ZYN002
ZYN2-CL-03

A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multiple Center, Multiple-Dose Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Patients with Partial Onset Seizures

Synthetic Transdermal Cannabidiol for the Treatment of Epilepsy
(STAR 1)

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PIND Number: 125547
Sponsor: Zynerba Pharmaceuticals Pty. Ltd.
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INVESTIGATOR’S AGREEMENT

I have received and read the protocol. I have read the ZYN2-CL-03 Amendment 04 dated 10 October 2016 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 and Title of Investigator

________________________________________
Signature of Investigator

________________________
Date
1. **SYNOPSIS**

| **Name of Sponsor/Company:** | Zynerba Pharmaceuticals Pty. Ltd. |
|-----------------------------|-----------------------------------|
| **Name of Investigational Product:** | ZYN002 |
| **Name of Active Ingredient:** | Cannabidiol (CBD) |
| **Title of Study:** | A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Multiple Center, Multiple-Dose Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Patients with Partial Onset Seizures (STAR 1) |
| **Study Centers:** | Australia, New Zealand |
| **Principal Investigator:** | Terence J. O’Brien MB, BS, MD, FRACP, FRCPE |
| **Studied period:** | Estimated date first patient enrolled: 01 June 2016 Estimated date last patient completed: 31 January 2017 |
| **Phase of development:** | 2A |

**Objectives:**

**Primary:**
To evaluate the efficacy of ZYN002 administered as a transdermal gel formulation for 12 weeks as adjunctive therapy for the treatment of partial onset seizures (POS).

**Secondary:**
To evaluate the safety and tolerability of ZYN002 in epilepsy patients receiving different treatments for POS.

**Methodology:**
This is a Phase 2A, randomized, double-blind, placebo-controlled, multiple-center, multiple-dose study to assess the efficacy and safety of ZYN002 administered as a transdermal gel, either as:
- Treatment A ZYN002 - CBD 195 mg every 12 hours (Q12 H) (± 2 hours), or
- Treatment B ZYN002 - CBD 97.5 mg Q12 H (± 2 hours) and placebo, or
- Treatment C placebo Q12 H (± 2 hours)

for 12 weeks to male and female patients with POS. At the end of week 12, patients will undergo a two-week blinded dose reduction. Patients will have their dose reduced by 50% at Week 13 and another 50% (only patients receiving Treatment A) at Week 14 and then treatment will be discontinued. Approximately 210 patients will be enrolled into the 8-week Baseline Period to ensure that 180 patients are randomized across all treatment groups.

**Baseline Period**
During the prospective 8-week Baseline Period, patients will record seizure frequency and type. During the Baseline Period, anti-epileptic drug (AED) blood samples will be collected at screening and Week 4 (Day -28 ± 3 days). All patients will have their seizure history and diagnosis reviewed and confirmed by the Epilepsy Study Consortium prior to randomization into the study.

**12-Week Maintenance Period**
Following the 8-week Baseline Period, eligible patients will be randomized in a 1:1:1 ratio to either placebo Q12 H (± 2 hours), Treatment A ZYN002 - CBD 195 mg Q12 H (± 2 hours), or Treatment B ZYN002 – CBD 97.5 mg Q12 H (± 2 hours) for 12 weeks.
### Prior to the Initial Dosing

Prior to the initial dosing on Study Day 1, patients will report to the investigative site to have a pre-dose blood sample drawn for plasma levels of CBD, THC and AEDs. All concomitant medications (prescription and over-the-counter (OTC)) will be recorded including dose and reason for use. Patients will be provided instructions on how to apply the gel and the first dose of study drug will be applied by the patient at this visit and visits at Weeks 4, 8 and 12. Patients will be required to visit the clinic every 2 weeks through Week 8 and at Week 12 to have a blood sample drawn for plasma levels of their AEDs.

At Weeks 4, 8, and 12 of the Maintenance Period, patients will have the following procedures completed: a blood sample for determination of CBD and THC, blood sample for AED plasma level, review of patient diaries, vital signs, targeted physical and neurological examination (at Weeks 4 and 8), electrocardiogram (ECG at Week 8), laboratory tests (at Week 8), pregnancy test (females only), concomitant medication review, study drug, skin irritation assessment and adverse event (AE) review. Patients will also be administered the Columbia Suicide Severity Rating Scale (C-SSRS).

Patients will be instructed to withhold their morning dose of ZYN002 until a blood sample is collected at these 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 may require adjusting if the patient experiences AEs that warrant a dose change.

Patients will be instructed to record their seizure frequency and type in their daily seizure diary which the Investigator will review during visits at Weeks 4, 8 and 12.

Patients will be instructed on proper application of the gel. Patients will be permitted to shower 30 minutes prior to study dose. Patients will apply all study drug to clean, intact skin, thoroughly massaging it into both the right and left shoulders and/or upper arms until the area is dry. The gel will be rubbed in completely and dry prior to dressing. Once the patient has completed the treatment application, they will wash their hands thoroughly with soap and water to remove any residual gel.

### Safety Monitoring

Patient safety will be monitored during the treatment visits using standard measures, including physical and neurological exams, examination of skin at application site, vital signs (including oral temperature), 12-lead ECGs, clinical laboratory tests (hematology, chemistry and urinalysis), testosterone (males only), urine pregnancy test (females only), C-SSRS, and AE monitoring.

Patients will be provided a diary to complete a daily skin irritation examination. Before each study dose patients will record the skin irritation score in their daily skin irritation diary. When skin irritation is noted, patients should apply the gel to a non-irritated area of the shoulders and/or upper arms. If the skin irritation score is “1” or Redness, the patient will contact the Investigator to determine if an Unscheduled Visit is required. If an Unscheduled Visit is not required, patients will be instructed to call the Investigator if the skin irritation worsens. The Investigator will use discretion in suspending dosing for patients with a skin irritation score of 4 but will in all cases complete an expedited report and contact their study Clinical Research Associate (CRA) and the Zynerba Medical Monitor.

