEDs) and review of all daily diaries will occur at each visit. In Period A, tthe Misuse Abuse and Diversion Drug Event Reporting System (MADDERS®) will be used in this study to systematically capture and adjudicate potential abuse-related events (Treister et al. 2016).

Parents/caregivers will be instructed to capture seizure frequency and type, and skin irritation scores, within daily diaries. The Investigator will review the daily diaries during each subsequent visit at Weeks 2, 4, 6, 14, and 26. Parents/caregivers will also complete:

(1) The University of Washington Caregiver Stress Scale at Day 1, Week 14, and Week 26

(2) Epilepsy and Learning Disabilities Quality of Life scale (ELDQOL - modified) at Day 1, Week 14 and Week 26 of the study

(3) Sleep Disturbance Scale for Children (SDSC) at Day 1, Week 14 and Week 26 of the study

(4) Vineland Adaptive Behavior Scale™ – 3 (VABS-3) at Day 1 and Week 26 of the study

(5) Parents/caregivers will also complete a daily Likert-type "good day/bad day" questionnaire

(6) Investigator will qualitatively capture changes (both improvement for the patient and family, such as but not limited to, daily activities, school attendance and alertness) and anything that has worsened for the patient and family at Week 26.

These assessments will also be completed at the Early Termination visit for patients who discontinue from the study before Week 26.

Parents/caregivers will be instructed on proper application of the gel. Patients will be permitted to [redacted]. Parents/caregivers will apply all study drug to clean, dry, intact skin, [redacted] and is dry to the touch.

Approved application sites for the gel are the right and left upper arms and the right and left upper thighs as specified below:

Daily Dose (mg)	**# of Sachets in Morning**	**# of Sachets in Evening**	**Primary Application Site(s) Q12H (± 2 hrs)**	**Alternative Application Site**
250	1	1	1 sachet to right **or** left upper arm/shoulder. Gel should be applied to alternating arms (ie. right at night, left in the morning). Where possible, parents/caregivers should apply the gel to the upper arms/shoulder area that the child does not lean on while sitting to avoid prematurely removing the gel.	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right or left upper thighs.

500	2	2	1 sachet to **each** right **and** left upper arm/shoulder.	
750	3	3	2 sachets to **either** the right **or** left upper arm/shoulder **and** 1 sachet to the opposite arm/shoulder. For the arm receiving 2 sachets parent/caregiver should ensure it is dry before applying the second sachet. It is acceptable for the parent/caregiver to apply the third sachet to the opposite arm and then come back to the first arm to apply the 2nd sachet. For the evening dose alternate the application site receiving 2 sachets from the morning dose (ie. If 2 sachets were applied to the left arm and 1 sachet was applied to the right arm for the morning dose, apply 2 sachets to the right arm and 1 sachet to the left arm at the evening dose).	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right and left upper thighs. Patients with low BMIs and/or small arms are allowed to have ZYN002 applied to the upper right **or** left thighs after consultation with Zynerba Medical Monitor. Sequence of application would be 1 sachet to **each** upper left **and** right arms **and** 1 sachet to the right **or** left upper thigh.
Daily Dose (mg)	**# of Sachets in Morning**	**# of Sachets in Evening**	**Primary Application Site(s) Q12H (± 2 hrs)**	**Alternative Application Site**
1000	4	4	2 sachets to **each** right **and** left upper arm/shoulder.	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right and left upper thighs. Patients with low BMIs and/or small arms are allowed to have ZYN002 applied to the upper right **or** left thighs after consultation with Zynerba Medical Monitor. Sequence of application would be 1 sachet to **each** upper left **and** right arm/shoulder **and** 1 sachet to **each** right **and** left upper thigh.

If applied to the right and/or left upper thighs the procedure is the same as described for the left and right upper arms/shoulders. Parents/caregivers applying the gel will wear gloves (provided by the Sponsor). The parent/caregiver will assure that the [redacted] and dry to the touch prior

to dressing. Once the patient/caregiver has completed the treatment application, they will discard the glove(s) and will wash their hands thoroughly with soap and warm water. Parents/caregivers will be instructed to keep the application site [redacted]. Parents/caregivers [redacted] / caregivers should also cover the application site to minimize sun exposure when going outside during the day.

Period B: Up to a 46-Week Extension Period

To be eligible to continue to Period B, patients must have completed Period A (i.e. must have completed 26 weeks of open-label treatment) and have had at least a 35% reduction from Baseline to Weeks 23 through 26 in any one (or more) qualifying seizures listed below. If seizure reduction is less than 35%, the evaluation may be extended from Baseline to Weeks 19 through 26.

- Generalized tonic-clonic ("primary generalized tonic-clonic') seizures
- Focal impaired awareness seizures
- Focal to bilateral tonic-clonic seizures
- Focal aware seizures with motor signs
- Tonic seizures
- Clonic seizures
- Atonic seizures
- Epileptic spasms (A cluster of epileptic spasms should be counted as a single seizure.)

These patients can immediately progress to Period B where they will receive up to an additional 46 weeks of open-label treatment (for a total treatment period of up to 72 weeks). Period B study visits will occur at Week 38, Week 50. During this extension period the site will perform a study Visit at Weeks 58, 66, and 72 in order to administer the CSSR-S and to dispense study treatment to the authorized parent/caregiver. Patients reaching Week 66 will have a study Visit 11 as defined by the Schedule of Assesements, wherein the site will complete a concomitant medication review, assess vital signs, perform ECG and laboratory tests including urinalysis, perform a pregnancy test (females only), administer the CSSR-S, perform a skin check examination, and review adverse events.

A reduction in seizure frequency of less than 35% in the above seizure types or changes in other seizure types felt to represent a clinically meaningful improvement should be discussed with the Zynerba Medical Monitor for approval to continue to Period B. Patients must continue to remain compliant (at least 90% compliant) with study medication use, daily seizure diary and skin check diary throughout the study. If at any time, [redacted] and will be discontinued from the study.

The first dose of study drug will be applied by the parent/caregiver at Week 26 before leaving the study site. Patients will then be required to attend study visits at Week 38, Week 50/ET to have the following study procedures completed: a blood sample for determination of CBD and Δ9-tetrahydrocannabinol (THC,), blood sample for AED plasma level, clinical laboratory tests, testosterone (males only), urine pregnancy test (females of childbearing potential only), vital signs, skin check examination, and the C-SSRS. ECGs, targeted physical and targeted neurological examinations will be completed at the End

of Study Visit. At each study visit, sites will also review concomitant medications, study drug compliance and adverse events (AEs).

On a daily basis throughout Period B up to Week 50, parents/caregivers are required to complete diaries capturing seizure frequency and type, skin irritation scores, and the 'good-day-bad-day' questionnaire. The Investigator will review the diaries at Visits 38 and 50. At Week 50 / ET parents /caregivers will also be required to complete the following measures:

(1) The University of Washington Caregiver Stress Scale

(2) ELDQOL – Modified

(3) SDSC

(4) The Vineland Adaptive Behavior Scale™ -3 (VABS-3)

(6) Investigator will qualitatively capture changes (both improvement for the patient and family, such as but not limited to, daily activities, school attendance and alertness) and anything that has worsened for the patient and family at Week 50.

During Period B, patients will continue to receive the same dose of ZYN002 as received at Week 26 (e.g. end of Period A). However, the Investigator may decrease the dose of ZYN002 as needed during treatment based on safety and tolerability. Patients taking CBD 250 mg Q12H (±2 hours); total daily dose 500 mg CBD may have their dose decreased to 125 mg CBD Q12H (±2 hours); total daily dose 250 mg CBD. Patients taking CBD 375 mg Q12H (±2 hours); total daily dose 750 mg CBD dose may have their dose decreased to 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD. Patients taking CBD 500 mg Q12H (±2 hours); total daily dose 1000 mg CBD dose may have their dose decreased to CBD 375 mg Q12H (±2 hours); total daily dose 750 mg or 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD.

Disposition of patients completing week 72 will be:

- Patients completing Week 72 - the site will determine whether the patient should be offered participation in the Special Access program:
  - If, in the investigator's medical opinion, the patient will continue to benefit from study drug, they will be offered participation in the Special Access program.
  - These patients will not have a taper period, nor have a telephone follow-up period but will have their EOS Visit completed at Week 72.
- Patients completing Week 72 that, in the investigator's medical opinion, will **not** receive benefit from continued use of study drug will:
  - Participate in the taper period with their EOS visit completed at the end of their one to three week taper period.
  - Patient should complete the 4-week telephone follow-up period.

If the [redacted] After the final tapered dose, patients will be followed weekly for 4 weeks by telephone to complete the Marijuana Withdrawal Checklist short form (Behavior Checklist). After the 4 week telephone follow-up calls, the patient will be discharged from the study.

[redacted]

Safety Monitoring:

Patient safety will be monitored during the treatment visits using standard measures, including physical and neurological exams, examination of skin at the application sites, vital signs (including oral, tympanic or forehead temperature), 12-lead ECGs, clinical laboratory tests (hematology, chemistry and urinalysis), testosterone (males only), [redacted], C-SSRS (Children), Marijuana Withdrawal Checklist short form (Behavior Checklist) and AE monitoring.

Parents/caregivers will be provided a diary to complete a daily skin check examination. Parents/caregivers will record the skin check score in the daily skin check diary once per day in the evening. When skin redness is noted, parents/caregivers should apply the gel to a non-red area of the shoulders and/or upper arms and/or right/left upper thighs. [redacted]

Plasma/Urine Samples for CBD and AEDs:

Blood samples for plasma levels of AEDs and CBD will be collected during Period A at Screening, [redacted]. Patients will be instructed to withhold their morning dose of ZYN002 until a blood sample is collected at clinic visits. Whenever possible, effort should also be made to obtain a trough sample for the concomitant AEDs. When collected, the AED name, time taken, and amount of the last dose will be captured before the blood samples are collected. The Investigator will review the concomitant AED plasma level and the dose of concomitant AEDs. Concomitant AEDs should not be changed unless the patient experiences AEs that warrant a dose change. If an AED is changed, the Sponsor Medical Monitor should be notified.

Plasma samples will be analyzed by an analytical laboratory selected by the Sponsor, using high-performance liquid chromatography (HPLC), with tandem mass spectrometry (MS/MS) detection, for the determination of CBD concentrations in plasma. Plasma and urine may also be analyzed for CBD metabolite concentrations. Analyses for CBD metabolites are exploratory and will be conducted if possible.

Plasma samples for AEDs will be analyzed by a central laboratory selected by the Sponsor.

Number of patients (planned): Approximately 55 patients will enter the 4-week Baseline period with 50 patients progressing to receive open-label treatment in Periods [redacted]

Diagnosis and Criteria for Inclusion:

Patients participating in this study will have a diagnosis of developmental and epileptic encephalopathy. Patients will be required to meet all of the inclusion and none of the exclusion criteria of the ZYN2-CL-025 (BELIEVE 1) study.

Main Inclusion Criteria:

1. Male or female, 3 to <18 years of age, inclusive, at the time of screening.
2. Judged by the Investigator to be in generally good health at the Screening Visit based upon the results of a medical history, physical examination, and clinical laboratory test results. Laboratory results that are acceptable, but outside of the reference range, must be documented as not clinically significant (NCS) by the Investigator.
3. Patients must have a diagnosis of developmental and epileptic encephalopathy (DEE) as defined by the International League Against Epilepsy Classification (Scheffer 2017) with generalized motor (i.e. generalized tonic-clonic, tonic, clonic, atonic, epileptic spasms), focal aware motor, focal impaired awareness or focal to bilateral tonic-clonic seizures. Examples of DEE that may be enrolled include, but are not limited to: Lennox-Gastaut Syndrome, Dravet Syndrome, West Syndrome/ Infantile Spasms and Doose Syndrome. The diagnosis must be established for ≥ 1 years and documented by history and examination and review of appropriate studies, which may include electroencephalogram (EEG), magnetic resonance imaging (MRI) scan, or genetic testing. The patient/legally authorized representation may elect to have the patient participate in genetic seizure panel testing to characterize a genetic diagnosis.
4. Patient must experience five or more seizures of the following type(s) in total during the baseline period: generalized motor (i.e. generalized tonic-clonic, tonic, clonic, atonic or epileptic spasms), focal motor, focal impaired awareness or focal to bilateral tonic-clonic seizures. A cluster of epileptic spasms should be counted as a single seizure.
5. Patient is currently being treated and maintained with a stable regimen of between one (1) and four (4) AEDs for at least 4 weeks before screening, and willing to maintain a stable regimen during the treatment period. If a benzodiazepine is used as a rescue medication > 2 time per week, it will be counted as an AED. Patient taking ethosuximide, felbamate and vigabatrin must be on stable therapy for at least 6 months. Patients taking felbamate must have had no clinically relevant changes in hematology or liver function tests.
6. Patient has history of developmental delay with regression, slowing or plateau in at least one developmental domain after seizure onset as determined by the Investigator.
7. All interventions for epilepsy must be stable for at least 4 weeks prior to screening.
8. Patient/caregiver is able and willing to maintain daily diaries for seizures, daily skin assessments and good day/bad day assessments.
9. Patient has a body mass index between 13 and 35 kg/m^2 and weighs no less than 12 kg.

10. Sexually active females of childbearing potential must use an acceptable method of contraception. Acceptable methods of contraception include: hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, vasectomy, and intrauterine device.
11. Females of childbearing potential must have a negative pregnancy test at the Screening Visit, as well as at Day 1.
12. Patient/caregiver agrees to abide by all study restrictions and comply with all study procedures.
13. Patient is reasonably stable medically and is unlikely to require changes in drug therapy during the Treatment Period of the study, or interfere with the objectives of the study, or the ability to adhere to protocol requirements.
14. Patient/caregiver/legally authorized representative (as appropriate) must be adequately informed of the nature and risks of the study and give written informed consent prior to screening.
15. In the Investigator's opinion, the patient and/or caregiver is reliable and is willing and able to comply with all protocol requirements and procedures.

Exclusion Criteria:

Any of the following is considered criterion for exclusion:

1. Patient has a history of significant allergic condition, significant drug-related hypersensitivity, or allergic reaction to any adhesives, compound, or chemical class related to ZYN002 or its excipients.
2. Patient has been exposed to any investigational drug or device < 30 days prior to screening or plans to take another investigational drug at any time during the study.
3. Patient has used cannabis or any CBD- or THC-containing product within 12 weeks of the Screening Visit.
4. Patient on the following AEDs for less than 6 months: ethosuximide, felbamate and vigabatrin.
5. Patient has had a change in AED regimen in the 4 weeks prior to screening.
6. Patient has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 3x the upper limit of normal (ULN) as determined from Screening safety laboratories.
7. Any clinically significant abnormality on ECG.
8. Patient/caregiver demonstrates behavior indicating unreliability or inability to comply with the requirements of the protocol.
9. Patient has had a change in epilepsy dietary therapy in the 4 weeks prior to screening.
10. Patient has seizures secondary to illicit drug or alcohol use.
11. Patient is using any strong inhibitor/inducer of CYP3A4 or sensitive substrate for CYP3A4 including the following medications: midazolam (can only be used as single dose given weekly as rescue medication, unless directed otherwise by the Investigator), oral ketoconazole, fluconazole, nefazodone, rifampin, alfentanil, alfuzosin, amiodarone, cyclosporine, dasatinib, docetaxel, eplerenone, ergotamine, everolimus, fentanyl, halofantrine, irinotecan, lapatinib, levomethadyl, lumefantrine, nilotinib, pimozide, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinoin, vincristine, vinorelbine and St. John's Wort.
12. Patient has a history of suicide attempt in the last 5 years or more than one lifetime suicide attempt.
13. Patients aged over 6 years that have the maturity and capacity to complete the C-SSRS (Children's) and respond "yes" to Question 4 or 5.
14. Patient is known to be positive for the presence of Hepatitis B surface antigen (HBsAg), Hepatitis C virus antibodies (HCV-Ab), or human immunodeficiency virus (HIV) antibodies.
15. Patient has a positive drug screen at Screening, indicating use of ethanol, cocaine, CBD, THC, barbiturates (except as AED medication), amphetamines, benzodiazepines (except as rescue medication), or opiates. A patient may be re-screened if there is a positive drug screen after consulting the Sponsor Medical Monitor.
16. Patient has any clinically significant condition or abnormal findings at the Screening Visit that would, in the opinion of the Investigator, preclude study participation or interfere with the evaluation of the study treatment.

17. Patient use of cosmetics, sunscreen and non-approved moisturizers on the shoulder/upper arms or upper thighs during the study.
18. Patient has known history of cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, cardiac conduction problems, exercise-related cardiac events including syncope and pre-syncope, or other serious cardiac problems.18Patient has any skin disease or condition, including eczema (on shoulders/arms, or thighs), psoriasis, melanoma, acne (on shoulders/arms/ or thighs), contact dermatitis, scarring, imperfections, lesions, tattoos, or discoloration that may affect treatment application, application site assessments, or absorption of the study drug.

Investigational Product, Dosage and Mode of Administration

ZYN002 (Cannabidiol: CBD), 4.2% gel, topical.