### Plasma Samples for CBD and AEDs:

| **Plasma Samples for CBD and AEDs:** |
|-----------------------------------|
| Patients will undergo a two-week blinded dose reduction at the end of Week 12. Patients will have their dose reduced by 50% at Week 13 and another 50% (only patients receiving Treatment A) at Week 14 and then treatment will be discontinued. |
| Patients will complete an End of Study Visit at Week 15. If the skin irritation score at Week 15 is > 0, the patient will continue to be followed through an Unscheduled Visit until the skin irritation score is recorded as ‘0’. At this time, the patient will be discharged from the study. |
Blood samples for trough plasma levels of CBD and THC will be collected at pre-dose on Study Day 1 and every 4 weeks through Week 12. In addition, blood samples for AED blood levels will be collected at screening, Week 4 of the Baseline Period, pre-dose on Study Day 1, and every 2 weeks through Week 8, and at Week 12. The times of blood sample collection, as well as the times of dosing, will be recorded. Plasma samples will be analyzed by a validated high-performance liquid chromatography (HPLC), with tandem mass spectrometry (MS/MS) detection for the determination of CBD and THC in the plasma. Plasma samples for AEDs will be analyzed through a central laboratory.

**Number of Patients (planned):**
Approximately 210 patients will be enrolled into the Baseline Period in order to ensure that 180 patients are randomized, assuming a screening failure rate of ≤ 15%. Patients who prematurely discontinue after randomization from the study will not be replaced.

**Diagnosis and Main Criteria for Inclusion:**
Patients participating in this study will have a diagnosis of POS. Patients must qualify based on complete inclusion and exclusion criteria to be eligible to enroll.

**Main Inclusion Criteria:**
1. Male or female adults, 18-70 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, 12-lead ECG, and clinical laboratory test results. Laboratory results outside of the reference range, but acceptable, must be documented as not clinically significant (NCS) by the Investigator.
3. Patients must have a diagnosis of focal epilepsy (POS) with or without secondary generalization (International League Against Epilepsy Classification) for ≥ 2 years which has been documented by review of the most informative electroencephalogram (EEG), magnetic resonance imaging (MRI) scan, and narrative from the physician who manages the patient’s epilepsy. All patient epilepsy diagnoses and seizure classification will be confirmed by expert review by the Epilepsy Study Consortium.
4. History of previous epilepsy surgery is acceptable provided seizure frequency is stable over the past 3 months prior to screening.
5. Presence of previous vagal nerve stimulator, deep brain stimulator or responsive neurostimulation (RNS) is acceptable if present for at least one year and settings have remained stable over the past 3 months prior to screening.
6. Based on history, patients have on average at least three (3) observable POS per month and would therefore, likely have at least six (6) POS during the 8-week Baseline Period and not more than 20 or more consecutive POS-free days.
7. Patient is currently being treated and maintained with a stable regimen of one, two, or three AEDs.
8. Patient is able and willing to maintain a daily seizure and daily skin irritation diary.
9. Patient has a body mass index between 18-35 kg/m².
10. Females of childbearing potential must have a negative serum pregnancy test at the Screening Visit, and negative urine pregnancy test at Day 1, Weeks 4, 8, and end of study. Females of childbearing potential and male patients with a partner of childbearing potential must use an acceptable method of contraception (as outlined below), from at least 21 days prior to the first dose of study drug and for 3 months after the last dose of study drug.
   a. Standard acceptable methods include use of a highly effective method of contraception, including; hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, spermicide, vasectomy, intrauterine device.

11. Patient agrees to abide by all study restrictions and comply with all study procedures.

12. Patient must be adequately informed of the nature and risks of the study and give written informed consent prior to screening.

13. In the Investigator’s opinion, the patient is reliable and is willing and able to comply with all protocol requirements and procedures.
Main 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 (except clinical study ZYN2-CL-01 or ZYN2-CL002), 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 four (4) weeks of the Screening Visit or during the study.
4. Patient has change in current tobacco product(s) use within 30 days of screening or plans to change their use during the study.
5. Patient has had a diagnosis of idiopathic (“primary”) generalized (e.g., juvenile myoclonic epilepsy, absence epilepsy), or mixed epilepsy (LGS) or non-epileptic seizures within the last 5 years prior to study entry.
6. Patient is using the following AEDs: clobazam, ethosuximide, felbamate or vigabatrin. If a benzodiazepine (excluding clobazam) is being used as a rescue medication, it will be counted as an AED if used more than two days a week.
7. Patient has had a change in AED regimen in the last 4 weeks.
8. Patient has had epilepsy dietary therapy initiated for < 3 months prior to enrollment.
9. Patient has only simple partial seizures without any observable motor component or has seizures occurring in a non-countable clustered pattern.
10. Patient has had an episode of status epilepticus within the 12 months prior to screening.
11. Patient has seizures secondary to illicit drug or alcohol use, infection, neoplasm, demyelinating disease, degenerative neurological disease or central nervous system (CNS) disease deemed progressive, metabolic illness, or progressive degenerative disease.
12. Patient has acute or progressive neurological disease, moderate or severe psychiatric disease, or severe mental abnormalities that are likely to require changes in drug therapy during the Maintenance Period of the study, or interfere with the objectives of the study, or the ability to adhere to protocol requirements.
13. Patient is using the following medications: midazolam, oral ketoconazole, fluconazole, nefazadone, rifampin, alfentanil, alfuzosin, amiodarone, cyclosporine, dasatinib, docetaxol, eplerenone, ergotamine, everolimus, fentanyl, halofantrine, irinotecan, lapatinib, levomethadyl, lumeferantrine, nilotinib, pimozone, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinoin, vincristine, vinorelbine and St. John’s Wort.
14. Women who are breastfeeding or lactating.
15. Patient has a history of actual suicide attempt in the last 5 years or more than one lifetime suicide attempt.
16. Patient responded “yes” to Question 4 or 5 of C-SSRS at the Screening Visit.
17. Patient has a positive result for the presence of Hepatitis B surface antigen (HBsAg), Hepatitis C virus antibodies (HCV-Ab), or human immunodeficiency virus (HIV) antibodies.
18. Patient has a positive drug screen, including ethanol, cocaine, THC, barbiturates (except as AED medication), amphetamines, benzodiazepines (except as rescue medication), and opiates.
19. 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.
20. Patient has any skin disease or condition, including eczema, psoriasis, melanoma, acne, contact dermatitis, scarring, imperfections, lesions, tattoos, or discoloration that may affect treatment application, application site assessments, or affect absorption of the study drug.
21. Patient has a history of treatment for, or evidence of, alcohol or drug abuse within the past year or
regular alcohol consumption exceeding an average of two units of alcohol per day.

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|----------------------------------------|-----------------
| 22. Patient demonstrates behavior indicating unreliability or inability to comply with the requirements of the protocol. |

| Randomization Criteria |
|------------------------|
| **1.** After the Baseline Period, patients will qualify for randomization if they continue to meet the inclusion criteria and have had at least six (6) POS seizures during the Baseline Period. |
| **2.** All exclusion criteria must be reviewed for eligibility for randomization. |

| Investigational Product, Dosage, and Mode of Administration: |
|-------------------------------------------------------------|
| ZYN002 gel, topical. The drug product concentration is 4.2% and the nominal fill weight is 2.32 g of product. Dosing volume will be four (4) sachets per day for each treatment. |
| Treatment A – CBD 195 mg applied Q12 H (± 2 hours); total daily dose of 390 mg. Each dose will consist of 2 sachets of ZYN002 4.2%. |
| Treatment B – CBD 97.5 mg applied Q12 H (± 2 hours); total daily dose of 195 mg. Each dose will consist of 1 sachet ZYN002 4.2% + 1 sachet placebo Q12H. |

| Duration of Treatment: |
|------------------------|
| Patients will receive twice daily applications of study drug for 12 weeks |

| Reference Therapy, Dosage and Mode of Administration: |
|-------------------------------------------------------|
| Treatment C - Placebo gel, topical. |
| Treatment C will consist of two (2) sachets of placebo gel applied Q12 H (± 2 hours). |
| Patients will receive the same number of treatments of placebo gel as the number of active study drug in order to maintain the study blind. |

| Criteria for Evaluation: |
|--------------------------|
| **Efficacy:** |
| Primary Endpoint: The primary efficacy analysis is based on the reduction in seizure frequency per 28-day period (SF28) comparing Baseline Period to the Maintenance Period. |
| Secondary Endpoints: |
| a) \( \ln(\text{SF28(Initial 14d)}) \) and \( \ln(\text{SF28(After Initial 14d)}) \) will be analyzed in same manner as the primary efficacy analysis. |
| b) 50% responder rate based on the Maintenance Period: Logistic regression with factors for treatment and center will be used to compare the two active treatment groups to placebo. |
| c) Percent change from baseline in seizure frequency per 28 days: \%\text{RedSF(Maintenance)}, \%\text{RedSF(Initial 14d)}, \%\text{RedSF(After Initial 14d)}. Descriptive statistics including number (N), mean, median, standard deviation (SD), minimum, and maximum will be presented by treatment group. Graphs of cumulative distribution functions for \%\text{REDSF} will be presented by treatment group. |
| d) Change from baseline in seizure frequency per 28 days: \text{RedSF(Maintenance)}, \text{RedSF(Initial 14d)}, \text{RedSF(After Initial 14d)}. Descriptive statistics including N, mean, median, SD, minimum, and maximum will be presented by treatment group. |
e) Freedom from POS (seizure-free days) over the treatment period (for patients who complete the study and have no missing data). Descriptive statistics including N, mean, median, SD, minimum, and maximum will be presented by treatment group.

f) 100% seizure free during the treatment period. Proportion of patient in each treatment group will be presented.

**Pharmacokinetics**
Steady-state plasma trough concentration will be determined for CBD. Steady-state plasma concentration will also be determined for the patients’ current AEDs and THC at appropriate time points.

**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), urine pregnancy test (females only), C-SSRS, and findings from the skin irritation examinations following treatment.

**Statistical Methods:**
**Efficacy Analyses:**
The primary inferential analysis, based on an analysis of covariance (ANCOVA) model with factors for treatment group and center, will be performed on the log transformed seizure frequency using the transformation \( \ln(SF28 + 1) \). Log transformed average seizure frequency during the Baseline Period will be used as the covariate. Pairwise comparisons of the two active treatments (Treatment A and Treatment B) to placebo (Treatment C) will be made using least squares (LS) means. The percent reduction over placebo will be estimated as:

\[
100\% \times (1 - \text{exponentiated difference of LS means between active treatment (A or B) and placebo})
\]

The secondary analyses include:

a) 50% responder rate: Logistic regression with factors for treatment and center will be used to compare the two active treatment groups to placebo.

b) Percent change from baseline in seizure frequency per 28 days: %RedSF. Descriptive statistics including number (N), mean, median, standard deviation (SD), minimum, and maximum will be presented by treatment group. Graphs of cumulative distribution functions for %REDSF will be presented by treatment group.

c) Change from Baseline Period in seizure frequency per 28 days: RedSF. Descriptive statistics including N, mean, median, SD, minimum, and maximum will be presented by treatment group.

d) Freedom from POS (seizure-free days) over the treatment period (for patients who complete the study and have no missing data). Descriptive statistics including N, mean, median, SD, minimum, and maximum will be presented by treatment group.