Study drug will be supplied as follows:

- [redacted] to deliver 125 mg of CBD / sachet

Study drug will be applied by using one (1) to four (4) sachets in the morning and evening to achieve the appropriate total daily dose for each patient based upon the treatment group.

The Treatments are as follows:

Treatment A - 125 mg CBD Q12H (±2 hours); for a total daily dose 250 mg CBD (1 sachet in morning and 1 sachet in evening).

Treatment B – 250 mg CBD Q12H (±2 hours); for a total daily dose of 500 mg CBD (2 sachets in morning and 2 sachets in evening).

Treatment C – 375 mg CBD Q12H (±2 hours); for a total daily dose of 750 mg CBD (3 sachets in morning and 3 sachets in evening).

Treatment D - 500 mg CBD Q12H (±2 hours); for a total daily dose of 1000 mg CBD (4 sachets in morning and 4 sachets in evening).

Duration of treatment:

Patients will receive twice daily applications (every 12 hours ±2 hours) of study drug for the 26-week treatment period and up to a 46-week extension period (72 week total treatment duration). [redacted]

Reference therapy, dosage and mode of administration:

N/A

Criteria for evaluation:

Safety:

Safety assessments will include collection of AEs, physical and neurological examinations, 12-lead ECG, clinical laboratory assessments (hematology, chemistry and urinalysis), testosterone (males only), Tanner staging scale, pregnancy tests (females of child-bearing potential only), C-SSRS (Children), Marijuana Withdrawal Checklist short form (Behavior Checklist) and findings from the skin check examinations following treatment. In Period A, the Misuse Abuse and Diversion Drug Event Reporting Systems (MADDERS®) will be used to systematically capture and adjudicate potential abuse-related events.

Efficacy:

The primary efficacy assessment will be the median percent change from baseline in the monthly (28 day) frequency of seizures (SF28) during Period A for the following types ("select countable seizures"):

- Generalized tonic-clonic ('primary generalized tonic-clonic') seizures (GTCS)
- Focal impaired awareness seizures (FIAS)
- Focal to bilateral tonic-clonic seizures (BTCS)

Secondary seizure endpoints include the median percent change from baseline in SF28 for the following:, as defined in the table below:

- All "countable seizures" (individually and in total):
  - Generalized tonic-clonic seizures (GTCS)
  - Focal impaired awareness seizures (FIAS)
  - Focal to bilateral tonic-clonic seizures (BTCS)
  - Tonic seizures (T)
  - Clonic seizures (C)
  - Atonic seizures (AT)
  - Epileptic spasms (ES)
  - Focal aware seizures with motor signs (FM)
- All focal-onset seizures (FIAS, BTCS, FM)
- Seizure type identified as the most disabling overall

The frequency of the following types of seizures during the daily period of observation that consistently occur with a countable frequency:

- Myoclonic seizures (M)
- Absence seizures (A)
- Focal aware seizures without motor signs (focal sensory seizures) (FAS)

The following table outlines the seizure types and groups that will be analyzed.

Seizure Type	Select Countable Seizures	All Countable Seizures	All Focal-Onset Seizures	Set Period Daily Count	None/ some/ lots	Seizure-free Days (Select Countable Seizures)
Easy to count seizures						
Generalized Tonic-Clonic Seizures (GTCS)	X	X	X			X
Focal Impaired Awareness Seizures (FIAS)	X	X	X			X
Focal to Bilateral Tonic-Clonic Seizures (BTCS)	X	X	X			X
Focal Aware Seizures with Motor Signs (FM)		X	X			
Tonic Seizures (T)		X				
Clonic Seizures (C)		X				
Atonic Seizures (AT)		X				
Epileptic Spasms (ES)		X				
Difficult to count seizures						
Absence Seizures (AS)				X	X	
Myoclonic Seizures (M)				X	X	
Focal Aware Seizures (FAS)				X	X	

Seizure count endpoints will be summarized by month (28 days), for Periods A and B individually and overall for the entire treatment period. Seizure count endpoints will also be summarized for the last four and the last eight weeks of treatment in Periods A and B.

Other seizure endpoints include:

- A three point Likert-type scale (none, some seizures and lots of seizures) captured on a daily diary will be used to assess myoclonic, absence and focal sensory seizures.
- The number of seizure free days (select countable seizures).
- The percentage of patients defined as a 35%, 50% and 90% responder for a specified period if for that patient the RedSF is $\geq$ 35%, 50% and 90% respectively.
- Video EEG Findings

Seizure endpoints will be summarized monthly, overall for Periods A and B and overall for the whole study.

Other secondary efficacy endpoints include:

- Change from Baseline to Weeks 14, 26 and 50/ET in the University of Washington Caregiver Stress Scale – total score
- Change from Baseline to Weeks 14, 26 and 50/ET in the subscale scores of the ELDQOL-modified
- Change from Baseline to Weeks 14, 26 and 50/ET in the total and subscale scores of the SDSC
- Change from Baseline in the "good day/bad day" assessment will be assessed for each period utilized to assess seizure frequency
- Change from Baseline to Week 26 and Week 50/ET in the VABS-3 composite and subscale scores

Pharmacokinetics

Plasma trough concentrations will be determined for CBD. Plasma and urine may also be analyzed for CBD metabolite concentrations. Analyses for CBD metabolites are exploratory and will be conducted if possible. Plasma concentration will also be determined for select AEDs at various time points.

Seizure Frequency: Seizure frequency data will be collected daily throughout the study. Video EEGs of 2, 4 or 24-hour duration will be performed based upon the investigators discretion and will be conducted at the same time of day and duration for a patient at Baseline, Week 26 and Week 50.

Seizures frequency captured via the daily diary will be analyzed per 28-day period (SF28). Patients must complete diaries for at least 80% of the days in the SF28 period for data to be used in that 28-day period. SF28 is calculated as the number of seizures in the period divided by the number of days in the period multiplied by 28. SF28 will be calculated and summarized monthly. A specific period includes the day after the previous period to the end of the current period. In addition, SF28 will be calculated over the entire treatment period, Period A, Period B and overall (the whole study).

The reduction from Baseline in seizure frequency (RedSF) is defined for each period as:

RedSF=SF28(Period X)-SF28(Baseline)

The percent reduction from Baseline in seizure frequency is defined as:

%RedSF=100*[SF28(Period X)-SF28 (Baseline)/SF28(Baseline)

In addition, a patient will be defined as a 35%, 50% and 90% responder for a specified period if for that patient the RedSF is ≥ 35%, 50% and 90% respectively.

The change in seizure frequency of the absence, myoclonic and focal non-motor seizures will be captured via daily diary and three point Likert-like scale and the change in difficult to count seizures will be analyzed separately.

The change in frequency of seizures captured via video EEG will be analyzed as a comparison of the 2-, 4- or 24-hour periods at Week 26, Week 50 and the period at Baseline. The videos will be centrally reviewed by an independent reader.

Change from Baseline to Weeks 14, 26, and 50/ET in The University of Washington Caregiver Stress Scale – total score;

Change from Baseline to Weeks 14, 26 and 50/ET in the subscale scores of the ELDQOL-modified;

Change from Baseline to Weeks 14, 26 and 50/ET in the total and subscale scores of the SDSC;

Change from Baseline in the “good day/bad day” assessment will be assessed for each period utilized to assess seizure frequency;

Change from Baseline to Week 26 and Week 50/ET in the VABS-3 composite and subscale scores;

Changes from baseline will be compared using a paired t-test or the Wilcoxon Signed-Rank test in the case that the normality assumption is not met. Responder endpoints (35% responder, 50% responder and 90% responder) will be summarized using counts, percentages and a one-sided test for binomial proportions.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AED	Anti-epileptic drug
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
AUC_{0-5}	Area under the curve from time 0 to 5 hours
AUC_{24}	Area under the curve at 24 hours
AUC_{0-24}	Area under the curve from 0 to 24 hours
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBD	Cannabidiol
CLB	Clobazam
Clr	Clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
CRA	Clinical Research Associate
C-SSRS	Columbia Suicidality Severity Rating Scale
CWE	children with epilepsy
CYP	Cytochrome P450enzyme
DEE	Developmental and Epileptic Encephalopathy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalogram
e.g.	Exampli Gratia – ‘for example’
ELDQOL	Epilepsy and Learning Disabilities Quality of Life Scale

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
EOS	End of Study
EMAS	Epilepsy with Myoclonic Atonic Seizures
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good clinical practice
GLP	Good laboratory practice
GPR55	G protein-coupled receptor 55
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibodies
HDEC	Health and Disability Ethics Committee
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HREC	Human Research Ethics Committee
ICF	Informed consent form
i.e.	id est – 'that is'
ILAE	International League Against Epilepsy
IV	Intravenous
IVIG	Intravenous immunoglobulin
Kg	Kilogram
LDL	Low density lipoprotein
LGS	Lennox-Gastaut Syndrome
LMT	Lamotrigine
LVT	Levetiracetam
MADDERS®	The Misuse Abuse and Diversion Drug Event Reporting System
MedDRA	Medical Dictionary for Regulatory Affairs
Mg	Milligram
MRI	Magnetic resonance imaging
MS/MS	Tandem mass spectrometry
N	Number

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
NCS	Not Clinically Significant
NOAEL	No observed adverse effect level
OA	Osteoarthritis
OAE	Other significant adverse event
OR	Odds ratio
OTC	Over-the-counter
pH	Negative log of hydrogen ion concentration
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PK	Pharmacokinetic
POS	Partial onset seizure
Q12 H	Every 12 hours
RBC	Red blood cell
RedSF	Reduction from Baseline in seizure frequency
RNS	Responsive neurostimulation
SAE	Serious adverse event
SC	Subcutaneous
SCN1A	Sodium voltage-gated channel alpha subunit 1
SD	Standard deviation
SF28	Seizure frequency per 28-day period
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIF	Seizure identification form
SDSC	Sleep Disturbance Scale for Children
T	Testosterone
THC	Δ9-tetrahydrocannabinol
T_{max}	Time to maximum observed concentration
TPM	Topiramate
ULN	Upper limit of normal

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
U.S.	United States
UV	Ultraviolet
VABS-3	Vineland Adaptive Behavior Scale™ 3
VPA	Valproic Acid
WBC	White blood cell
w/w	Weight/weight

5. INTRODUCTION

5.1. Background Information

Developmental and Epileptic Encephalopathy

Definition

The term developmental and epileptic encephalopathy (DEE) was recently introduced by the International League Against Epilepsy (ILAE) Task Force on Classification and Terminology (Scheffer et al. 2017) to more fully describe the clinical presentation of co-existing developmental impairment and epileptic encephalopathy. Historically, epileptic encephalopathy, without the term 'developmental,' was used in the broader sense to encompass both concepts. In 2001, ILAE recognized epileptic encephalopathies as a distinct category (Engel 2001). The ILAE defined an *epileptic encephalopathy* as a condition in which "the epileptiform EEG abnormalities themselves are believed to contribute to a progressive disturbance in cerebral function." In 2010, the ILAE redefined epileptic encephalopathy as a condition where the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time (Berg et al. 2010). The most recent change to include 'developmental' in the description was done to allow specific recognition of patients who present with both developmental impairment and epileptic encephalopathy verses developmental impairment without frequent epileptic activity associated with developmental impairment or epileptic encephalopathy where there is no pre-existing development impairment. A key component of the concept is that amelioration of the epileptiform activity may have the potential to improve the developmental consequences of the disorder (Scheffer et al. 2017).

Epidemiology

The overall incidence and prevalence of developmental epileptic encephalopathies are low. Patients with DEE may include, but are not limited to, patients with Lennox-Gastaut syndrome, Dravet syndrome, Doose syndrome (Epilepsy with Myoclonic Atonic Seizures (EMAS), West syndrome (Infantile Spasms), Landau-Kleffner syndrome, or genetic disorders such as CDKL5 encephalopathy and CHD2 encephalopathy. A recent population cohort study utilizing the Norwegian Mother and Child Cohort Study assessed the epidemiology of seizure disorders, including DEE, utilizing the new guidance from the ILAE Task Force (Aaberg et al. 2017). The overall study population included 112,744 children, age at end of follow up was 3–13 years (median = 7 years). Of the total population, 606 children (0.54%) had a validated diagnosis of epilepsy, 162 with onset at <1 year of age, 273 with onset at age 1–4 years, and 169 with onset at age ≥ 5 years. DEEs were found in 60 per 100,000 children (0.06%). Eleven percent (11%) of children with epilepsy (CWE) were classified as having DEEs, with the highest proportion for those with epilepsy onset in infancy (32%). Population estimates for some of DEEs found in the study are shown in the table below.

Table 3: Developmental Epileptic Encephalopathies per ILAE 2017 Epilepsy Classification

	Population Proportion Per 100,000 N= 112,744		**All CWE** N=606	
DEE Type	N	%	N	%
Lennox-Gastaut syndrome	11	0.01	12	2
Dravet syndrome	4	0.004	5	0.83
West syndrome	42	0.04	47	8
Landau-Kleffner syndrome	<4	<0.004	<5	<1
Doose syndrome	<4	<0.004	<5	<1

Source: (Aaberg et al. 2017)

The findings by Aaberg et al are in line with an earlier study by Kramer et al regarding the relative frequency and age of onset of the different seizure types (Kramer et al. 1998). Kramer et al conducted a study of a 20-year cohort of patients at a pediatric neurology outpatient clinic of an urban hospital that serves the majority of the population in Tel Aviv, Israel. The percent of patients with seizures classified as a DEE subtype according to the IALE were as follows: West syndrome 9%, Lennox-Gastaut syndrome 1.5%, Landau-Kleffner syndrome 0.2%, Ohtahara syndrome 0.2% and Doose syndrome/myoclonic astatic epilepsy 0.2%. It should be noted that 50-90% of children with West syndrome evolve to have other syndromes, most frequently Lennox-Gastaut syndrome, or to non-syndromic conditions within the definition of DEE (Wirrell 2016).

Treatment

The seizures in patients with DEE are generally refractory to standard antiepileptic drugs (AEDs). As a result, more aggressive adjunctive use of AEDs considered effective in suppressing interictal epileptiform discharges (e.g., benzodiazepines, valproic acid, and lamotrigine), immunomodulatory therapies (e.g., corticosteroids, intravenous immunoglobulin [IVIG], plasmapheresis), ketogenic diet, and surgical options are often considered.

While patients with DEE may present with a variety of seizure types and sub-disorders, the only DEE subtypes for which one or more AEDs are currently approved by the US FDA for adjunctive therapy are Lennox-Gastaut syndrome and infantile spasms (see below). No medicines are currently approved for the treatment of Dravet syndrome or other DEE subtypes in the U.S. Stiripentol is approved as adjunctive therapy with clobazam and valproate for Dravet syndrome in Europe, Canada, Japan and New Zealand. Approval is pending in Australia.

Table 4: Current US FDA Approved Medicines by DEE Subtype*

DEE Subtype	US FDA Approved Medicines
Lennox-Gastaut syndrome	Cannabidiol, clobazam, lamotrigine, rufinamide, topiramate, felbamate, clonazepam
Dravet Syndrome	Cannabidiol, stiripentol
Infantile spasms (West Syndrome)	Vigabatrin, adrenocorticotropic hormone (ACTH)

*Source: fda.gov December 2018.

Given treatment refractoriness and limited approved medicines with evidence from controlled trials, clinicians are often left with using standard AEDs in a trial and error fashion, largely based on clinical experience or open label trials. Lennox-Gastaut syndrome and Dravet syndrome have been the DEE subtypes for which the most evidence from controlled trials of antiepileptic drugs has been generated. A review of each is provided.

Lennox-Gastaut Syndrome

A Cochrane review of antiepileptic drug (AED) treatment for Lennox-Gastaut syndrome (LGS), conducted in 2013, included eight studies of seven drugs utilized as adjunctive therapy (Hancock 2013). The conclusion was that no one drug appears highly effective in LGS over and above another; lamotrigine, rufinamide, topiramate, and felbamate may all be useful as adjunctive therapy and clobazam may be useful for drop attacks. No benefit was shown for cinromide or low-/high-dose thyrotropin-releasing hormone.

Cross et al convened a panel of five epileptologists to develop consensus recommendations for LGS management, based on the latest available evidence from literature review and clinical experience. (Cross et al. 2017). This group concluded that current evidence favors the use of sodium valproate (VPA) as the first line treatment for patients with newly diagnosed *de novo* LGS. If VPA is ineffective alone, evidence supports lamotrigine, or subsequently rufinamide, as adjunctive therapy. If seizure control remains inadequate, the choice of next adjunctive antiepileptic drug (AED) should be discussed with the patient/parent/caregiver/clinical team, as current evidence is limited. While VPA has not been specifically approved for use in LGS, clinical application of VPA as a broad-spectrum AED results in many patients presenting with generalized or multiple seizure types being treated with VPA.

Support for the use of VPA monotherapy and in combination with other AEDs was recently demonstrated in a prospective observational study in a cohort of 43 consecutive newly diagnosed patients with Lennox– Gastaut syndrome who were evaluated monthly over a 6-month period (Rathaur et al. 2017). Overall 81.4% of patients responded to treatment with VPA alone (2.3%), the combination of VPA + clobazam (CLB; 32.6%) or VPA + CLB + levetiracetam (LVT; 46.5%). The remaining 18.6% of patients only responded to the four-drug combination of VPA + CLB + LVT + lamotrigine (LMT; 7%) or the five-drug combination of VPA + CLB + LVT + LMT + topiramate (TMP: 11.6%). While this study provides some support for the use of VPA alone or in combination, it also demonstrates the relative treatment refractory nature of LGS and

the need for more effective therapies to hopefully less the need and possible side effects of polypharmacy.

Dravet Syndrome

The primary AEDs used in the treatment of Dravet syndrome are valproate and benzodiazepines, with clobazam being the preferred benzodiazepine. The combination of valproate and clobazam is commonly considered the regimen of choice for the initial treatment of patients, as recently supported by the North American Consensus Panel on optimizing the diagnosis and management of Dravet syndrome (Wirrell et al 2017).

The study of AEDs in controlled trials in patients with Dravet Syndrome has been very limited. In fact, through December 2016, a review by the Cochrane Collaboration only identified 2 randomized controlled trials, both studying the use of stiripentol added on to valproate and clobazam, in a total of 64 children (Brigo and Igwe 2015, Chiron and Marchand 2000, Guerrini et al 2002). A significantly higher proportion of participants had 50% or greater reduction in seizure frequency in the stiripentol group compared with the placebo group (67%, 22/33 versus 6%, 2/31; RR 10.40, 95% CI 2.64 to 40.87). A significantly higher proportion of participants achieved seizure freedom in the stiripentol group compared with the placebo group (36%, 12/33 versus 3%, 1/31; RR 7.93, 95% CI 1.52 to 41.21). It should be noted that stiripentol raises clobazam and *N*-desmethylclobazam levels significantly (Diacomit SPC 2014), so the overall impact to stiripentol itself may be less clear when used in combination with clobazam. The efficacy of stiripentol, when added to valproate and clobazam, was also recently compared in in the presence or absence of *SCN1A* mutations in patients with Dravet syndrome to investigate if any difference may exist given 70% or more of patients who are tested may have a *SCN1A* mutation (Cho et al. 2017, Scheffer et al. 2017). The study included 32 patients, 15 with definite *SCN1A* mutations and 17 with variants of unknown significance or benign variants. The study found that stiripentol appears to be more effective in patients with definite *SCN1A* mutations. The seizure frequency relative to baseline reduced by 72.53±23.00% (mean±SD) in the mutation group versus 50.58±40.14% in the nonmutation group (p=0.004); leading the authors to conclude that the efficacy of stiripentol was significantly better in patients with definite *SCN1A* mutations than in those without mutations.

Topiramate and levetiracetam have also been studied as adjunctive therapy in open-label trials. In three open-label studies, more than half of patients receiving topiramate as add-on therapy achieved >50% reduction in seizure frequency, with 17% becoming seizure-free for at least four months in all cases (Nieto et al. 2009, Coppola et al. 2002, Kröll-Seger et al. 2006). Similar results were demonstrated in a single open-label trial of levetiracetam, with 64% of patients experiencing >50% reduction in tonic-clonic seizures at 12 weeks (Striano et al. 2007).

Fenfluramine, a medicine originally approved as an appetite suppressant, has also been studied prospectively in patients with Dravet syndrome. A small open-label trial was recently published and data from a phase 3 trial randomized, double-blind trial was recently presented (Schoonjans et al. 2017, Lagae et al. 2017*)*. Nine patients were treated in the open-label trial with low dose fenfluramine (0.25–1.0 mg/kg/day) for a median duration of 1.5 (range, 0.3–5.1) years and reported a median frequency of major motor seizures of 15.0/month in the baseline period. All patients demonstrated a reduction in seizure frequency during the treatment period with a median reduction of 75% (range, 28–100%). Seven patients (78%) experienced a ≥50% reduction in major motor seizure frequency. Similar topline results were presented from the phase 3 trial.

The primary efficacy measure was a comparison of the change in mean monthly convulsive seizure frequency during the 14-week treatment period compared with the 6-week baseline observation period. Patients taking fenfluramine (0.8 mg/kg/day) achieved a 63.9% reduction in mean monthly convulsive seizures compared to placebo (33>7%) ($p<0.001$). The median percent reduction in monthly convulsive seizure frequency was 72.4% among fenfluramine patients compared to 17.4% in placebo patients. Additional the proportion of patients who achieved ≥50% reductions in monthly convulsive seizures was 70% in the fenfluramine group vs 7.5% of patients in the placebo group. A lower dose of fenfluramine (0.2 mg/kg/day) produced lower rates but were also significant vs placebo.

While rufinamide appears to be effective in the DEE subtype of Lennox-Gastaut syndrome, (Hancock et al. 2013, Coppola et al 2014) a retrospective European multi-center study of 20 patients with Dravet syndrome (16 with the SCN1A mutation), reported a responder rate of only 20% at 6 months and only 5% having a 50% seizure reduction after 18 months of treatment. Seizure control was worse in one third of the patients. There results lead the authors to conclude that rufinamide does not seem to be a suitable option for long-term treatment in patients with Dravet syndrome (Mueller et al. 2011).

Aggravation of seizures in patients with Dravet syndrome has also been seen with lamotrigine, carbamazepine and vigabatrin (Chiron and Dulac 2011). The exact cause for worsening of some seizures is not clear, but it has been postulated to be related to the mechanism of action of the medicines. As a result, the use of sodium channel blocking AEDs is avoided due to a tendency to increase seizures. (lamotrigine, carbamazepine, oxcarbazepine, phenytoin, eslicarbazepine).

Supportive evidence for the use of Cannabidiol in DEE subtypes

Cannabidiol (CBD) is one of more than 100 cannabinoid compounds found in the *Cannabis* plant. It is the main non-psychoactive component of *Cannabis* and has low affinity for CB_1 and CB_2 receptors. However, CBD produces multiple effects, including blocking the equilibrative nucleoside transporter, the orphan G-protein receptor GPR-55, and the transient receptor potential of ankyrin type 1 channel, and regulating the intracellular effects of calcium. The influence of CBD on these targets, each of which is known to play a role in neuronal excitability, is the scientific basis for its antiepileptic potential. The expectation of a wide margin of safety in humans is founded in the results of well-controlled studies in which CBD has exhibited high tolerability across several modes of administration.

The use of cannabidiol (CBD) has been explored prospectively in the treatment of patients with treatment-resistant epilepsy, including patients who fall within the DEE subtypes of Lennox-Gastaut syndrome, Dravet syndrome, Doose syndrome, CDKL5 mutations, and Ohtahara syndrome (Devinsky et al. 2016, 2016 Thiele et al. 2016, Devinsky et al. 2017). While the open-label trial with oral cannabidiol (Devinsky et al. 2016) included patients with different DEE subtypes in the overall population, the majority of patients diagnosed with a DEE subtype were either patients with Lennox -Gastaut (n=30) or Dravet syndromes (n=32). In fact, patients with Lennox-Gastaut and Dravet syndromes made up 45% of the efficacy population (52/137 patients), allowing the sub analyses of the efficacy results for each of these groups. Significantly fewer patients were diagnosed with Doose syndrome (n=8), CDKL5 mutations (n=5), or Ohtahara syndrome (n=2). As such, conclusions about the efficacy and safety in these subtypes cannot be drawn beyond those reported for the overall study population.

The open-label study investigated the effect of an oral solution of extracted cannabidiol [Epidiolex®, GW Pharmaceuticals, London, UK; 100 mg per mL sesame oil-based solution] titrated to a maximally tolerated dose or 25mg/kg/day in 2 divided doses in patients aged 1-22 years, median of 10.5 years (efficacy population). Titration to a maximum dose of 50 mg/kg per day was done in 48 (30%) patients, 23 of whom received a dose of more than 25 mg/kg per day during the 12-week observation period; only 19 patients were receiving >25 mg/kg per day at the week 12 visit. The maximum dose at the 12-week visit was 41 mg/kg per day. Five (3%) patients were titrated to 50 mg/kg per day during the 12 weeks, but their dose was reduced before the week 12 visit. The mean cannabidiol dose at 12 weeks was 22.7 mg/kg (efficacy population).

The open-label study post hoc analysis of the Lennox-Gastaut subgroup (n=30) revealed a median reduction of 37% in motor seizures and 37% of patients had a 50% reduction in total seizures. Drop seizures were reduced by a median of 69% in the 14 patients with atonic seizures. For patients with Dravet syndrome in the efficacy group (n=32), the median reduction in monthly motor seizures was 49.8%. Sixteen (50%) of the patients had a reduction of 50% or greater. A median reduction of 42.7% was reported in monthly total seizures for all seizure types. There was also a median change of -69.2% in monthly tonic seizures (n=6), of -46.7% in monthly tonic-clonic seizures (n=29), and a reduction of -83.3% in non-motor focal seizures (n=10). Adverse events, excluding convulsions, reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhea (n=31 [19%]), and fatigue (n=21 [13%]). While a post hoc analysis found no relationship between the number of adverse events reported and the dose of cannabidiol, patients who were taking more than 15 mg/kg per day cannabidiol were more likely to report diarrhea or related side-effects (e.g., weight loss) than those taking doses less than 15 mg/kg per day (three [9%] of patients receiving a low cannabidiol dose *vs* 40 [31%] of 128 patients receiving a high dose; odds ratio [OR] 4.5, 95% CI 1.4 – 19.6). The authors concluded that the diarrhea and weight loss might have resulted from cannabidiol use or the sesame oil in which cannabidiol is dissolved or could be unrelated.

Data from a recent randomized, double-blind, placebo-controlled trial of cannabidiol as add-on therapy in 171 patients with Lennox Gastaut syndrome aged 2-55 years (mean of 15 years) supported the efficacy seen in the open-label study (Thiele et al. 2016). Patients received an oral solution of cannabidiol [Epidiolex®, GW Pharmaceuticals, London, UK; 100 mg per mL sesame oil-based solution] titrated to a dose of 20mg/kg/day or placebo in 2 divided doses. A median reduction in total seizures of 45% in the CBD group vs 15% in the placebo group was reported. Drop seizures were reduced by a median of 49% in the CBD group compared to 20% in the placebo group. The most common adverse events (>10% of cannabidiol-treated patients) were similar to those seen in the open-label study and included diarrhea, somnolence, decreased appetite, pyrexia, and vomiting.

Data supportive of the open-label results in patients in Dravet syndrome have also been reported from a recent randomized, double-blind, placebo-controlled trial of 120 children and young adults (mean age of 9.8 years, range of 2.3 to 18.4 years) (Devinsky et al. 2017). Patients received an oral solution of cannabidiol [Epidiolex®, GW Pharmaceuticals, London, UK; 100 mg per mL sesame oil-based solution] titrated to a dose of 20mg/kg/day or placebo in 2 divided doses. The primary endpoint was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period. The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol

group and the placebo group in change in seizure frequency, −22.8 percentage points; 95% confidence interval [CI], −41.1 to −5.4; P=0.01). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). The frequency of total seizures of all types was significantly reduced with cannabidiol (P=0.03), but there was no significant reduction in non-convulsive seizures. Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests.

ZYN002 is being developed as a clear, transdermal gel to provide consistent, controlled cannabidiol (CBD) delivery with twice daily (every 12 hours [Q12 H]) dosing. Because CBD is virtually insoluble in water, ethanol and propylene glycol are used as solubilizing agents and diethylene glycol monoethyl ether (brand name: Transcutol® HP) is used as a permeation enhancer. While ZYN002 has not been studied in the treatment of DEEs, a study (ZYN2-CL-03) in patients with focal epilepsy in adults was non-conclusive. The results may be due in part to a higher than anticipated placebo response rate (24% achieving ≥50% reduction in seizure frequency) and the use of relatively lower doses of CBD as compared to those used in the studies with Epidiolex® (highest dose of ZYN002 390 mg/day vs 20 mg/kg/day of Epidiolex®). ZYN002 doses of 195 mg/day and 390 mg/day were very well tolerated with an incidence of adverse events comparable to placebo and no significant differences between the active treatment groups. No adverse events occurring in at least 5% of patients and greater for ZYN002 were reported in more than 7% of patients in receiving ZYN002. The only adverse events reported in greater than 5% of patients were nausea (7%, 3%, 3%), fatigue (5%, 6%, 2%) and headache (5%, 6%, 2%) for ZYN002 390 mg/day, ZYN002 195 mg/day and placebo.

In summary, there is evidence supporting the use of cannabidiol in patients diagnosed with DEEs, however the following gaps in the current evidence may be addressed by the current study:

- Assessment of safety and efficacy of cannabidiol in patients diagnosed with a DEE subtype in addition to patients with Lennox-Gastaut syndrome or Dravet syndrome.
- Assessment of the tolerability of a non-oral formulation of cannabidiol that may be associated with less gastrointestinal-related events (diarrhea, vomiting, weight loss) than those seen with Epidiolex®.

5.2. Nonclinical Summary

To support the clinical development of ZYN002, Zynerba will rely upon:

- Data from non-clinical safety studies conducted by Zynerba with ZYN002, ZYN002 placebo gel, or CBD, the active ingredient in ZYN002,
- Publicly available information about the toxicity/safety of CBD and the excipients in ZYN002, and
- Clinical safety data generated by Zynerba with CBD and ZYN002.

Published nonclinical studies with CBD indicate that it does not produce adverse effects on nervous system, respiratory, or gastrointestinal function, although it does exhibit beneficial activity in some nervous system disorders (e.g., anti-convulsant and anxiolytic activity) and

gastrointestinal disorders (e.g., anti-inflammatory activity). In a GLP-compliant study conducted by Zynerba, CBD did not affect cardiovascular system function even at an estimated plasma concentration (4350 ng/mL) that is 256 times greater than the expected plasma Cmax in patients over a 14-day period (17 ng/mL). Based on this information, human subjects using ZYN002 are unlikely to experience adverse effects on nervous system, cardiovascular, respiratory, or gastrointestinal function.

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Repeat-dose toxicity studies in rats and minipigs with ZYN002 have revealed no effects on endocrine systems or reproductive organs in either species. Published information suggests that CBD has the potential to affect reproductive function in animals, at least in males, possibly secondary to effects on sex hormone levels (Dalterio et al. 1984; Dalterio and deRooij, 1986).

Published information also suggests that administration of CBD to pregnant mice has the potential to affect development of offspring, at least to males (Dalterio et al. 1984; Dalterio and deRooij 1986).

CBD does not absorb UV or visible light over 290-700 nm (Hazekamp et al. 2005) and so ZYN002 does not present a potential phototoxicity hazard to human subjects.

[redacted]

In the completed clinical pharmacology studies, ZYN002 was not associated with any impairment in critical areas of cognitive functioning often impacted by CNS drugs, including divided attention and working memory and focused attention after single or repeat doses of ZYN002 at doses up to 250 mg as a single or BID dose. Assessments of psychological health also demonstrated no changes in depression and anxiety symptoms, or positive and negative affect, following administration of ZYN002. Results from three completed Phase 1 studies, along with a population pharmacokinetic (PK) model, which includes results from ZYN2-CL-03, ZYN2-CL-004 and ZYN2-CL-004, have adequately described the PK of CBD following application of ZYN002 transdermal gel. Pharmacokinetic conclusions for these studies are as follows:

- [redacted]
- THC was not quantifiable in either plasma or urine.
- There is adequate animal NOAEL:human exposure ratios for AUC and C_{max}.

Population pharmacokinetic analyses indicate approximately 85% of steady-state is reached by Day 14.

Because CYP3A4 and CYP2C19 are the major isoforms responsible for CBD metabolism, concomitant administration of drugs that inhibit these enzymes may result in higher exposure to CBD and drugs that induce these enzymes may result in lower exposure to CBD; therefore, strong inhibitors or inducers of CYP3A4 may increase or decrease the plasma concentrations of CBD and should be administered with caution.

As a potential perpetrator, CBD would not cause a clinically significant induction of CYP isoenzymes. However, CBD exhibited time-dependent inhibition of CYP2D6 and CYP1A2, which was reversible, and of CYP3A4, which was irreversible. Sensitive CYP3A4 substrates with a narrow therapeutic index or risk for severe toxicity should be avoided until this risk has been assessed with ZYN002. CBD did not inhibit human efflux and uptake transporters.

Overall, these results support further clinical development of ZYN002 transdermal gel.

5.3. Clinical Summary

CBD studies completed with oral, inhaled, and intravenous (i.v.) formulations support a favorable tolerability and efficacy profile in several disease states. These efficacy and tolerability data provide a rationale for development of the transdermal delivery of synthetic CBD which is not subject to gastric acid degradation and first pass metabolism in the liver, and may achieve consistent blood levels for the treatment of child and adolescent patients.

5.3.1. ZYN002 Phase 1 Studies

Three Phase 1 (ZYN2-CL-01, ZYN2-CL-02, and, ZYN2-CL-08) of ZYN002 (CBD) administered via a transdermal delivery system have been conducted in healthy subjects and patients with epilepsy.[redacted]

These efficacy and tolerability data provide a rationale for development of a transdermal delivery of synthetic CBD which is not subject to first pass metabolism and may achieve consistent blood levels for the treatment of patients with FXS and epilepsy.