The trough plasma concentration for CBD will be determined from blood samples collected prior to next dose of study drug. Elapse time between last study drug dose and time of blood sample collection will be recorded. In addition, trough plasma concentration for THC will also be determined.

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 by treatment group at each nominal blood sampling time (pre-dose Day 1, pre-dose Week 4, pre-dose Week 8, and pre-dose Week 12). Exploratory analyses on the effect of ZYN002 on plasma levels of AEDs, or vice versa, may be explored.

**AED Medications:**

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

- Plasma concentration at screening, Week 4 of the Baseline Period, and Day 1 before dosing with study drug and Weeks 2, 4, 6, 8 and 12.
- Elapsed 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 plasma concentrations and elapse time will be presented by treatment group at screening, Week 4 of the Baseline Period, pre-dose Day 1 and Weeks 2, 4, 6, 8, and 12.

**Safety Analyses:**

AEs will be tabulated by treatment group and classified by system organ class and preferred term using the Medical Dictionary for Regulatory Affairs (MedDRA). For each preferred term, the two active groups will each be compared to the placebo group with a Fisher Exact test. Additionally, AEs will be tabulated overall (total number of AEs and total number of patients with AEs).

Descriptive statistics (count, percentage of yes/no responses) will be provided by treatment group for Questions 4 and 5 of the C-SSRS at each time point.

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

Safety laboratory test results and change from Baseline will be tabulated by treatment group and time point with descriptive statistics.

Application site irritation scoring as determined by the Investigator(s) will be summarized for each treatment group at Weeks 4, 8, 12 and any unscheduled visits using counts and percentages at each respective site irritation score (0, 1, 2, 3, or 4).
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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

| Abbreviation | Definition |
|--------------|------------|
| 5-HT         | Serotonin  |
| Ae0-24       | Amount excreted in the urine during the total 24-hour urine collection time |
| AE           | Adverse event |
| AED          | Anti-epileptic drug |
| ALT          | Alanine transaminase |
| ANCOVA       | Analysis of covariance |
| AST          | Aspartate transaminase |
| CB1          | Cannabinoid receptor type 1 |
| CB2          | Cannabinoid receptor type 2 |
| CBD          | Cannabidiol |
| CBN          | Cannabinol |
| CFR          | Code of Federal Regulations |
| Clr          | Clearance |
| Cmax         | Maximum observed concentration |
| CNS          | Central nervous system |
| CRA          | Clinical Research Associate |
| C-SSRS       | Columbia Suicidality Severity Rating Scale |
| CT           | Computed tomography |
| Discover     | Diagnostic Interview for Seizure Classification Outside of Video EEG Recording |
| DNA          | Deoxyribonucleic acid |
| DRF          | Diagnostic review form |
| ECG          | Electrocardiogram |
| eCRF         | Electronic case report form |
| ENT1         | Equilibrative nucleoside transporter 1 |
| EEG          | Electroencephalogram |
| FDA          | Food and Drug Administration |
| GCP          | Good clinical practice |
| GLP          | Good laboratory practice |
| GPR55        | G protein-coupled receptor 55 |
| HBsAg        | Hepatitis B surface antigen |
| hCG          | Human chorionic gonadotropin |
| HCV-Ab       | Hepatitis C virus antibodies |
| HDL          | High density lipoprotein |
| HIPAA        | Health Insurance Portability and Accountability Act |
| HIV          | Human immunodeficiency virus |
| HPLC         | High-performance liquid chromatography |
| ICF          | Informed consent form |
| IEC          | Independent Ethics Committee |
| IRB          | Institutional review board |
| ITT          | Intent-to-treat |
| Abbreviation | Definition |
|--------------|------------|
| IV           | Intravenous |
| LDL          | Low density lipoprotein |
| LGS          | Lennox-Gastaut Syndrome |
| LH           | Luteinizing hormone |
| LHRH         | LH releasing hormone |
| LPS          | Lipopolysaccharide |
| LS           | Least squares |
| MedDRA       | Medical Dictionary for Regulatory Affairs |
| MRI          | Magnetic resonance imaging |
| MS/MS        | Tandem mass spectrometry |
| N            | Number |
| NCS          | Not clinically significant |
| O₂           | Oxygen |
| OTC          | Over-the-counter |
| pCO₂         | Partial pressure of carbon dioxide |
| pH           | Negative log of hydrogen ion concentration |
| PK           | Pharmacokinetic |
| pO₂          | Partial pressure of oxygen |
| 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 |
| SD           | Standard deviation |
| SF28         | Seizure frequency per 28 day period |
| SGOT         | Serum glutamic oxaloacetic transaminase |
| SGPT         | Serum glutamic pyruvic transaminase |
| SIF          | Seizure identification form |
| T            | Testosterone |
| TBD          | To be determined |
| THC          | Δ⁹-tetrahydrocannabinol |
| T_max        | Time to maximum observed concentration |
| VR1          | Vanilloid type-1 |
| WBC          | White blood cell |
| w/w          | Weight/weight |
4. **INTRODUCTION**

4.1. **Background Information**

Cannabidiol (CBD) is the primary non-psychoactive cannabinoid found in the Cannabis plant. Cannabis has low affinity for CB1 and CB2 receptors, and 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 on the results of well-controlled studies in which CBD has exhibited high tolerability across several modes of administration.