A summary of the safety results from the Zynerba studies further supports the development of ZYN002. Four Period A safety and tolerability study results as follows:

- ZYN2-CL-01, a single rising-dose study in healthy subjects (n=32) and patients with epilepsy (n=10) receiving ZYN002 (50, 100, 125, and 250 mg) or placebo showed that ZYN002 was safe and well tolerated at all doses. The incidence of treatment-emergent adverse events (TEAEs) associated with ZYN002 was similar to placebo in healthy volunteers. There were no serious adverse events (SAEs), no clinically significant changes in ECGs, vital signs or clinical laboratory results. ZYN002 had good skin tolerability, and there was no post-dosing erythema at 24, 48, 72, and 96 hours.
- ZYN2-CL-02, a seven-day repeat application, multiple rising dose study of healthy subjects (n=24) receiving ZYN002 (200, 250, 500 mg/day), and patients with epilepsy (n=12), receiving 500 mg/day showed that ZYN002 was safe and well tolerated at all doses. One subject receiving placebo discontinued due to an SAE, a device related infection (catheter) not related to trial drug. Most TEAEs were mild in intensity and there was only one severe TEAE of back pain in a healthy subject administered ZYN002 500 mg. Most TEAEs were considered related to trial drug and either resolved or were resolving. Application site disorders were the most frequently reported TEAEs for both healthy subjects and epilepsy patients. The most frequently reported TEAEs were application site dryness and application site pruritus. Headache was the most frequently reported TEAE that was not associated with the application site. There were no clinically significant changes in ECGs or vital signs.
- [redacted]
- ZYN2-CL-08, a 14-day repeat application study in healthy subjects (n=42) receiving ZYN002 (394.8, 500, and 504 mg/day) or placebo showed that ZYN002 was safe and well tolerated at all doses. Most TEAEs were mild in intensity. Most TEAEs were considered not related to trial drug and either resolved or were resolving at the time of database lock. No SAEs were reported and no subjects discontinued from the study due to a TEAE. Headache and upper respiratory tract infection were the most frequently reported TEAEs and occurred in similar incidence for both ZYN002 and placebo. Application site dryness, application site pain, and application site pruritus were the next frequently reported TEAEs.

In the completed clinical pharmacology studies, ZYN002 was not associated with any impairment in critical areas of cognitive functioning often impacted by central nervous system (CNS) drugs, including divided attention and working memory and focused attention after single or repeat doses of ZYN002 at doses up to 250 mg as a single or BID dose. Assessments of psychological health also demonstrated no changes in depression and anxiety symptoms, or positive and negative affect, following administration of ZYN002.

5.3.2. ZYN002 Phase 2 Studies

Two Phase 2 studies have been completed in patients with epilepsy (ZYN2-CL-03) and osteoarthritis (OA) (ZYN-CL-005).

- ZYN2-CL-03, a randomized, double-blind, placebo-controlled, multiple-dose study was conducted at 10 sites in Australia and 4 sites in New Zealand, to assess the efficacy and safety of ZYN002 administered as a transdermal gel to patients with focal epilepsy. The results showed ZYN002 to be safe and well tolerated with a safety profile consistent with previous studies. A total of 188 patients were randomized to receive either 195 or 390 mg/day of ZYN002 or placebo for 12 weeks. AEs were reported by 26 of 63 (41.3%) of placebo-treated patients, 31 of 63 (49.2%) of patients randomized to 195 mg/day of ZYN002 and 32 of 62 (51.6%) of patients randomized to 390 mg/day of ZYN002. For each dosing group, the majority of AEs were mild to moderate in intensity. The TEAE that occurred more frequently in patients on drug than those on placebo and occurred in at least 2% of patients included: fatigue, headache, nausea, application site dryness, anxiety, urinary tract infection, diarrhea, application site pruritus, thermal burn (secondary to seizure related accident), ataxia, oropharyngeal pain and erythema.
- ZYN2-CL-005, a randomized, double-blind, placebo-controlled, multiple center, multiple dose study, was conducted at 10 sites in Australia, to assess the efficacy and safety of a 12 week repeat application in patients diagnosed with OA of the knee. The results showed ZYN002 to be safe and well tolerated with a safety profile consistent with previous studies. A total of 320 patients were randomized to receive ZYN002 at 250 or 500 mg/day or placebo for 12 weeks. Patients experiencing at least one treatment-emergent adverse event were similar between those on trial drug (n=106, 50%) and those on placebo (n=45, 42%). The TEAEs that occurred more frequently in patients on drug than those on placebo and occurred in at least at 2% of patients included: headache, dizziness, application site dryness, application site reaction, and application site pain.

5.3.3. Ongoing ZYN002 Clinical Studies

Four clinical ZYN002 studies are ongoing as follows:

1. ZYN2-CL-009 is an ongoing open-label trial to assess the safety and efficacy of ZYN002 administered as a transdermal gel to children and adolescents with Fragile X Syndrome (FXS). The trial is being conducted at three investigative sites in Australia. The 12-week treatment period included a 6-week titration period, after which the patient was to remain on their maintenance dose over the next 6 weeks of treatment. Following completion of the first 12 weeks of treatment, patients had the option of continuing into an extension phase of the trial, which allowed for them to receive trial drug for up to 24 additional months. The last patient is expected to complete the extension phase in September 2019.

   Twenty-two patients were screened for the study and 20 were enrolled. Of the 20 patients, 18 completed the 12 weeks of open-label treatment and 13 of those 18 patients continued into the extension phase of the study. Currently, 12 patients are ongoing in the extension phase.

   Initial results of the 12-week treatment period include:

Safety Results: Seventeen patients reported 33 TEAEs in this 12-week open-label trial. The majority of TEAEs were mild (25 [76%]) or moderate in intensity (8 [24%]) and were considered unrelated to treatment with CBD (25 [76%]). There were no SAEs reported, and 1 of 20 patients (5%) discontinued treatment due to a TEAE (i.e., exacerbation of eczema).

The most common treatment emergent adverse event was mild-moderate gastroenteritis (6 [18%]), not related to trial drug and resolved during the study period. This was followed by upper respiratory tract infection, viral infection, influenza, otitis media, and tonsillitis (7 [21%], not related to trial drug and all resolved during the study period. One patient developed a moderate application rash 35 days after starting trial drug. Trial drug was withheld for one day and the application site was changed to the thighs for 6 days while the rash resolved. The rash did not recur. This patient also had a high eosinophil count, considered probably related to the skin rash. Upon a repeat laboratory test, the eosinophil count had decreased to just above normal. This patient currently is in the extension phase of the study.

Other adverse events considered possibly related included symptoms of FXS (e.g., sensorial hyperactivity, nightmares, increased bedwetting and increase in self stimulatory talk).

There were no clinically significant changes in vital signs, ECG, clinical laboratory results (other than eosinophilia noted above), and no reports of suicidal ideation for any patient throughout the trial.

Through Week 38 there were no clinically significant changes in vital signs, ECGs, or clinical laboratory results. Through Week 38 there were a total of 43 TEAEs reported in the study, all mild to moderate in severity, with the majority judged by the Investigator as not related to trial drug. No SAEs have been reported. Gastroenteritis and upper respiratory tract infections continue to be the most commonly reported adverse events.

Efficacy Results: Eighteen patients completed the efficacy assessments through Week 12 of the study. Validated clinician- and caregiver-rated FXS scales were used to measure Baseline symptom severity and changes in symptoms between Baseline and Week 12 of the treatment period in this open-label trial.

The primary endpoint was the change from Baseline to Week 12 in the total score of the ADAMS, a caregiver-rated scale. Compared to the Baseline total score, the ZYN002 treated patients had a 45.81% reduction ($p<0.0001$) in the ADAMS Total Score. Furthermore, ZYN002 treated patients had statistically and clinically significant improvement compared to Baseline in all but one of the ADAMS subscales (i.e., Manic/Hyperactive Behavior, Social Avoidance, General Anxiety, and Compulsive Behavior) at Week 12. A significant change was not observed for the Depressed Mood subscale of the ADAMS, clinically meaningful changes were observed for all other assessments, including in the ABC-CFXS, PARS-R, and Visual Analog Scale (VAS).

Data from the extension phase of the study highlight continued gains in the primary and key secondary efficacy outcomes. The improvement observed during the initial 12-week period has been sustained through 38 weeks. A 59.2% reduction in ADAMS Total Score was observed between Screening and Week 38, relative to a 48.6% reduction from Screening to Week 12 (among the 12 patients enrolled through Week 38 of the extension phase). Similar changes were observed for Social Avoidance as measured by both the ADAMS (52.5%

[n = 12] at Week 12 vs. 61.6% [n = 12] at Week 38) and ABC-CFXS (57.9% [n = 12] at Week 12 vs. 75.4% [n = 9] at Week 38).

2. ZYN2-CL-004 is an ongoing open-label extension study to allow patients with focal epilepsy who completed ZYN2-CL-03 to continue to receive ZYN002. The primary objective is to assess the long-term safety and tolerability of ZYN002 in adult epilepsy patients over an 18-month period. The secondary objective is to evaluate efficacy in this population. Patients had to complete the 12 weeks of study treatment on protocol ZYN2-CL-03. ZYN002 is being administered as a transdermal gel with all patients starting on ZYN002 at doses equal to or higher than those used in the blinded study – CBD 195 mg every 12 hours (Q12 H) (+2 hours) (390 mg daily), with the option that after Month 1 to either increase or reduce the dose of ZYN002. The dose may be increased to 292.5 mg Q12H (+2 hours) (585 mg daily). After one month at the 585 mg daily dose, the Investigator has the option to increase the dose to 390 mg Q12H (+ 2 hours) (780 mg daily). Of the patients who completed the blinded 12-week phase, 171 (98%) enrolled in the open-label extension study. Seizure control was evaluated as a function of duration on ZYN002, regardless of initial randomization group or dose. Longer exposure to ZYN002 resulted in greater improvements in seizure frequency, with median percent change in seizures from -16.3% at 3 months (n=170), to -27.3% at 6 months (n=148), -50.2% at 9 months (n=98), and -58.0% at 12 months (n=70).

   ZYN002 has been well tolerated, with excellent skin tolerability. The most common adverse events were upper respiratory tract infection (viral and bacterial; 16%), headache (11%), fatigue (7%), and laceration (5%).

3. ZYN2-CL-025 is an ongoing open-label study to evaluate over a 26-week treatment period, the safety and tolerability of ZYN002 in approximately 50 children and adolescent patients with developmental and epileptic encephalopathies (DEE). Patients weighing ≤ 25 kg will receive 125 mg CBD Q12H (+2 hours), for a total daily dose of 250 mg CBD (2 sachets) for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose can remain at 250 mg CBD daily or be increased to 250 mg CBD Q12H (+2 hours), for a total daily dose of 500 mg CBD (4 sachets) for the remaining 22 weeks of the treatment period. Patients weighing > 25 kg will receive 250 mg CBD Q12H (+2 hours), for a total daily dose of 500 mg CBD (4 sachets) for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose can remain at 500 mg CBD daily or be increased to 375 mg CBD Q12H (+2 hours), for a total daily dose 750 mg CBD (6 sachets) for the remaining 22 weeks of the treatment period. No sooner than Week 10, after evaluation of the patient's seizure diary and CBD plasma concentration from Weeks 4 and/or 6, the Investigator in conjunction with the Zynerba Medical Monitor, may determine that the patient's dose can be increased. An unscheduled visit will be required in order to increase the dose. Patients taking 500 mg CBD daily may be increased to 750 mg CBD daily (6 sachets) and patients taking 750 mg CBD daily may be increased to 1000 mg CBD (8 sachets) daily for the remainder of the treatment period. The study was initiated and as of 09 July 2018, three patients have started treatment after a 4-week baseline period.

4. ZYN2-CL-016 is an ongoing, randomized, double-blind, placebo-controlled, multiple-center study, to assess the efficacy and safety of ZYN002 for the treatment of child and adolescent patients with FXS. Male and female patients with FXS will be treated for 12 weeks with a two-week single-blind placebo lead-in preceding the 12-week double-blind treatment period.

Approximately 204 male and female patients, ages 3 to < 18 years, will be randomized 1:1 to either trial drug or placebo. Randomization will be stratified by gender, weight category and region. In a blinded fashion, ZYN002-treated patients who weigh < 35 kg will receive 125 mg CBD Q12H (every 12 hours) (± 2 hours); for a total daily dose of 250 mg CBD. Patients who weigh > 35 kg will receive 250 mg CBD Q12H (+2 hours); for a total daily dose of 500 mg CBD. All patients will remain on their assigned dose during the 12-week treatment phase of the study.

5.3.4. Completed Clinical Studies in Literature

CBD has been clinically studied in healthy subjects with a variety of conditions. Highlights of clinical study information are summarized below. Additional information is provided in the Investigator's Brochure.

- Most assessments have used a 600 mg oral dose of CBD, but subjects in several trials have been treated with oral CBD doses of 1200 mg or more (Zuardi et al, 2010; Matsuyama and Fu 1981), and one study employed a 1500 mg dose (Zuardi et al. 2006). More recent epilepsy studies have titrated doses up to 25 – 50 mg/kg of oral doses in patients (age 1-30 years) (Devinsky et al. 2016, Devinsky et al. 2017). The mean CBD dose at 12 weeks was 22.9 mg/kg corresponding to a 732 mg oral dose for an average 10-year old patient. At the highest dose, Zynerba has studied a 780 mg daily dose of CBD (ZYN002 4.2%, 4.64 g twice a day). This study will investigate Zynerba at the highest daily dose of 1000 mg ZYN002 (4.2% concentration).
- Because the zero-order delivery from ZYN002 should provide a lower C_{max} than oral or buccal routes of delivery, ZYN002 usage may result in less systemic exposure, placing it well below the threshold of safety in humans that has been established at higher systemic doses with oral, inhalation and injectable formulations.
- The 600 mg oral dose of CBD has been monitored in multiple long-term treatment situations. In at least six studies, study periods of 3 months have been used (Martin-Sanots et al. 2012; Bhattacharyya et al. 2012; Winton-Brown et al. 2011; Fusar-Poli et al. 2010; Bhattacharyya et al. 2010; Fusar-Poli et al. 2009; Borgwardt et al. 2008), and several patients have taken CBD for 4.5 months (Cunha et al. 1980).
- Psychoactive effects associated with CBD have not been widely reported until recently. Previous reports suggest the absence of psychoactive effects whether CBD is administered intravenously (Perez-Reyes et al. 1973) or orally (Englund et al. 2013; Martin-Santos et al. 2012, Bhattacharyya et al. 2012; Bhattacharyya et al. 2010; Zuardi et al. 2009), and pre-treatment with oral CBD 600 mg has been shown to inhibit the psychosis and cognitive impairment associated with intravenous THC 1.5 mg (Englund et al. 2013 and Bhattacharyya et al. 2010). Recent studies with Epidiolex show high rates of somnolence (36%) and fatigue (20%) (Devinsky et al. 2017). These effects could be due to drug, underlying disease, potential conversion of oral CBD to THC or a combination of these factors. Previous work has shown that in the presence of acidic reagents, CBD isomerizes to tetrahydrocannabinol (Ganoi and Mecoulam, 1966). In simulated gastric fluid, cannabidiol converts to Δ^9-tetrahydrocannabinol, 9-α-hydroxy-hexahydrocannabinol and 8-hydroxy-iso-

hexahydrocannabinol. All have psychoactive activity (Merrick et al. 2016; Watanabe et al. 2007).

- CBD-treated subjects in clinical studies have shown no treatment-related effects on key vital sign indicators, including blood pressure and heart rate (Perez-Reyes et al. 1973; Martin-Santos et al. 2012; Hallak et al. 2011; Fusar-Poli et al. 2009; Borgwardt et al. 2008; Zuardi et al. 1993; Consroe et al. 1991; Zuardi et al. 1982), as well as electrocardiography (Guy and Flint 2003; Carlini and Cunha 1981; Cunha et al. 1980).
- Findings from functional magnetic resonance imaging and behavioral studies show that CBD modulates function in regions not usually implicated in response inhibition. In terms of clinical sequelae, these data help to explain why CBD does not impair motor or cognitive performance and has anxiolytic effects (Borgwardt et al. 2008).

In addition, studies completed with oral, inhaled, and intravenous (IV) CBD support an excellent tolerability profile and efficacy in several disease states. These efficacy and tolerability data provide a rationale for development of a transdermal delivery of synthetic CBD which is not subject to first pass metabolism and may achieve consistent blood levels for the treatment of adolescent and adult patients with epilepsy and Fragile X Syndrome.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To evaluate, over the entire treatment period, the safety and tolerability of ZYN002 in child and adolescent epilepsy patients with developmental and epileptic encephalopathies (DEE).

6.2. Secondary Objectives

To evaluate the efficacy of ZYN002 in terms of seizure frequency, caregiver stress, quality of life, sleep disturbances, adaptive behavior among epilepsy patients and an overall daily assessment of the patient's day ("good day / bad day").

To evaluate the pharmacokinetics of CBD [redacted] following administration of ZYN002 in child and adolescent epilepsy patients with DEE.