Clinical and nonclinical data suggest that CBD has dramatic effects on reducing seizures in patients with epilepsy. ZYN002 (CBD gel) may provide an effective treatment for refractory epilepsy based on data highlighting anticonvulsant effects of CBD shown in multiple *in vivo* models of epilepsy and the results of small controlled clinical trials in which CBD-treated epilepsy patients showed a reduction in numbers of seizures. Epilepsy specialists and patient organizations have shown considerable interest in the potential therapeutic role of CBD in adults with epilepsy and, especially, children with Dravet’s syndrome or Lennox-Gastaut Syndrome (LGS), both of which are rare and severe forms of pediatric epilepsy. The epilepsy specialists have also expressed interest in the role of CBD treatment for adolescent and adult patients with focal epilepsy (complex partial seizures) because of treatment resistance to currently approved therapies.

ZYN002 is being developed as a clear, transdermal gel to provide consistent, controlled CBD delivery with twice daily (every 12 hours [Q12 H]) dosing. A 4.2% (w/w) CBD gel will be evaluated in the current study. 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.

4.2. **Nonclinical Summary**

The pharmacology of CBD has been investigated for many decades, with emphasis on the pharmacodynamic benefit in a wide variety of diseases and disorders, including but not limited to epilepsy, pain, cancer, psychosis, metabolic disorders, Huntington’s disease, colitis, and diabetes. While the precise mode of action has yet to be totally elucidated, the action of CBD on the equilibrative nucleoside transporter, the orphan G-protein coupled receptor 55 (GPR55), the transient receptor potential of vanilloid type-1 (VR1) channel, the serotonin (5-HT1a) receptor and/or the α3 and α1 glycine receptors could contribute to the pharmacodynamic action.

The safety of CBD on vital pharmacologic system, including the central nervous system, the respiratory system and the cardiovascular and hemodynamic system, has been confirmed in numerous animal and human studies published over the past several decades. CBD lacks the psychoactive properties of other cannabinoids, although it can lead to central nervous system (CNS) depression at near lethal doses. Studies have repeatedly demonstrated no perturbation on spontaneous motor activity, exploratory behavioral activity or on stance or gait at clinically relevant doses. CBD possesses anticonvulsant properties that may provide benefit to patients.
with complex partial seizures. Studies in the cardiopulmonary effects of CBD in dogs revealed no perturbation of blood pressure, lung resistance, arterial blood partial pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCO₂), or pH but a slight increase in heart rate, a reduction in cardiac output and bradycardia. In contrast, in anesthetized rats, there were no appreciable effects on blood pressure or respiratory minute volume at comparable parenteral doses. Pretreatment with CBD in rats normalized lipopolysaccharide (LPS)-induced intestinal hypomotility and reduced the induced inflammatory response serologically and histologically.

CBD is well absorbed by a variety of routes, especially via the proposed transdermal route, but provides for low (∼6%) and variable bioavailability via the oral route. It is rapidly (80% within 5 minutes post-dose) and extensively metabolized to a large number of well-characterized metabolites in humans and many animal model systems. Pharmacokinetic (PK) data from the topical application of ZYN002 CBD gel onto the skin of rats, guinea pigs, and squirrel monkeys, plus published studies with other species are described in the Investigator’s Brochure. All human metabolites are present in all of the animal models studied. CBD can inhibit some cytochrome P450 enzyme systems, so drug interactions are possible with select drugs.

The toxicology of CBD has been reported from animals and humans in the literature. CBD has a low order of toxicity after oral and parenteral dosing. The median lethal oral dose in mice was in excess of 12.7 g/kg. In rats the median lethal intravenous dose was in excess of 230 mg/kg. Deaths occurred in a few rhesus monkeys when dosed intravenously with ≥200 mg/kg, but doses of ≤200 mg/kg elicited only transient hypopnea in survivors and no further evidence for toxicity. Rats inhaling CBD of 1.2 mg/kg/day for 17-25 days were slightly sedated or prostrate, had reduced gonadal weights and reduced spermatogenesis but no other evidence for toxicity. Rhesus monkeys given oral CBD to 300 mg/kg/day for 90 consecutive days exhibited some transient soft stools, slightly transient reduced heart rates and some mild decreases in the erythron. Histopathology was confined to the testes, wherein spermatogenesis was partially inhibited. The Sativex® (CBD + Δ⁹-tetrahydrocannabinol [THC]) monograph reported numerous other CBD toxicology studies, including intravenous rat studies of 14 and 28 days of duration and a 90-day dietary study in rats. The monograph summarized these data on CBD, emphasizing the very low acute toxicity and excellent safety margins for clinical doses, the absence of behavioral or CNS functional deficits, some variable weight changes in select organs and tissues, albeit most without histopathologic correlates, and some inhibitory effects on certain hormones, resulting in a potential for reduced spermatogenesis.

There have been numerous studies assessing the potential for genotoxicity arising from CBD. These studies have indicated a possibility for clastogenic but not mutagenic activity. Cannabinoids CBD, THC, 11-OH-Δ⁹-THC and cannabinol (CBN) were all reported to not induce unscheduled deoxyribo nucleic acid (DNA) synthesis in cultured human fibroblasts. A traditional Bacterial Reverse Mutation Assay mutagenicity assay has been performed by BioReliance Corporation (Rockville, MD) for ZYN002. Most of the currently published data on the potential developmental and reproductive toxicity of CBD has focused on the adverse effects on spermatogenesis and the resultant impact on fertility. Numerous studies have evaluated the role of testosterone (T), luteinizing hormone (LH), LH...
releasing hormone (LHRH), human chorionic gonadotropin (hCG) and brain biogenic amines in the pathogenesis of this perturbation of spermatogenesis. These effects have been reported in various species at high doses. There are no data regarding these effects in humans. Developmental and reproductive toxicity studies for ZYN002 have not yet been performed.