6.3. Exploratory

The identification of CBD metabolite(s) from collected plasma and urine may be conducted.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a sequential, multi-stage, open-label, multi-national, multiple-center, multiple-dose study to assess the long-term safety and tolerability of ZYN002 (transdermal CBD gel) in child and adolescent epilepsy patients 3 to <18 years of age with seizures associated with developmental and epileptic encephalopathies (DEE) according to the International League Against Epilepsy (ILAE) classification (Scheffer et al. 2017). In Period A, patients will undergo a baseline period of 4-weeks, followed by a 4-week titration period, and a 22-week flexible dosing maintenance period. Patients will be treated for a total of 26 weeks in Period A. No sooner than Week 10, based on the investigator's assessment of seizure frequency, tolerability of study medication and CBD level determinations from Weeks 4 and/or 6, the CBD dose may be increased. Patients with any moderate or severe adverse event that is ongoing after Week 6 must attend an unscheduled visit at Week 10 for an assessment of study drug safety and tolerability before the dose can be increased. At Week 10, patients taking 500 mg CBD daily may be increased to 750 mg CBD daily (6 sachets) and patients taking 750 mg CBD daily may be increased to 1000 mg CBD (8 sachets). There is no requirement for patients to attend an unscheduled visit at Week 10 if they have no moderate or severe ongoing AEs after Week 6. If the CBD level from the blood sample obtained at Week 4 or 6 is > 60 ng/ml, the investigator should discuss the planned Week 10 dose increase with the Zynerba Medical Monitor.

During the Period B extension (Weeks 38 to 72) the site will perform a study Visit at Weeks 58, 66, and 72 in order to administer the CSSR-S and to dispense study treatment to the authorized parent/caregiver.

Patients reaching Week 66 will have a study Visit 11 as defined by the Schedule of Assesements, wherein the site will complete a concomitant medication review, assess vital signs, perform ECG and laboratory tests including urinalysis, perform a pregnancy test (females only), administer the CSSR-S, perform a skin check examination and review adverse events.

In Period B, patients will continue to receive ZYN002 for up to an additional 46 weeks at the same maintenance dose they were receiving at Week 26 (e.g. end of Period A) for a total treatment period of up to 72 weeks.

Disposition of patients at Week 72 will be as follows:

- Patients completing Week 72 - the site will determine whether the patient should be offered participation in the Special Access program:
    - If, in the investigator's medical opinion, the patient will continue to benefit from study drug, they will be offered participation in the Special Access program.
    - These patients will not have a taper period, nor have a telephone follow-up period but will have their EOS Visit completed at Week 72.
- Patients completing Week 72 that, in the investigator's medical opinion, will **not** receive benefit from continued use of study drug will:
    - Participate in the taper period with their EOS visit completed at the end of their one to three week taper period.
    - Patient should complete the 4-week telephone follow-up period.

7.2. Number of Patients

Approximately 55 patients will enter the 4-week Baseline period with 50 patients progressing to receive open-label treatment. [redacted]

7.3. Dose Rationale

The rationale for dose selection in this study is to:

- [redacted]
- In Period B, the dose that patients received at Week 26 of Period A will be continued for up to 46-weeks, for a total of 72 weeks.

The ZYN2-CL-03 study used a top dose of ZYN002 of 390 mg/day in adults, whereas a dose of 780 mg/day is currently being evaluated in the ZYN2-CL-004 study. For patients weighing ≤ 25 kg, 250 mg/day will serve as the lower dose, 500 mg/day as the middle dose and 750 mg/day as the highest dose. For patients weighing > 25 kg, 500 mg/day will serve as the lower dose, 750 mg/day as the middle dose and 1000 mg/day as the highest dose. Following discussions with the Sponsor Medical Monitor, patients that weighed ≤ than 25kg at Baseline may have their dose increased to 1000 mg at Week 14 if their weight is > 25kg and the PK data at weeks 4 and 6 support the increase.

[redacted]

Simulation results are presented for each weight group in Table 5, with the exposure relative to 390 mg BID (780 mg/day) in adults. [redacted]

[redacted] [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5:

The current dose of CBD being studied in children and adults with refractory epilepsy for Dravet Syndrome and LGS is 20 mg/kg/day given orally (twice daily dosing) in a sesame oil-based solution (Epidiolex®, GW Pharmaceuticals, London, UK). The pharmacokinetics of this formulation were assessed in 7 children, mean age of 8.7 years (range 5.4 to 10.7years) (Wong et al. 2016).

The animal and human safety profile support further evaluation of ZYN002 at higher doses.

7.3.1. Safety Criteria for Decreasing or Stopping Doses

The Investigator may choose to suspend or reduce the dose of study medication at his/her discretion based upon tolerability.

Parents/caregivers will be provided a diary to complete a daily skin check examination. Parents/caregivers will record the skin check score in the daily skin check diary once per day in the evening. If the skin check score is higher than "2" at any time, the parent/caregiver will contact the [redacted]

After starting the treatment with study drug, patients taking CBD 250 mg Q12H (±2 hours); total daily dose 500 mg CBD may have their dose decreased to 125 mg CBD Q12H (±2 hours); total daily dose 250 mg CBD. Patients taking CBD 375 mg Q12H (±2 hours); total daily dose 750 mg CBD dose may have their dose decreased to 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD. After Week 10, patients taking CBD 500 mg Q12H (±2 hours); total daily dose 1000 mg CBD dose may have their dose decreased to 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD.

The reason for the dose reduction or for stopping the dose will be noted in the e-CRF.

7.4. Criteria for Study Withdrawal

Each patient has the right to withdraw from the study at any time without prejudice. If a patient withdraws from the study, the reason(s) must be stated on the electronic case report form (eCRF), and a final evaluation of the patient should be performed.

The investigator may discontinue any patient's participation if he or she feels it is necessary for any reason during the study. The investigator and Sponsor may discontinue any patient's participation for any reason including: any adverse event, clinically significant worsening in seizure frequency, adverse change in any laboratory test, or failure to comply with the protocol. Samples for a post-study laboratory profile and follow-up safety exams should be obtained as soon after patient discontinuation as possible.

Patients who withdraw from the study after completing the 4-week titration period will not be replaced. All effort will be made to ensure that the Early Termination procedures will be completed at the time of discontinuation.

Following early termination of treatment, patients should complete the 1-3 week taper period based on the dose they were receiving at the time of treatment termination. Patients should complete the 4-week follow-up period where the 'behaviour checklist' will be completed and symptoms of withdrawal assessed.

Patients are to have treatment withdrawn if any of the following occurs:

- Any suicide attempt. Note that any completed suicide or suicidal attempt will be collected as an SAE.

- A “Yes” response to Questions “4” or “5” on the C-SSRS by patients aged over 6 years that have the capacity and maturity to respond to the questions. The investigator will determine if further evaluation is required and provide additional treatment as required. Any exceptions to this must be approved by the Sponsor Medical Monitor, in discussion with the investigator.
- Pregnancy.
- Any new clinically significant ECG abnormality as determined by the Investigator and / or central read.
- Elevated serum transaminases (liver function test (LFT)) abnormalities) confirmed to be:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 x upper limit of normal (ULN);
    - ALT or AST >3 x ULN for more than 2 weeks;
    - ALT or AST >3 x ULN and total bilirubin >2 x ULN (Hy’s Law); or
    - ALT or AST >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.

7.5. Study Assessments

7.5.1. Overview of Study Assessments

Study procedures will be performed as summarized in this section and as depicted in the study schematic presented in Table 6 and Table 7 Schedule of Assessments.

Table 6: Schedule of Assessments Period A Screening Through Week 26

Assessment	Screening (Period A)	Baseline (Period A)	Treatment (Titration) Period (Period A)			Maintenance Treatment (Period A)			Taper Period[m]	End of Study Visit[n]	Telephone Follow-up Period[o]	Unscheduled Visits[i]
	Visit 1 Day -60 to -29	Days -28 to -1	Visit 2 Day 1 (±3 days)	Visit 3 Week 2 (±3 days)	Visit 4 Week 4 (±3 days)	Visit 5 Week 6 (±3 days)	Visit 6 Week 14 (±3 days)	Visit 7 Week 26 (±3 days)	1 to 3 weeks following withdrawal of treatment	±3 days after last taper dose	4 weeks following End of Study Visit	
Informed consent.	X							X[l]				
Review eligibility criteria.	X		X									
Medical History & Demographics.	X											
Concomitant medications.	X		X	X	X	X	X	X		X		X
Physical and neurological examination.	X							X				
Targeted Physical and neurological examination.			X		X		X			X[j]		X
Vital signs[a.]	X		X	X	X	X	X	X		X		X
12-lead ECG.	X				X		X	X		X		
Laboratory tests and urinalysis[b.]	X				X		X	X		X		
Urine Drug Screen.	X											
Pregnancy Test[c.]	X		X		X	X	X	X		X		
C-SSRS (Children) [d.]	X		X	X	X	X	X	X		X		X
[redacted]	X							X				
Marijuana Withdrawal Checklist (short form) [e]			X					X	X		X	

Table 6: Schedule of Assessments Period A Screening Through Week 26 (Continued)

Assessment	Screening (Period A)	Baseline (Period A)	Treatment (Titration) Period (Period A)			Maintenance Treatment (Period A)			Taper Period[m]	End of Study Visit[n]	Telephone Follow-up Period[o]	Unscheduled Visits[i]
	Visit 1 Day -60 to -29	Days -28 to -1	Visit 2 Day 1 (±3 days)	Visit 3 Week 2 (±3 days)	Visit 4 Week 4 (±3 days)	Visit 5 Week 6 (±3 days)	Visit 6 Week 14 (±3 days)	Visit 7 Week 26 (±3 days)	1 to 3 weeks following withdrawal of treatment	±3 days after last taper dose	4 weeks following End of Study Visit	
Seizure Diary (Daily).		X	X	X	X	X	X	X				X
Video EEG.		X						X				
Skin Check Diary (Daily)[f]			X	X	X	X	X	X	X	X		X
[redacted]			■		■	■	■	■				
AED blood sample[g]	X		X		X	X	X	X				
Seizure Diary Review.		X	X	X	X	X	X	X				X
Skin Check Diary Review.			X	X	X	X	X	X		X		X
Skin check examination.[h, k]			X	X	X	X	X	X		X		X
Univ Washington Caregiver Stress Scale.			X				X	X				
Daily Questionnaire ("Good Day, Bad Day")		X	X	X	X	X	X	X				
ELDQOL Quality of Life (Modified)			X				X	X				
SDSC Sleep Questionnaire.			X				X	X				
Vineland Adaptive Behavior Scale™-3 (VABS-3).			X					X				
Qualitative Investigator Assessment								X				

Table 6: Schedule of Assessments Period A Screening Through Week 26 (Continued)

Assessment	Screening (Period A)	Baseline (Period A)	Treatment (Titration) Period (Period A)			Maintenance Treatment (Period A)			Taper Period[m]	End of Study Visit[n]	Telephone Follow-up Period[o]	Unscheduled Visits[i]
	Visit 1 Day -60 to -29	Days -28 to -1	Visit 2 Day 1 (±3 days)	Visit 3 Week 2 (±3 days)	Visit 4 Week 4 (±3 days)	Visit 5 Week 6 (±3 days)	Visit 6 Week 14 (±3 days)	Visit 7 Week 26 (±3 days)	1 to 3 weeks following withdrawal of treatment	±3 days after last taper dose	4 weeks following End of Study Visit	
Genetic Seizure Panel (optional).	X											
Adverse events.	X	X	X	X	X	X	X	X	X	X	X	X
Dose.			X	X	X	X	X	X	X			
MADDERS Medication Use Survey Review										X		

Table 6 Period A Footnotes:

a. Vital signs (including blood pressure, heart rate, respiratory rate, and oral, tympanic or forehead temperature) will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be taken prior to blood draws.

b. Fasting laboratory tests will be completed at approximately the same time of day. Male patients will have serum testosterone measured.

c. Women of child-bearing potential. Can be serum or urine pregnancy test.

d. Patients six years of age and older and capable of understanding and answering the questions, in the investigator's opinion.

e. [redacted]

f. Parents/caregivers will assess their dosing site and record all skin redness in their daily skin check diary once per day in the evening. When skin redness exists, efforts will be made to apply the gel to a non-red area of the shoulders and/or upper arms. If the skin check score is higher than a "2", the patient/caregiver will contact the Investigator to determine if an Unscheduled Visit is required.

g. Patients will have a blood sample drawn for plasma level of AED(s). Where possible, effort should be made to get a trough sample for the AED. If not, the AED morning dose may be administered prior to the clinic visit. The time of the prior doses of study drug and AEDs in addition to the time of each blood sample collection will be recorded

h. A complete skin check examination will be conducted at each study visit, including unscheduled visits and End of Study visit for skin redness follow-up. Skin erythema scores >0 at the EOS or an ET visit will be followed until score = 0.

i. An unscheduled visit must be conducted at Week 10 for all patients with any AE ongoing from the previous visit assessed as moderate in severity or higher.

j. A complete physical exam may be conducted at the EOS visit if considered clinically relevant by the Principal Investigator (PI).

k. [redacted]

l. Consent for Period B to be obtained prior to first extension dose

m. [redacted]

n. [redacted].

o. Patients who participate in a Special Access or Authorized Prescriber program not required to complete the follow-up period.

Table 7: Schedule of Assessments Period B Week 38 up to Week 72

Assessment	Period B Extension Treatment					Taper Period[m]	End of Study Visit[n]	Telephone Follow-up Period[o]	Unscheduled Visits[j]
	Visit 8 Week 38 (±3 days)	Visit 9 Week 50[i] (±3 days)	Visit 10 Week 58 (±3 days)	Visit 11 Week 66 (±3 days)	Visit 12 Week72 (±3 days)	1 to 3 weeks following withdrawal of treatment	±3 days	4 weeks following End of Study Visit	
Concomitant medications.	X	X		X			X		X
Physical and neurological examination.		X							
Targeted Physical and neurological examination.							X[k]		X
Vital signs[a.]	X	X		X			X		X
12-lead ECG.	X	X		X			X		
Laboratory tests and urinalysis[b.]	X	X		X			X		
Pregnancy Test[c.]	X	X		X			X		
C-SSRS (Children) [d.]	X	X	X	X	X		X		X
[redacted].		X							
Marijuana Withdrawal Checklist (short form) [e]		X				X		X	
Seizure Diary (Daily).	X	X							X
Video EEG.		X							
Skin Check Diary (Daily)[f]	X	X				X	X		X
CBD/Urine/CBD [redacted]	[redacted]	[redacted]							
AED blood sample[g]	X	X							
Seizure Diary Review.	X	X							X
Skin Check Diary Review.	X	X					X		X
Skin check examination.[h, l]	X	X		X			X		X

Table 7: Schedule of Assessments Period B Week 38 up to Week 72, (Continued)

Assessment	Extension Treatment (Period B)					Taper Period[m]	End of Study Visit[n]	Telephone Follow-up Period[o]	Unscheduled Visits[j]
	Visit 8 Week 38 (±3 days)	Visit 9 Week 50/ET (±3 days)	Visit 10 Week 58 (±3 days)	Visit 11 Week 66 (±3 days)	Visit 12 Week 72 (±3 days)	1 to 3 weeks following withdrawal of treatment	±3 days	4 weeks following End of Study Visit	
Univ Washington Caregiver Stress Scale.		X							
Daily Questionnaire ("Good Day, Bad Day")		X							
ELDQOL Quality of Life (Modified)		X							
SDSC Sleep Questionnaire.		X							
Vineland Adaptive Behavior Scale™-3 (VABS-3).		X							
Qualitative Investigator Assessment		X							
Adverse events.	X	X	X	X	X	X	X	X	X
Dose.	X	X				X			
Dispense Study Drug.	X	X	X	X	X	X			
MADDERS Medication Use Survey Review		X					X		

Table 7 Period B Footnotes

a. Vital signs (including blood pressure, heart rate, respiratory rate, and oral, tympanic or forehead temperature) will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be taken prior to blood draws.

b. Fasting laboratory tests will be completed at approximately the same time of day. Male patients will have serum testosterone measured.

c. Women of child-bearing potential. Can be serum or urine pregnancy test.

d. Patients six years of age and older and capable of understanding and answering the questions, in the investigator's opinion.

e. Patients and/or caregivers will be contacted weekly by phone during the taper period and for 4 weeks after the patient is off study drug to complete the Marijuana Withdrawal Checklist (modified). The checklist is not completed during the taper period or at the End of Study Visit for patients that continue to access study drug via a Special Access or an Authorized Prescriber program.

f. Parents/caregivers will assess their dosing site and record all skin redness in their daily skin check diary once per day in the evening. When skin redness exists, efforts will be made to apply the gel to a non-red area of the shoulders and/or upper arms. If the skin check score is higher than a "2", the patient/caregiver will contact the Investigator to determine if an Unscheduled Visit is required.

g. Patients will have a blood sample drawn for plasma level of AED(s). Where possible, effort should be made to get a trough sample for the AED. If not, the AED morning dose may be administered prior to the clinic visit. The time of the prior doses of study drug and AEDs in addition to the time of each blood sample collection will be recorded

h. A complete skin check examination will be conducted at Weeks 38, 50,66, unscheduled visits and End of Study visit for skin redness follow-up. Skin erythema scores >0 at the EOS or an ET visit will be followed until score = 0.

i. ET applies to a patient who discontinues from the study before Week 50.

j. An unscheduled visit must be conducted at Week 10 for all patients with any AE ongoing from the previous visit assessed as moderate in severity or higher.

k. A complete physical exam may be conducted at the EOS visit if considered clinically relevant by the Principal Investigator (PI).

[redacted]

7.5.2. Informed Consent

Signed informed consent will be obtained at Screening for all patients and at Week 26 for all patients already enrolled in the study and continuing to Period B. The informed consent form (ICF) will be signed by the patient and/or legal authorized representative before any study procedures are undertaken. Details about how the ICF will be obtained and documented are provided in Section 16.3.

7.5.3. Medical History and Demographics

A complete medical history and collection of patient demographic information will be obtained at Screening.

7.5.4. Concomitant Medication Review

Medication (prescription and over the counter [OTC) will be recorded at Screening and reviewed and updated at all study visits.

7.5.5. Complete and Targeted Physical and Neurological Examinations

A complete physical exam, including neurological exam will be conducted at the Screening, Week 26 and Week 50 or Early Termination visits. Targeted physical (including heart, lungs, abdomen, extremities, and body weight) and neurological exams (mental status, gait/cerebellar testing, extraocular movements, and reflexes with additional areas depending on patient) will be conducted on Day 1, Weeks 4, 14 and the at End of Study visit. Any clinically significant changes will be documented and record as an AE if appropriate.

Patient weight will be collected with minimal clothing (e.g., no coats, shoes, jumpers or jackets). Height, at baseline and Week 50, will be measured without shoes.

A complete physical examination will only be performed at the End of Study visit if considered clinically relevant.

7.5.6. Vital Signs

Vital sign determinations, including blood pressure, heart rate, respiratory rate and temperature (oral, tympanic or forehead), will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be assessed at Screening, Day 1 prior to dosing, and at each visit through to Week 50, and Week 66, or the End of Study Visit and at any Unscheduled Visits. Vital signs will be taken prior to plasma blood sample collection at all visits.

7.5.7. Electrocardiogram

A 12-lead resting ECG will be obtained at Screening, Weeks 4, 14, 26, 38, 50, 66, and at the End of Study Visit. Patients who terminate early will have an ECG at their End of Study Visit. As applicable, ECGs will be conducted pre-dose and before pathology samples are collected. A qualified physician will interpret, sign, and date the ECGs. Only clinical interpretations (normal, abnormal but not clinically significant, or abnormal and clinically significant) will be recorded in the eCRF. ECGs will also be reviewed by a central, independent reader and abnormal ECGs will be reviewed by the Zynerba Medical Monitor.

7.5.8. Laboratory Test and Urinalysis

All blood samples will be collected and handled in accordance with the instructions from the central laboratory. For collection of laboratory samples, patients should fast for approximately 8 hours prior to having blood drawn for blood laboratory analysis and samples should be taken at approximately the same time of day.

Male patients will have serum testosterone measured.

All abnormal laboratory test results will be followed to a satisfactory resolution. Instructions regarding the collection, processing, and shipping of these samples will be provided by the laboratory chosen for this study.

Samples will be collected at Screening, Weeks 4, 14, 26, 38, 50, 66, and at the End of Study/ET visit. Patients who terminate early from the study will only have laboratory samples collected at the time of termination.

7.5.8.1. Specific Laboratory and Urine Tests

- Routine blood chemistry tests will include: glucose, total bilirubin, serum glutamic oxaloacetic transaminase/aspartate transaminase (SGOT/AST), serum glutamic pyruvic transaminase/alanine transaminase (SGPT/ALT), alkaline phosphatase, blood urea nitrogen, creatinine, amylase, total protein, uric acid, sodium, chloride, bicarbonate, potassium, calcium, phosphorous, albumin, triglycerides, cholesterol: low density lipoprotein (LDL) and high density lipoprotein (HDL).
- Testosterone (males only, total and free). Blood sample for testosterone should be collected at the same time of day throughout the study.
- Routine hematology tests will include: white blood cell (WBC) with differential count, red blood cell (RBC), hematocrit, hemoglobin, and platelet count.
- Urine specimens will be tested for routine urinalysis (specific gravity, pH, protein, glucose, ketones, bilirubin, blood, leukocyte esterase and nitrite) and microscopic analysis if indicated.

7.5.9. Urine Drug Screen

A urine drug screen will be performed at Screening to detect the use of ethanol, cocaine, CBD, THC, barbiturates (except as AED medication), amphetamines, benzodiazepines (except as rescue medication), or opiates. [redacted]. A patient with a positive drug screen will be excluded from entry into the study.

7.5.10. Pregnancy Test-Females of Childbearing Potential

A serum or urine pregnancy test will be performed for female patients of childbearing potential during Period A at Screening, Day 1 and at Weeks 4, 14, 26, 38, 50, Early Termination, Week 66, and at the End of Study visit. Any patient that is pregnant will be excluded or discontinued from the study as applicable.

7.5.11. Suicidality - Columbia Suicidality Severity Rating Scale (C-SSRS) for Children

The C-SSRS (children version) is to be completed at Screening and all study visits by the investigator or his/her qualified designee (Appendix 20.1). A 'qualified designee' is defined as someone who has completed the C-SSRS training within the past two years. The survey should be completed by the same assessor, where possible, throughout the study. Assessments will be conducted only if patients are of an appropriate age (six years of age and older) and capable of understanding and answering the questions, in the investigator's opinion.

Questions concerning suicidal behavior, suicidal ideation and intensity of ideation will be asked. At the Screening visit, questions will be in relation to lifetime experiences (Children's Baseline). All subsequent questioning will be in relation to the last visit (Children's Since Last Visit).

Any patient who responds "Yes" to Questions "4" or "5" on the C-SSRS will be discontinued from the study and the investigator will determine if further evaluation is required and provide for this evaluation and treatment. Any exceptions to this must be approved by the Sponsor Medical Monitor, in discussion with the investigators. Note that any completed suicide or suicidal attempt will be collected as a SAE.

7.5.12. [redacted]

[redacted]

7.5.13. Marijuana Withdrawal Checklist – short form (Behavior Checklist)

The Marijuana Withdrawal Checklist short form (Behavior Checklist) will be completed at Day 1, Week 26 and 50/ET. The checklist is also completed weekly by phone during the taper period, at the End of Study Visit, and during the 4 week follow-up period for patients that complete treatment or withdraw from treatment early (Appendix 20.3). The checklist is not completed during taper, at the End of Study Visit, or during the follow-up period for patients that are approved to receive study drug beyond the End of Study visit via a Special Access or an Authorized Prescriber program.

7.5.14. Seizure Diary and Review

A seizure diary will be distributed to Parents/caregivers during Period A at Screening with instructions on how to record daily seizure counts during the study (Appendix 20.4).

During the 4-week Baseline period, parents and/or caregivers will record the number of seizures of the following types in a seizure diary:

- Generalized tonic-clonic ("primary generalized tonic-clonic') seizures
- Focal impaired awareness seizures

- Focal to bilateral tonic-clonic seizures
- Focal aware seizures with motor signs
- Tonic seizures
- Clonic seizures
- Atonic seizures
- Epileptic spasms (A cluster of epileptic spasms should be counted as a single seizure.)

Seizures of the following types will be captured in the daily diary at the same time and for the same duration every day, as determined by the investigator (e.g., 6:00 PM for 10 minutes):

- Myoclonic seizures
- Absence seizures
- Focal aware seizures without motor signs (e.g. focal sensory seizures)

In addition, caregivers will rate their impression of absence, myoclonic and focal sensory seizures daily using a 3-point Likert-type scale of 0= no seizures, 1=some seizures and 2 = lots of seizures as directed by the Investigator.

The Investigator will identify the most disabling seizure type the patient experiences. This is based on the clinical view of the Investigator.

The patient's daily seizure diary, including the seizure codes used, will be reviewed by the investigator from Baseline through to the Week 50/ET. Data from the diaries will not be collected during the taper period. All data from diaries will be recorded in the eCRF.

7.5.15. [redacted]

[redacted]

7.5.16. Skin Check Diary – Completion and Review

Parents/caregivers will be provided the Skin Check Diary and will be instructed on completion of the daily skin check diary at Day 1 (Appendix 20.5). Parent/caregivers will record the skin check score in the daily skin check diary once per day in the evening. When skin redness is noted, parents/caregivers should apply the gel to a non-red area of the shoulders and/or upper arms and/or right/left thighs.[redacted]

The patient's skin check diary will be reviewed by the investigator at all visits through Week 50, including any unscheduled skin visits.

7.5.17. Skin Check Examination

A complete skin check examination will be conducted by the Investigator at each study visit following the first dose of study medication, including Unscheduled visits Week 50, Week 66, and the End of Study visit for skin redness follow-up.

When skin redness exists, efforts will be made to apply the gel to a non-red area of the shoulders and/or upper arms and right/left thighs. The Investigator will use discretion in using an unaffected site (upper arm or thigh) [redacted]

[redacted]

Refer to Table 8 for the Skin Check Scale to be used for skin redness examinations.

Table 8: Skin Check Scale

Score	Definition
0	No erythema
1	Minimal erythema
2	Moderate erythema with sharply defined borders
3	Intense erythema with or without edema
4	Intense erythema with edema and blistering/erosion

7.5.18. Blood/Urine Samples for AEDs and CBD/CBD Metabolite(s)

At [redacted]. Patients will be instructed to withhold their morning dose of ZYN002 until a blood sample is collected at clinic visits. When possible, effort should be made to obtain a trough sample for the AEDs. AED name, time taken, and amount of the last dose will be captured before the blood samples are collected. The Investigator will review the concomitant AED plasma level and the dose of concomitant AEDs.

Concomitant AEDs should not be changed unless the patient experiences AEs that warrant a dose change.

[redacted].

7.5.19. University of Washington Caregiver Stress Scale

The University of Washington Caregiver Stress Scale will be completed on Day 1 and at Weeks 14 and 26 and 50/ET. (Appendix 20.6)

7.5.20. Daily Questionnaire (Good Day / Bad Day)

Parents/caregivers will be instructed on completion of the Daily Questionnaire (Good Day / Bad Day) (Appendix 20.7) on Day 1. The questionnaire will be answered at the end of each day, beginning on Day 1 and continue through Week 50.

7.5.21. Epilepsy and Learning Disabilities Quality of Life (ELDQOL) Scale- Modified

The Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale- modified (Appendix 20.8) will be completed on Day 1 and at Weeks 14, 26 and 50/ Early Termination.

7.5.22. Investigator Qualitative Assessment

Each Investigator will qualitatively capture improvements for the patient and family (such as but not limited to daily activities, school attendance and alertness) as well as anything that has worsened for the patient/family at Week 26 and Week 50.

7.5.23. Sleep Disturbance Scale for Children (SDSC)

The Sleep Disturbance Scale for Children (SDSC) will be completed on Day 1 and at Weeks 14, 26 and 50/ Early Termination (Appendix 20.9).

7.5.24. Vineland Adaptive Behavior Scale™- 3 (VABS-3)

The Vineland Adaptive Behavior Scale™ -3 (VABS-3) will be completed on Day 1 and at Weeks 26 and 50/ Early Termination (Appendix 20.10)

7.5.25. Genetic Seizure Panel

The patient/legally authorized representation may elect to have the patient participate in genetic seizure panel testing to characterize a genetic diagnosis at Screening. Patients who have not had genetic testing or for whom their prior testing was less complete than the testing being utilized for this study will be eligible.

7.5.26. Adverse Event Review

A review of AEs will be performed at all study visits.

Detailed information regarding AEs can be found in Section 12.2.

7.5.27. Taper Period

At the end of the 72-week treatment period, there will be a taper period ranging from one to three weeks, depending a patient's dose at the time of the taper. [redacted].
Patients who withdraw early from treatment should complete the taper period based on the dose administered at the time of treatment termination. The taper period should commence immediately following the ET visit.

Table 9: ZYN002 Taper Schedule by Dose

Week 72 Daily Dose or Dose When Patient Discontinues the Study	Taper Week 1 Daily Dose	Taper Week 2 Daily Dose	Taper Week 3 Daily Dose	End of Study Visit
250 mg	125 mg	Discontinue Treatment		
500 mg	250 mg	125 mg	Discontinue Treatment	Discontinue Treatment
750 mg	500 mg	250 mg	125 mg	Discontinue Treatment
1000 mg	500 mg	250 mg	125 mg	Discontinue Treatment

[redacted]

7.5.28. Study Drug Application and Dispensing

Parents/caregivers will be provided instructions on how to apply the gel and the first dose of study drug will be applied by the parent/caregiver at this visit on Day 1. Parent/caregivers will apply the gel daily except at Weeks 2, 4, 6, 14, 26, 38, and 50, when the gel will be applied during the clinic visit.

Parents/caregivers will be instructed on proper application of the gel. [redacted] Parents/caregivers will apply all study drug to clean, dry, intact skin, [redacted] and is dry to the touch.

Approved application sites for the gel are the right and left upper arms/shoulders and the right and left upper thighs as specified below:

Table 10: Daily Dose, Primary, and Alternative Application Site(s)

Daily Dose (mg)	**# of Sachets in Morning**	**# of Sachets in Evening**	**Primary Application Site(s)** **Q12H (± 2 hrs)**	**Alternative Application Site(s)**
250	1	1	1 sachet to right **or** left upper arm/shoulder. Gel should be applied to alternating arms (i.e. right at night, left in the morning). Where possible, parents/caregivers should apply the gel to the upper arms/shoulder area that the child does not lean on while sitting to avoid prematurely removing the gel.	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right or left upper thighs.
500	2	2	1 sachet to **each** right **and** left upper arm/shoulder.	

Table 10: Daily Dose, Primary, and Alternative Application Site(s) (Continued)

Daily Dose (mg)	# of Sachets in Morning	# of Sachets in Evening	Primary Application Site(s) Q12H (± 2 hrs)	Alternative Application Site(s)
750	3	3	2 sachets to **either** the right **or** left upper arm/shoulder **and** 1 sachet to the opposite arm/shoulder. For the arm receiving 2 sachets parent/caregiver should ensure it is dry before applying the second sachet. It is acceptable for the parent/caregiver to apply the third sachet to the opposite arm and then come back to the arm first arm to apply the 2nd sachet. For the evening dose alternate application site receiving 2 sachets from the morning dose (i.e. If 2 sachets were applied to the left arm and 1 sachet was applied to the right arm for the morning dose, apply 2 sachets to the right arm and 1 sachet to the left arm at evening dose).	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right and left upper thighs. Patients with low BMIs and/or small arms are allowed to have ZYN002 applied to the upper right **or** left thighs after consultation with Zynerba Medical Monitor. Sequence of application would be 1 sachet to **each** upper left **and** right arms **and** 1 sachet to the right **or** left upper thigh.
1000	4	4	2 sachets to **each** right and left upper arm/shoulder.	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right and left upper thighs. Patients with low BMIs and/or small arms are allowed to have ZYN002 applied to the upper right **or** left thighs after consultation with Zynerba Medical Monitor. Sequence of application would be 1 sachet to **each** upper left **and** right arm/shoulder **and** 1 sachet to **each** right **and** left upper thigh.

If applied to the right and/or left upper thighs the procedure is the same as described for the left and right upper arms/shoulders.

Parents/caregivers applying the gel will wear gloves (provided by the Sponsor). The parent/caregiver will assure that the gel is rubbed in completely [redacted] and dry to the touch prior to dressing. Once the parent/caregiver has completed the treatment application, they will discard the glove(s) and will wash their hands thoroughly with soap and warm [redacted].

Commencing on Day 1, sufficient study drug will be dispensed at each visit to allow administration per the protocol for the period between the scheduled visits (14, 28, 56 or 72 days). The dose administered during each scheduled visit will be from a kit dispensed at that visit and will be applied by the patient/caregiver. All sachets from a kit must be used before opening an additional kit.

At Day 1, one additional kit will be dispensed and will be used as a spare in the event a visit is delayed or a kit is damaged. Patients must bring the spare kit to each visit where the site will check the patients compliance with treatment and assess whether study drug has been over administered. If allowed by local policy, the kit can be returned to the patient with all used sachets removed. The kit is then returned 'in full' when all sachets are used, at the EOS visit, or the kit has expired (whichever occurs first). If local policy does not allow the return of partially used kits, a new 'spare' kit should be dispensed if sachets have been used.