CBD was reported to be a mild sensitizer (Grade III) in a guinea pig sensitization study. Regarding skin tolerability, Zynerba recently completed a Seven-Day Pilot Toxicokinetic and Dermal Tolerance Study of ZYN002 Administered as a Single Subcutaneous Dose or as Repeated Topical Doses in Male Miniature Swine study - testing two concentrations of ZYN002 (2.5%, and 7.5%) wherein ZYN002 was very well tolerated. The porcine model is used for repeat application studies as pig skin most closely resembles human skin. The experimental design for 16 animals was:

- Group 2 – 2.5% concentration 20 grams applied on Day 1 and Day 4
- Group 3 – 7.5% concentration 40 grams applied on Day 1 and Day 4
- Group 4 – 2.5% concentration 20 grams applied on Days 1, 2, 3, 4, 5, 6, and 7
- Group 5 – 7.5% concentration 40 grams applied on Days 1, 2, 3, 4, 5, 6, and 7

ZYN002 was applied to the same application site for each group (10% of the animal’s body surface). Animals were scored daily for erythema. There was nothing of significance reported in this study regarding skin irritation (erythema). No animal in Group 2 or Group 3 showed signs of erythema. One animal in Group 4 had an erythema score of ‘2’ (well-defined) on Day 4, however, the finding was resolved by Day 6. There were no other findings greater than a score of ‘1’ (slight) and only sporadic erythema findings of greater than ‘0’ (none) for the remainder of the study. It is also felt that the one erythema score of ‘2’ was an outlier, as it could have been caused by the pig rubbing up against the cage.

### 4.3. Clinical Summary

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

- **High dosing** — 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). This study will investigate topical CBD at the highest daily dose of 390 mg of CBD 4.2%.
• **Less systemic exposure** — Because the zero-order delivery from topical ZYN002 should provide a lower $C_{\text{max}}$ 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.

• **Long-term exposure** — 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** — 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 (21%) and fatigue (17%) (Devinsky et al. AES 2015 and AAN 2015). 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 Δ9-tetrahydrocannabinol, 9-a-hydroxy-hexahydrocannabinol and 8-hydroxy-iso-hexahydrocannabinol. All have psychoactive activity (Merrick 2016; Watanabe 2007).

• **No effects on vital signs or clinical laboratory tests** — 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).

• **No association with response inhibition** — 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).
Potential anti-seizure effects — Since CBD appears to provide benefit in the treatment of patients with epilepsy, with oral doses of 100 – 300 mg achieving symptomatic improvement and freedom from seizures with no serious adverse events (SAEs) over more than 4 months of therapy (Ames and Cridland 1986; Cunha et al. 1980; Mechoulam and Carlini 1978; Trembly and Sherman 1990), there is a need for well-controlled studies in this patient population.

Transdermal delivery — Two clinical Phase 1 studies with ZYN002 via a transdermal delivery system have been completed.

Study ZYN2-CL-01 was entitled: A Phase 1, Five-Period, Randomized, Placebo-Controlled, Double-Blinded, Single Center, Single, Ascending-Dose Study to Assess the Safety and Pharmacokinetics of ZYN002 Administered as a Transdermal Gel to Healthy Subjects and Patients with Epilepsy. The study was the first-in-human study to assess the safety and PK of two concentrations (1% and 2.5%) and two doses (5 g and 10 g) of ZYN002 administered as a transdermal gel to healthy male and female subjects and male and female patients with epilepsy. Each period utilized a randomized, double-blinded, placebo-controlled, parallel-group study design; eight healthy volunteers participated in each of Periods 1 to 4 (total 32 subjects) and 12 patients with epilepsy with a diagnosis of partial onset seizures ([POS] focal seizures) participated in Period 5. Qualified subjects were randomized in 3:1 ratio to receive either ZYN002 or placebo. ZYN002 had excellent skin tolerability, there was no post-dosing erythema at 24, 48, 72, and 96 hours. The incidence of treatment-emergent adverse events (TEAEs) associated with ZYN002 was similar to placebo in healthy volunteers. Results from the single rising dose study in the first four cohorts of healthy volunteers (n=32) receiving ZYN002 - CBD (50 – 250 mg) study showed that ZYN002 was safe and well tolerated at all doses. There were no serious adverse events (SAEs), no clinically significant changes in electrocardiograms (ECGs), vital signs or clinical laboratory results. ZYN002 had excellent skin tolerability, there was no post-dosing erythema at 24, 48, 72, and 96 hours.

Study ZYN2-CL-02 was entitled: A Phase 1, Three-Period, Randomized, Double-Blind, Placebo-Controlled, Multiple-Center, Multiple-Dose Study to Assess the Safety and Pharmacokinetics of ZYN002 Administered as a Transdermal Gel to Healthy Subjects and Patients with Epilepsy. The study was a three-period, randomized, double-blind, placebo-controlled, single center, multiple-dose study to assess the safety, tolerability, and PK of ZYN002 at either a 1% or 2.5% concentration administered as a transdermal gel either once daily or twice daily for seven consecutive days to healthy male and female subjects and male and female patients with epilepsy. The study also was to determine the appropriate dose for administration to patients with epilepsy. In Period 1, eight subjects received either 2.5% ZYN002 10 g applied once daily (total daily dose of 250 mg) or placebo for seven consecutive days. In Period 2, eight subjects each received either 2.5% ZYN002 10 g applied twice daily (total daily dose of 500 mg) or placebo in cohort 1 or 1.0% ZYN002 10 g applied twice daily (total daily dose of 200 mg) or placebo in cohort 2 for seven consecutive days. In Period 3, twelve patients with epilepsy with POS (focal seizures) received either 2.5% ZYN002 10 g applied twice daily (total daily dose of 500 mg) or placebo for seven consecutive days. Safety results from the multiple-dose study of ZYN002 at either a 1% or 2.5% concentration administered either once daily or twice daily for seven consecutive days to healthy subjects (N=24) and patients with epilepsy (N=12) showed that ZYN002 was safe
and well tolerated at all doses. One subject who was administered placebo experienced an SAE of suspected catheter-related blood stream infection (not related to study drug) and was discontinued from the study. There were no clinically significant changes in ECGs, vital signs or clinical laboratory results. ZYN002 had good skin tolerability, with minimal skin erythema. Skin dryness at the application site was reported by most subjects.

- Application site disorders were the most frequently reported TEAEs and occurred in similar incidence for both ZYN002 and placebo. The most frequently reported TEAEs were application site dryness and application site pruritus that were reported in more healthy volunteers than patients with epilepsy. Headache was the most frequently reported TEAE that was not associated with the application site. All application site TEAEs were considered related to study drug, with application site dryness and application site pruritus being the most frequently reported related events. Most occurrences of headache were also considered related to study drug. The distribution of TEAEs between healthy volunteers and patients with epilepsy was similar.

- Study ZYN2-CL-08 was entitled: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Single-Center, Multiple-Dose Study to Assess the Safety and Pharmacokinetics of ZYN002 Administered as a Transdermal Gel to Healthy Subjects. The study was a Phase 1, randomized, double-blind, placebo-controlled, parallel-group, single-center, multiple-dose study to assess the safety and PK of ZYN002 of seven treatments administered as a transdermal gel twice a day for 13 consecutive days with a morning dose on Day 14, to healthy male and female subjects. The study was to determine the safety and tolerability of ZYN002 administered as a transdermal gel formulation twice daily for 14-days to healthy subjects. Six subjects were randomized for each treatment; four subjects receiving ZYN002 and two subjects receiving placebo. Application sites varied between the upper arms/shoulders and/or upper thighs with two different concentrations of ZYN002 (4.2% or 2.5%) and three different daily doses (394.8, 504 or 500 mg) and three different application amounts (4.7, 6.0, or 10.0 grams). Safety results from the multiple-dose study of ZYN002 at either a 2.5% or 4.2% concentration administered twice daily for 14 consecutive days to healthy subjects (N=42) showed that ZYN002 was safe and well tolerated at all doses (398.5, 500, and 504 mg/day). Safety results from the placebo multiple dose study of the formulation excipients administered twice daily for 14 consecutive days to healthy subjects (N=5) showed that excipients in the ZYN002 formulation are safe and well tolerated.

- ZYN2-CL-005 is an ongoing Phase 2A, randomized, double-blind, placebo-controlled, multiple-center, multiple-dose study to assess the efficacy and safety of ZYN002 administered as a transdermal gel for 12 weeks to approximately 320 (300 randomized) male and female adult patients with knee pain due to osteoarthritis (OA) of the knee.

- In addition, studies completed with oral (up to 1280 mg), inhaled (up to 32 mg), and IV (up to 30 mg) CBD supports 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 patients with epilepsy, Fragile X Syndrome, and patients diagnosed with osteoarthritis.
5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective
To evaluate the efficacy of ZYN002 administered as a transdermal gel formulation for 12 weeks as adjunctive therapy for the treatment of POS.

5.2. Secondary Objectives
To evaluate the safety and tolerability of ZYN002 in epilepsy patients receiving different treatments for POS.
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This study is a Phase 2A, randomized, double-blind, placebo-controlled, multiple-center, multiple-dose study to assess the safety and efficacy of ZYN002 administered as a transdermal gel, either as:

- Treatment A ZYN002 - CBD 195 mg Q12 H (± 2 hours), or
- Treatment B ZYN002 - CBD 97.5 mg Q12 H (± 2 hours) and placebo, or
- Treatment C placebo Q12 H (± 2 hours)

for 12 weeks to male and female patients with POS. At the end of Week 12, patients will undergo a two-week blinded dose reduction. Patients will have their dose reduced by 50% at Week 13 and another 50% (only patients receiving Treatment A) at Week 14 and then treatment will be discontinued.

Approximately 210 patients will be enrolled in the 8-week Baseline Period to ensure that 180 patients are randomized across all treatment groups.

Baseline Period

During the prospective 8-week screening and Baseline Period, patients will record seizure frequency and type. During the Baseline Period, AED blood samples will be collected at screening and Week 4. All patients will have their seizure history and diagnosis reviewed and confirmed by the Epilepsy Study Consortium prior to randomization into the study.

12-Week Maintenance Period

Following the 8-week prospective Baseline Period, eligible patients will be randomized in a 1:1:1 ratio to receive either placebo Q12 H, or Treatment A (ZYN002 – CBD 195 mg Q12 H) or Treatment B (ZYN002 - CBD 97.5 mg Q12 H) for 12 weeks.

Prior to the initial dosing on Study Day 1, patients will report to the investigative site to have a pre-dose blood sample drawn for plasma levels of CBD, THC and AEDs. All concomitant medications (prescription and OTC) will be recorded including dose and reason for use. Patients will be provided instruction on how to apply the gel and the first dose of study drug will be applied by the patient at this visit and visits at Weeks 4, 8, and 12 (Appendix 19.1). Patients will be required to visit the clinic every 2 weeks through Week 8 and at Week 12 to have a blood sample drawn for plasma levels of their AEDs.

At Weeks 4, 8, and 12 of the Maintenance Period, patients will visit the clinic and have the following procedures completed: a blood sample for determination of CBD, THC and AED plasma levels, review of patient diaries, vital signs, targeted physical and neurological examination (Weeks 4 and 8), ECG (Week 8), laboratory tests (Week 8), pregnancy test (females only), concomitant medication review, study drug, skin irritation assessment and AE review. Patients will also be administered the Columbia Suicide Severity Rating Scale (C-SSRS). Patients will be instructed to withhold their morning dose of study drug until a blood sample is collected at these visits. When possible, effort should be made to obtain a trough sample for the AED. If not, 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 AED(s) may require adjusting if the patient experiences AEs that warrant a dose change.