8. SELECTION AND WITHDRAWAL OF PATIENTS

Patients participating in this study will have a diagnosis of developmental and epileptic encephalopathy. Patients will be required to meet all of the inclusion and none of the exclusion criteria of the ZYN2-CL-025 (BELIEVE 1) study

8.1. Patient Inclusion Criteria

1. Male or female, 3 to <18 years of age, inclusive, at the time of screening.
2. Judged by the Investigator to be in generally good health at the Screening Visit based upon the results of a medical history, physical examination, and clinical laboratory test results. Laboratory results that are acceptable, but outside of the reference range, must be documented as not clinically significant (NCS) by the Investigator.
3. Patients must have a diagnosis of developmental and epileptic encephalopathy (DEE) as defined by the International League Against Epilepsy Classification (Scheffer 2017) with generalized motor (i.e. generalized tonic-clonic, tonic, clonic, atonic, epileptic spasms), focal motor, focal impaired awareness or focal to bilateral tonic-clonic seizures examples of DEE that may be enrolled include, but are not limited to: Lennox-Gastaut Syndrome, Dravet Syndrome, West Syndrome/ Infantile Spasms and Doose Syndrome. The diagnosis must be established for ≥ 1 years by history and examination and review of appropriate studies, which may include electroencephalogram (EEG), magnetic resonance imaging (MRI) scan, or genetic testing. The patient/legally authorized representation may elect to have the patient participate in genetic seizure panel testing to characterize a genetic diagnosis.
4. Patient must experience five or more seizures of the following type(s) during the baseline period: generalized motor (i.e. generalized tonic-clonic, tonic, clonic, atonic or epileptic spasms), focal motor, focal impaired awareness or focal to bilateral tonic-clonic seizures. A cluster of epileptic spasms should be counted as a single seizure.
5. Patient is currently being treated and maintained with a stable regimen of between one (1) and four (4) AEDs for at least 4 weeks before screening, and willing to maintain a stable regimen during the treatment period. If a benzodiazepine is used as a rescue medication > 2 time per week, it will be counted as an AED. Patient taking ethosuximide, felbamate and vigabatrin must be on stable therapy for at least 6 months. Patients taking felbamate must have had no clinically relevant changes in hematology or liver function tests
6. Patient has history of developmental delay with regression, slowing or plateau in at least one developmental domain after seizure onset as determined by the Investigator.
7. All interventions for epilepsy must be stable for at least 4 weeks prior to screening.
8. Patient/caregiver is able and willing to maintain daily diaries for seizures, daily skin assessments and good day/bad day assessments.
9. Patient has a body mass index between 13 and 35 kg/m^2 and weighs no less than 12 kg.
10. Sexually active females of childbearing potential must use an acceptable method of contraception. Acceptable methods of contraception include: hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, vasectomy, and intrauterine device.

11. Females of childbearing potential must have a negative pregnancy test at the Screening Visit, as well as at Day 1.
12. Patient/caregiver agrees to abide by all study restrictions and comply with all study procedures.
13. Patient is reasonably stable medically and is unlikely to require changes in drug therapy during the Treatment Period of the study, or interfere with the objectives of the study, or the ability to adhere to protocol requirements.
14. Patient/caregiver/legally authorized representative (as appropriate) must be adequately informed of the nature and risks of the study and give written informed consent prior to screening.
15. In the Investigator's opinion, the patient and/or caregiver is reliable and is willing and able to comply with all protocol requirements and procedures.

8.2. Patient Exclusion Criteria

Any of the following is considered criterion for exclusion:

1. Patient has a history of significant allergic condition, significant drug-related hypersensitivity, or allergic reaction to any adhesives, compound, or chemical class related to ZYN002 or its excipients.
2. Patient has been exposed to any investigational drug or device < 30 days prior to screening or plans to take another investigational drug at any time during the study.
3. Patient has used cannabis or any CBD- or THC-containing product within 12 weeks of the Screening Visit.
4. Patient on the following AEDs for less than 6 months: ethosuximide, felbamate and vigabatrin.
5. Patient has had a change in AED regimen in the 4 weeks prior to screening.
6. Patient has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 3x the upper limit of normal (ULN) as determined from Screening safety laboratories.
7. Any clinically significant abnormality on ECG.
8. Parent/caregiver demonstrates behavior indicating unreliability or inability to comply with the requirements of the protocol.
9. Patient has had a change in epilepsy dietary therapy in the 4 weeks prior to screening.
10. Patient has seizures secondary to illicit drug or alcohol use.
11. Patient is using any strong inhibitor/inducer of CYP3A4 or sensitive substrate for CYP3A4 including (but not limited to) the following medications: midazolam (can only be used as single dose given weekly as rescue medication, unless directed otherwise by the Investigator), oral ketoconazole, fluconazole, nefazodone, rifampin, alfentanil, alfuzosin, amiodarone, cyclosporine, dasatinib, docetaxel, eplerenone, ergotamine, everolimus, fentanyl, halofantrine, irinotecan, lapatinib, levomethadyl, lumefantrine, nilotinib, pimozide,

quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinoin, vincristine, vinorelbine and St. John's Wort.

12. Patient has a history of suicide attempt in the last 5 years or more than one lifetime suicide attempt.
13. Patients aged over 6 years that have the maturity and capacity to complete the C-SSRS (Children's) and respond "yes" to Question 4 or 5.
14. Patient is known to be positive for the presence of Hepatitis B surface antigen (HBsAg), Hepatitis C virus antibodies (HCV-Ab), or human immunodeficiency virus (HIV) antibodies.
15. Patient has a positive drug screen at Screening, indicating use of ethanol, cocaine, CBD, THC, barbiturates (except as AED medication), amphetamines, benzodiazepines (except as rescue medication), or opiates. [redacted].
16. Patient has any clinically significant condition or abnormal findings at the Screening Visit that would, in the opinion of the Investigator, preclude study participation or interfere with the evaluation of the study treatment.
17. Patient use of cosmetics, sunscreen and non-approved moisturizers on the shoulder/upper arms or upper thighs during the study.
18. Patient has known history of cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, cardiac conduction problems, exercise-related cardiac events including syncope and pre-syncope, or other serious cardiac problems.
19. Patient has any skin disease or condition, including eczema (on shoulders/arms, or thighs), psoriasis, melanoma, acne (on shoulders/arms/ or thighs), contact dermatitis, scarring, imperfections, lesions, tattoos, or discoloration that may affect treatment application, application site assessments, or absorption of the study drug.

8.3. Patient Withdrawal Criteria

Each patient has the right to withdraw from the study at any time without prejudice. If a patient withdraws from the study, the reason(s) must be stated on the eCRF, and a final evaluation of the patient should be performed.

The investigator may discontinue any patient's participation if he or she feels it is necessary for any reason during the study. The investigator and Sponsor may discontinue any patient's participation for any reason including: any adverse event, clinically significant worsening in seizure frequency, adverse change in any laboratory test, or failure to comply with the protocol. All efforts will be made to follow-up adverse events until resolution.

Any patient who responds "Yes" to Questions "4" or "5" on the C-SSRS will be discontinued from the study and the investigator will determine if further evaluation is required and provide for this evaluation and treatment. Any exceptions to this must be approved by Sponsor Medical Monitor, in discussion with the investigator. Note that any completed suicide or suicidal attempt will be collected as a SAE.

Samples for a post-study laboratory profile and follow-up safety exams should be obtained as soon after patient discontinuation as possible.

All effort will be made to ensure that patients who withdraw early from treatment should complete the taper period based on the dose administered at the time of treatment termination. The taper period should commence immediately following the ET visit.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

ZYN002 is a synthetically manufactured Cannabidiol (CBD) in a clear permeation-enhanced gel formulation. The drug product will be supplied as a 4.2% w/w gel to be applied topically.

Study drug will be supplied as follows:

- Sachets [redacted] gel to deliver 125 mg of CBD /sachet

Study drug will be applied by using one (1) to four (4) sachets in the morning and evening to achieve the appropriate total daily dose for each patient based upon the treatment group.

The treatments are as follows:

Treatment A - 125 mg CBD Q12H (±2 hours); for a total daily dose 250 mg CBD

- One (1) sachet containing 125 mg CBD applied in the morning and one (1) sachet applied in the evening.

Treatment B - 250 mg CBD Q12H (±2 hours); for a total daily dose of 500 mg CBD

- Two (2) sachets containing 250 mg CBD applied in the morning and two (2) sachets applied in the evening.

Treatment C - 375 mg CBD Q12H (±2 hours); for a total daily dose of 750 mg CBD

- Three (3) sachets containing 375 mg CBD applied in the morning and three (3) sachets applied in the evening.

Treatment D - 500 mg CBD Q12H (±2 hours); for a total daily dose of 1000 mg CBD

- Four (4) sachets containing 250 mg CBD applied in the morning and four (4) sachets applied in the evening.

9.2. Concomitant Therapy

Patients may take hormonal contraception and AEDs during study participation. Other prescription or over-the-counter (OTC) medications may be taken as approved in advance by the investigator and recorded in the eCRF.

Concomitant AEDs should not be changed unless the patient experiences AEs that warrant a dose change.

If a benzodiazepine is being used as a rescue medication, it will be counted as an AED if used more than two days a week. Use of clobazam as a maintenance AED is an allowed during the study.

The following additional medications are not allowed: midazolam (midazolam (can only be used as single dose given weekly as rescue medication, unless directed otherwise by the Investigator), oral ketoconazole, fluconazole, nefazodone, rifampin, alfentanil, alfuzosin, amiodarone, cyclosporine, dasatinib, docetaxel, eplerenone, ergotamine, everolimus, fentanyl, halofantrine, irinotecan, lapatinib, levomethadyl, lumefantrine, nilotinib, pimozide, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinoin, vincristine, vinorelbine and St. John's

Wort.

Subjects may be using a ketogenic diet in addition to AED therapy. The diet may be adjusted to maintain requisite metabolic parameters, but a ketogenic diet should not be initiated or stopped during Period A of the study.

The use of cannabis or any CBD or THC-containing products (other than the study medication) is not allowed during the study.

9.3. Treatment Compliance

The investigator will keep a current and accurate inventory of all clinical supplies received from the Sponsor. Any deviations from the protocol will be recorded. Patients must continue to remain compliant (at least 90% compliant) with study medication use, daily seizure diary and skin check diary throughout the study. If at any time, compliance falls below 90%, patients will not be eligible for study continuation and will be discontinued from the study.

All patients will be provided with a sufficient supply of study drug during their site visit. Patients will bring the used and unused sachets, in the appropriate baggie, to the site at each visit. The site will perform drug accountability (if all sachets were completely or partially utilized) at each visit and record patient compliance.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

ZYN002 Transdermal Synthetic Cannabidiol Gel is a clear transdermal gel containing CBD for topical application. [redacted]

10.2. Study Drug Packaging and Labeling

ZYN002 drug product will be packaged in sachets.

Study supplies will be labeled with a computer-generated label, which will include the following information:

- Protocol Number
- Intended Use
- Storage Conditions
- Labeled: Keep out of reach of children
- Identification Manufacturer/Sponsor

10.3. Study Drug Storage

Study drug is to be stored between 15°C - 25°C / 59°F - 77°F.

10.4. Study Drug Preparation

Study drug will be applied as noted in the section above.

10.5. Study Drug Accountability

Patients will bring the unused and used sachets, in the appropriate box kit (unused sachets) and empty sachets in a baggie, to the site at each visit. The site will perform drug accountability (if all sachets were completely or partially utilized) at each visit and record patient compliance since the previous visit.

10.6. Study Drug Handling and Disposal

The site will place all used returned sachets in the baggie in the kit box labeled with the appropriate patient information. For drug accountability purposes the patient number, initials and Visit will be written on the outside of the baggie.

The study monitor will confirm the number of unused sachets of study drug with the research facility and coordinate return or disposal of the used and unused supplies.

11. ASSESSMENT OF EFFICACY

11.1. Seizure Frequency

The primary efficacy assessment will be the median percent change from baseline in the monthly (28 day) frequency of seizures (SF28) during Period Afor the following types in total ("select countable seizures"):

- Generalized tonic-clonic ("primary generalized tonic-clonic') seizures (GTCS)
- Focal impaired awareness seizures (FIAS)
- Focal to bilateral tonic-clonic seizures (BTCS)

Secondary seizure endpoints include the median percent change from baseline in SF28 for the following (as defined in the Table below):

- All "countable seizures" (individually and in total)
    - Generalized tonic-clonic seizures (GTCS)
    - Focal impaired awareness seizures (FIAS)
    - Focal to bilateral tonic-clonic seizures (BTCS)
    - Tonic seizures (T)
    - Clonic seizures (C)
    - Atonic seizures (AT)
    - Epileptic spasms (ES)
    - Focal aware seizures with motor signs (FM)
- All focal-onset seizures (FIAS, BTCS, FM)
- Seizure type identified as the most disabling overall

The frequency of the following types of seizures during the daily period of observation that consistently occur with a countable frequency:

- Myoclonic seizures (M)
- Absence seizures (A)
- Focal aware seizures without motor signs (focal sensory seizures) (FAS)

Table 11 outlines the seizure types and groups that will be analyzed.

Table 11: Seizure Types and Groups to be Analyzed

Seizure Type	Select Countable Seizures	All Countable Seizures	All Focal-Onset Seizures	Set Period Daily Count	None/ some/ lots	Seizure-free Days (Select Countable Seizures)
Easy to count seizures						
Generalized Tonic-Clonic Seizures (GTCS)	X	X	X			X
Focal Impaired Awareness Seizures (FIAS)	X	X	X			X
Focal to Bilateral Tonic-Clonic Seizures (BTCS)	X	X	X			X
Focal Aware Seizures with Motor Signs (FM)		X	X			
Tonic Seizures (T)		X				
Clonic Seizures (C)		X				
Atonic Seizures (AT)		X				
Epileptic Spasms (ES)		X				
Difficult to count seizures						
Absence Seizures (AS)				X	X	
Myoclonic Seizures (M)				X	X	
Focal Aware Seizures (FAS)				X	X	

Seizure count endpoints will be summarized by month (28 days), for Periods A and B individually and overall for the entire treatment period. Seizure count endpoints will also be summarized for the last four and the last eight weeks of treatment in Periods A and B.

Other seizure endpoints include:

- A three point Likert-type scale (none, some seizures and lots of seizures) captured on a daily diary will be used to assess myoclonic, absence and focal sensory seizures.
- The number of seizure free days (select countable seizures).
- The percentage of patients defined as a 35%, 50% and 90% responder for a specified period if for that patient the RedSF is $\geq$ 35%, 50% and 90% respectively.
- Video-EEG findings.

Video-EEG findings will also be analyzed. Video EEGs of 2, 4 or 24 hours in duration will capture information including:

- Characteristics of the waking and sleep EEG background,
- Interictal epileptiform and non-epileptiform abnormalities.

EEG and clinical features of seizures will be evaluated. Video EEG interpretation will be completed by an independent reviewer.

Seizure frequency captured via the daily diary will be analyzed per 28-day period (SF28). Patients must complete diaries for at least 80% of the days in the SF28 period for data to be used in that 28-day period. SF28 is calculated as the number of seizures in the period divided by the

number of days in the period multiplied by 28. SF28 will be calculated and summarized monthly. A specific period includes the day after the previous period to the end of the current period.

SF28 = (Total Number of Seizures in D days)*(28/D)

The reduction from Baseline in seizure frequency (RedSF) is defined for each period as:

RedSF=SF28(Period X)-SF28(Baseline)

The percent reduction from Baseline in seizure frequency is defined as:

%RedSF=100*[SF28(Period X)-SF28 (Baseline)/SF28(Baseline)

In addition, a patient will be defined as a 35%, 50% or 90% responder for a specified period if for that patient the RedSF is ≥ 35%, 50% or 90%, respectively.

Seizure endpoints will be summarized monthly, overall for Periods A and B, and overall for the whole study.

11.2. Other Efficacy Assessments

Efficacy assessments will also include change in caregiver stress, quality of life, sleep disturbances, adaptive behavior among epilepsy patients and assessment the patient's day ("good day / bad day").

The assessments will be conducted using the following:

- Caregiver stress
  - The University of Washington Caregiver Stress Scale at Day 1, Week 14, Week 26 and Week 50.
- Quality of life
  - Epilepsy and Learning Disabilities Quality of Life scale (ELDQOL - modified) at Day 1, Week 14, Week 26 and Week 50 of the study
- Sleep disturbance
  - Sleep Disturbance Scale for Children (SDSC) at Day 1, Week 14, Week 26 and Week 50 of the study
- Adaptive behavior among epilepsy patients
  - Vineland Adaptive Behavior Scale™ – 3 (VABS-3) at Day 1, Week 26 and Week 50 of the study
- Assessment the patient's day ("good day / bad day")
  - Parents/caregivers will also complete a daily Likert-type "good day/bad day" questionnaire
- Investigator Qualitative Assessment
  - Each Investigator will qualitatively capture improvements for the patient and family (such as but not limited to daily activities, school attendance and alertness)

as well as anything that has worsened for the patient/family at Week 26 and Week 50.

These assessments will also be completed at the Early Termination visit for patients who discontinue from the study.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety assessments will include collection of AEs, physical and neurological examinations, 12-lead ECG, clinical laboratory assessments (hematology, chemistry and urinalysis), testosterone (males only), [redacted], Marijuana Withdrawal Checklist short form (Behavior Checklist), urine pregnancy test (females of child bearing potential only), C-SSRS (Children) and findings from the skin check examinations following treatment.

12.1.1. Blood Levels of CBD and AEDs

12.1.1.1. Blood Sample Collection

[redacted] Where possible, effort should be made to get a trough sample for the AED. The date and time of blood sample collection, as well as the date, time and dose of CBD and AEDs should be recorded for each sample. The times of the first dose of study drug on Day 1 and the previous dose of study drug for each blood draw at subsequent visits should be recorded. AED samples will be analyzed by a central laboratory.

[redacted]:

[redacted]

An inventory of the samples shipped will accompany the package.

12.1.1.2. Sample Analysis

[redacted]

Plasma samples for AEDs will be analyzed through a central laboratory.

All analysis will be completed to Good Laboratory Practice (GLP) standards. Results will be provided in a separate bioanalytical report.

12.2. Adverse and Serious Adverse Events

Throughout the study, the investigator will monitor each patient for evidence of drug intolerance and for the development of clinical and/or laboratory evidence of an AE. An AE assessment will be made by the investigator on a routine basis throughout treatment at each visit. In order to standardize the approach to assessing the occurrence of AEs, the investigator should make a judgment as to any change in condition or AEs that were not present before study drug administration when he obtains the patient's response to how they are feeling. Patients having AEs will be followed until they return to normal or become stabilized.

Investigators and study staff will be trained to recognize abuse, misuse and addiction. They will be instructed to document all cases in which study drug is taken in a manner that deviates from the protocol, is unaccounted for, or is used by anyone other than the study participant. There will be a dedicated CRF for recording these events. In addition, the Misuse Abuse and Diversion Drug Event Reporting Systems (MADDERS®) will be used to systematically capture and adjudicate abuse-related events in this study (Treister et al. 2016).

All AEs that occur during the study must be reported in detail on the appropriate eCRFs and patient's source document record and on any other report form required by national law.

All adverse events, including those that meet the seriousness criteria will be recorded from informed consent through the final follow-up telephone call.

Serious Adverse Events (SAEs) will be followed until their signs and symptoms have remitted or stabilized, until the patient is lost to follow-up, until 30 days following the last follow-up telephone call, or the patient administers their first dose of study drug under a Special Access or Authorized Prescriber program, whichever occurs first.

Should the site be made aware of any SAE within the 30 days following the last follow-up telephone call that upon review they believe is related to a study drug, they must report it to the sponsor in accordance with protocol **Section 12.5**. As patients that continue to receive study drug after the End of Study Visit via a Special Access or Authorized Prescriber program are not required to complete follow-up calls, this requirement does not apply to these patients. The reporting of SAEs that occur while receiving treatment via these programs fall outside the scope of this study protocol.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (e.g., diabetes, congestive heart failure, rheumatoid arthritis, psoriasis) that occurs at any time after signing of the ICF whether it is considered to be related to treatment. Worsening of an existing medical condition is when a condition present at the time of signing of the ICF (e.g., cancer, diabetes, gout) becomes more severe, more frequent, or increased in duration during the study. Hospitalizations for pretreatment conditions (e.g.,

elective cosmetic procedures) or surgeries that were planned before entry into the study are not considered AEs.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value represents for the patient a change from the time of signing of the ICF. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as AEs. Clinically significant changes occurring after the signing of the ICF are considered AEs; however, the reported adverse event should include the underlying diagnosis or resulting clinical sequelae.

Throughout the study, the investigator will monitor each patient for evidence of drug intolerance and for the development of clinical and/or laboratory evidence of an adverse event. An AE assessment will be made by the investigator on a routine basis throughout the study. All AEs which occur during the course of the study must be reported in detail on the appropriate eCRF page and on any other report form required by national law.

[redacted]

If a patient reports a worsening of skin erythema after a period of improvement, the investigator should assess whether the event is indicative of a delayed hypersensitivity reaction. If in the opinion of the Investigator the event is a delayed hypersensitivity reaction, this will be recorded as an AE.

All study drug application site signs/symptoms will be recorded as AEs, except erythema scores of 1, 2 or 3. The event term should specify “application site disorder - [specify sign or symptom]”.

If a patient becomes pregnant during or after exposure to a study drug received in this study, the investigator will immediately discontinue the patient from the study and contact the Sponsor or designee. The investigator will complete the Sponsor’s (or designee’s) Clinical Pregnancy Notification Form and email it to the Sponsor within two days of learning of the pregnancy. Diligent efforts will be made to determine the outcome for all pregnancy exposures in the clinical trial. Information on the status of the mother and the child will be forwarded to the Sponsor.

Generally, follow-up will occur within 6 to 8 weeks following the estimated pregnancy delivery date. Any premature termination of the pregnancy will be reported. Both maternal and paternal exposure will be collected. For exposure involving the female partner of a male patient, the necessary information must be collected from the patient, while respecting the confidentiality of the partner.

Although pregnancy occurring in a clinical trial is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and will be followed as such. A spontaneous abortion is always considered to be a SAE.

12.2.1.2. Serious Adverse Event

Any adverse event that results in one or more of the following is considered a serious adverse event (SAE).

1. Death.
2. Life Threatening - The patient was at risk of death at the time of the event. It does not refer to the hypothetical risk of death if the adverse event were more severe or were to progress.
3. In-patient hospitalization (admission or prolongation of existing hospitalization).
4. Persistent or significant disability / incapacity - Any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions. This includes the inability to work. This is not intended to include transient interruptions of daily activities.
5. Congenital abnormality or birth defect - Any structural abnormality in patient offspring that occurs after intrauterine exposure to treatment.

For the purposes of this study any suicide attempt is considered serious and must be reported as such.

Other Medically Important Events - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Planned hospitalizations to treat a pre-existing condition or an inpatient stay required by the protocol is not considered to be an SAE unless otherwise specified in the study protocol. If there is any doubt whether the hospitalization constitutes an SAE, it should be treated as serious and reported to Zynerba.

12.2.1.3. Other Adverse Event

Other adverse events (OAEs) will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient/patient from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

12.3. Relationship to Study Drug

The following information will be collected for each adverse event and the relationship of the adverse event to the study drugs will be assessed using the following definitions:

Related - An adverse event has a strong temporal relationship to study drug or recurs on re-challenge, and another etiology is unlikely.

Not related - An adverse event is due to underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology). The alternative etiology will be recorded on the eCRF.

12.4. Recording Adverse Events

Adverse events spontaneously reported by the patient/patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. However, abnormal values that lead to discontinuation of administration of study drug must be reported and recorded as an AE. AEs will be collected from the signing of the ICF until the last Telephone Follow-Up Call.

The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the date of onset and resolution, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the Sponsor's or their representative's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.5. Reporting Serious Adverse Events and Protocol Defined Expedited Events

If any protocol defined expedited event, or serious, life-threatening, or fatal AE occurs whether related to study drug or not, the Investigator must notify the Sponsor within 24 hours by telephone and facsimile.

[redacted]

The definition for a 'protocol defined expedited event' for the purposes of this study is a Skin Check Scale score of 4, "intense erythema with edema and blistering/erosion" (see Section 7.5.17).

The investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by email to the Sponsor.

Additional follow-up information, if required or available, should all be emailed to the Sponsor within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

All SAEs (related and unrelated) will be followed from the signing of the ICF until their signs and symptoms have remitted or stabilized, until the patient is lost to follow-up, until 30 days following the last follow-up telephone call, or until the patient administers their first dose of study drug under a Special Access or Authorized Prescriber program, whichever occurs first. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator up to 30 days after the last follow-up telephone call should be reported unless the patient has continued treatment via Special Access or an Authorized Prescriber program. All SAEs must be reported to the Sponsor within one business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by email PDF to the Sponsor and their representative.

Additional follow-up information, if required or available, should all be emailed to the Sponsor or their representative within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

The Sponsor representative is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the HREC or HDEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its HREC or HDEC of these additional SAEs.

13. STATISTICS

13.1. Determination of Sample Size

This study is exploratory in nature and as such, a formal sample size was not determined.

13.2. Analysis Populations

13.2.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all patients who have taken at least one dose of study medication and have at least one post-baseline efficacy assessment. The ITT population will be used for all efficacy summaries.

13.2.2. Safety Population

All patients who receive at least one dose of study drug will be included in the safety population. Safety population will be used for all safety evaluations.

13.2.3. Pharmacokinetic Population

[redacted]

13.3. Efficacy Summary

No inferential analyses of efficacy will be conducted. However descriptive summaries will be presented.

Efficacy variables will be summarized descriptively for all patients by the dose levels as described in the statistical analysis plan (SAP).

Seizures frequency captured via the daily diary will be analyzed per 28-day period (SF28). Patients must complete diaries for at least 80% of the days in the SF28 period for data to be used in that 28-day period. SF28 is calculated as the number of seizures in the period divided by the number of days in the period multiplied by 28. SF28 will be calculated and summarized monthly. A specific period includes the day after the previous period to the end of the current period.

The reduction from Baseline in seizure frequency (RedSF) is defined for each period as:

RedSF=SF28(Period X)-SF28(Baseline)

The percent reduction from Baseline in seizure frequency is defined as:

%RedSF=100*[SF28(Period X)-SF28 (Baseline)/SF28(Baseline)

In addition, a patient will be defined as a 35%, 50% and 90% responder for a specified period if for that patient the RedSF is $\geq$ 35%, 50% and 90%.

The primary efficacy endpoint of the median percent change in the SF28 of seizures by type is described in Section 11.1.

Changes from baseline will be compared using a paired t-test or the Wilcoxon Signed-Rank test in the case that the normality assumption is not met. Responder endpoints (35%, 50% and 90%

responder) will be summarized using counts, percentages and a one-sided test for binomial proportions.

13.4. Pharmacokinetic Analyses

13.4.1. CBD and CBD Metabolite (s)

The following PK parameters for CBD will be calculated/derived from the data. Plasma PK will be calculated on:

Trough: Steady-state plasma concentration occurring just prior to the next dose of ZYN002.

Elapsed time between the last ZYN002 dose and time of plasma sample collection.

Descriptive statistics (arithmetic mean, median, SD, minimum, maximum, coefficient of variation, geometric mean [plasma concentration]) for the plasma trough concentrations and elapsed time will be presented for all patients combined at each nominal blood sampling time [redacted]

[redacted]

13.4.2. AED Medications

The following data will be summarized separately for each AED medication:

Plasma concentration occurring at Day 1

Elapse time between last AED dose and the time of plasma sample collection.

Descriptive statistics (arithmetic mean, median, SD, minimum, maximum, coefficient of variation, geometric mean [plasma concentration]) for the AED plasma trough concentrations and elapse time will be presented for all patients at [redacted]

13.5. Safety Analyses

All safety summaries will be presented for patients and also by the dosing cohorts listed below, which are based on the treatment (total daily dose).

Treatment A - 125 mg CBD Q12H (±2 hours); for a total daily dose 250 mg CBD

Treatment B – 250 mg CBD Q12H (±2 hours); for a total daily dose of 500 mg CBD

Treatment C – 375 mg CBD Q12H (±2 hours); for a total daily dose of 750 mg CBD

Treatment D - 500 mg CBD Q12H (±2 hours); for a total daily dose of 1000 mg CBD

Duration of treatment on each dose will be summarized with descriptive statistics.

AEs will be tabulated by the actual treatment dose of drug received at the time of initiation of the adverse event and classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Additionally, AEs will be tabulated overall (total number of AEs and total number of patients with AEs).

The Misuse Abuse and Diversion Drug Event Reporting System (MADDERS®) will be used in this study to systematically capture and adjudicate abuse-related events (Treister et al. 2016). Data from the MADDERS® will be summarize and presented separately from other AEs.

Descriptive statistics (count, percentage of yes/no responses) will be provided for each item of the C-SSRS that is completed at each time point. Note that if a patient answers "No" to question "1" or question "2", then the patient will not be asked to answer question "4" or question "5".

Vital signs collected by time point will be summarized using descriptive statistics (N, mean, SD, minimum, and maximum). Changes from Day 1 in the vital signs will also be summarized by time point.

Safety laboratory test results and change from Day 1 will be summarized by time point with descriptive statistics.

Application site erythema scoring as determined by patients will be summarized at 4-week time periods using counts and percentages and duration (i.e., number of days during the 4-week time periods) at each respective site irritation score (0, 1, 2, 3 or 4).

Total time (number of days) on each of the possible study doses will be determined for each subject. A summary of time on each dose will be provided with descriptive statistics.

Application site erythema scoring as determined by the investigator will be summarized at all visits (scheduled, unscheduled and End of Study).

Symptoms of withdrawal will be assessed by comparing change over time in the total score on the Marijuana Withdrawal Checklist short form (Behavior Checklist) from Day 1 to Week 50 (or until the time of withdrawal from the study), weekly during the taper period and weekly for 4 weeks after the patient stops study drug. A description of the statistical methods to be employed, including timing of any planned interim analysis.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

A face-to-face visit for the pre-study visit and site initiation will be completed by a monitor from the Sponsor or their representative.

During the study, a monitor from the Sponsor or their representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRF with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor or their representative.
- Confirm AEs and SAEs have been properly documented in the eCRF and confirm any SAEs have been forwarded to the Sponsor or their representative and those SAEs that met criteria for reporting have been forwarded to the HREC/HDEC.

The monitor will be available between visits if the investigator(s) or other staff have questions or needs information or advice.

14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or HREC/HDEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the Sponsor and their representative immediately if contacted by a regulatory agency about an inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Original patient records such as research facility records and laboratory reports should be available at each site for source document review by Sponsor personnel. Source document review is the verification of the information recorded on eCRFs with that recorded in the original patient records. In this study, source document review of specific types of information will be conducted for all patients.

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor or their representative may conduct a quality assurance audit. Please see Section 17.1 for more details regarding the audit process.

16. ETHICS

16.1. Human Research Ethics Committee / Health and Disability Ethics Committee

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the ICF, and all other forms of patient information related to the study (e.g., advertisements used to recruit patients) and any other necessary documents be reviewed by HREC/HDEC. HREC/HDEC approval of the protocol, ICF and patient information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require HREC/HDEC approval prior to implementation of any changes made to the study design.

16.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki and GCP guidelines. The investigator is responsible for reporting to the HREC/HDEC modifications, safety updates, amendments, and deviations of the protocol that impact on patient.

At appropriate intervals, the Sponsor or their representative will visit the site during the clinical study and assure that the Investigator's obligations are being fulfilled. Per GCP requirement for confirmatory proof of patient files**,** a copy of all records must be retained with the files of the principle investigator[redacted]. These records include the Confidential Follow-up Forms and other documents such as ICFs, laboratory reports, and other source documents, drug accountability forms, HREC/HDEC approvals, protocols, and eCRFs.

16.3. Patient Information and Informed Consent

The study protocol and ICF must be approved by the investigator's HREC/HDEC and a copy of the approved ICF must be supplied to the Sponsor. The patient and / or legal authorized representative will be asked to read the consent form. If the decision is made for the patient to participate in the study, the patient and /or legal authorized representative will be asked to sign and date the form as evidence of consent. Each patient and / or legal authorized representative must voluntarily sign and date a consent form before participating in this study. It is the obligation of the Investigator or their representative to explain the nature of the study to the patient and / or caregiver. The physician will document in the patient's medical chart that the patient and / or legal authorized representative has signed an ICF to participate in an investigational trial, a copy of the ICF will be given to the patient and / or legal authorized representative, and the original should be retained with the patient's study records.

Patient names will remain confidential. Only the patient number, patient initials, and birth date will be recorded on the eCRF. The patient and / or legal authorized representative will give explicit permission for representatives of the regulatory authorities and the HREC/HDEC to inspect their medical records to verify the information collected. The patients and / or legal authorized representative will be informed that all protected health information and clinical data are saved in a confidential manner.

All study data are confidential with restricted access. Information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws.,

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

In addition, the Investigator will permit trial-related audits, HREC/HDEC review, and regulatory inspection(s), providing direct access to source data documents.

17.2. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 15 years from study completion. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

All information concerning ZYN002 and the Sponsor's operations, such as ZYN002 patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by the Sponsor and not previously published, is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by the Sponsor in connection with the development of ZYN002. This information may be disclosed as deemed necessary by the Sponsor. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide the Sponsor with complete test results and all data developed in this study.

This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to others without the written consent of the Sponsor, and shall not be used except in the performance of this study.

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20. APPENDICES

20.1. Columbia Suicidality Severity Rating Scale (C-SSRS) for Children

Children's Baseline/Screening – Screening Visit

C-SSRS-Children-BaselineScreening_AU1

Children's Since Last Visit

C-SSRS-Children-SinceLastVisit_AU3.0_en

20.2. [redacted]

Tanner Staging
Licensed from Elsevie

20.3. Marijuana Withdrawal Checklist short form (Behavior Checklist)

MWC-short_Zynerba .doc

20.4. Seizure Diary

SeizureDiary.doc

20.5. Skin Check Diary

Skin Check Diary.docx

20.6. University of Washington Caregiver Stress Scale

20.7. Daily Questionnaire- Good day / Bad day

Daily Questionnaire Good-Bad-Day.DOC

20.8. Epilepsy Learning and Disabilities Quality of Life (ELDQOL) Scale-Modified

ELDQOL_modified.PDF

20.9. Sleep Disturbance Scale for Children (SDSC)

SDSC_past month.doc

20.10. Vineland Adaptive Behavior Scale™- 3 (VABS-3)

VABS-3 Interviewer Domain-Level.pdf

20.11. Application of Gel Instructions

Application of
ZYN002 Gel Instructic