Patients will be instructed on proper application of the gel. Patients will be permitted to shower 30 minutes prior to study dose. Patients will apply all study drug to clean, dry, intact skin, thoroughly massaging it into both the right and left shoulders and/or upper arms until the area is dry. The gel application sites will be rubbed in completely and dry prior to dressing. Once the patient has completed their treatment application, they will wash their hands thoroughly with soap and water to remove any residual gel.

Patients will undergo a two-week blinded dose reduction at the end of Week 12. Patients will have their dose reduced by 50% at Week 13 and another 50% (only patients receiving Treatment A) at Week 14 and then treatment will be discontinued.

Patients will complete an End of Study Visit at Week 15. If the skin irritation score at Week 15 is > 0, the patient will continue to be followed through an Unscheduled Visit until the skin irritation score is recorded as ‘0’. At this time, the patient will be discharged from the study.

6.2. Number of Patients

Approximately 210 patients will be enrolled in the Baseline Period to ensure that 180 patients are randomized. Patients who prematurely discontinue after randomization will not be replaced.

6.3. Dose Rationale

The doses chosen for this study are based on an extrapolation from the literature of human plasma levels of CBD following oral administration. Oral doses of 10 mg/kg of CBD administered daily for 6 weeks in patients with Huntington’s disease resulted in mean plasma levels of 5.9–11.2 ng/mL (Consroe 1991). This equates to 700 mg/day and with an estimated 6% oral bioavailability, equating to 42 mg CBD delivering plasma levels between 5.9–11.2 ng/mL.

In epilepsy, the current dose being studied in patients with refractory epilepsy for Dravet or Lennox Gastaut Syndrome is 25 mg/kg. For an average adult weighing 70 kg, this would be 1,750 mg per day in divided doses. With 6% oral bioavailability, 105 mg/day would be expected to deliver a CBD plasma level of 14.75–28 ng/mL when extrapolated from the Consroe data. However, if the oral bioavailability was 12%, or double the reported oral bioavailability of CBD, the plasma concentration from the available 210 mg CBD dose would be 29.50–48 ng/mL.
6.4. Treatment Assignment

Following the 8-week prospective Baseline Period, eligible patients will be randomized in a 1:1:1 ratio to receive either placebo Q12 H, Treatment A (ZYN002 - CBD 195 mg Q12 H), or Treatment B (ZYN002 – CBD 97.5 mg Q12 H) for 12 weeks.

6.5. Dose Adjustment Criteria

Patients will receive their assigned dose of ZYN002 or placebo and it is anticipated that no dose adjustments will be made. The Investigator will review the concomitant AED plasma level and the dose of concomitant AED(s) may be adjusted if the patient experiences adverse events that warrant a dose change. The dosage adjustment of the AED and reason for adjustment will be recorded in the electronic case report form (eCRF).

6.6. Study Assessments

6.6.1. Overview of Study Assessments

Study procedures will be performed as summarized in the study schematic presented in Table 3 Schedule of all Assessments.
## Table 3: Schedule of All Assessments

| Study Procedures                      | Screening Visit | Baselinea | Day 1 (+3 days) | Week 2 (+3 days) | Week 4 (+3 days) | Week 6 (+3 days) | Week 8 (+3 days) | Week 12 (+3 days) | Study Drug Dose Tapering (No Study Visit) | Skin Irritation Follow-up | End of Study Visitb | Follow-up |
|---------------------------------------|-----------------|-----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------------------------------------|--------------------------|----------------------|-----------|
| Informed consent                      |                 |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Review eligibility criteria           | X               |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Medical history                       | X               |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Demographics                          | X               |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Concomitant medications               |                 |           | X               |                 |                 |                 |                 |                 |                                           | X                        |                      |           |
| Complete physical and neurological examination | X |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Targeted physical and neurological examination | X |           | X               |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Epilepsy diagnosis                    |                 |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Vital signs                           | X               |           | X               |                 |                 |                 |                 |                 |                                           | X                        |                      |           |
| 12-lead ECG                           | X               |           | X               |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| HIV-Ab 1+2 + Hepatitis B+ C           | X               |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Laboratory tests and urinalysis       |                 |           |                 |                 |                 |                 |                 |                 |                                           | X                        |                      |           |
| Serum / urine pregnancy test         |                 |           |                 | X               |                 |                 |                 |                 |                                           |                          |                      |           |
| Urine drug screen                     | X               |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| C-SSRS                                |                 |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Randomization                         | X               |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Study drug application (Daily)c       |                 |           | X               |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Seizure Diary (Daily)                 |                 |           | X               |                 |                 |                 |                 |                 |                                           |                          |                      |           |
| Skin Irritation Diary (Daily)d        |                 |           |                 |                 |                 |                 |                 |                 |                                           |                          |                      |           |

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a Baseline includes health history and physical examination.

b Unscheduled Visit(s) depends on specific criteria.
c Study drug application may vary daily.
d Skin irritation may require follow-up visits.

d Epilepsy diagnosis criteria.
e Laboratory tests may include additional evaluations.
f Urinalysis tests may be performed more frequently.
g Pregnancy tests are crucial for women of reproductive age.
h Additional tests may be conducted as indicated.

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| Study Procedures            | Screening Visit | Baseline | Day 1 (+3 days) | Week 2 (+3 days) | Week 4 (+3 days) | Week 6 (+3 days) | Week 8 (+3 days) | Week 12 (+3 days) | Week 13 (+3 days) | Week 14 (+3 days) | Un-scheduled Visit(s) | End of Study Visit | Follow-up |
|-----------------------------|-----------------|----------|-----------------|------------------|------------------|------------------|------------------|-------------------|-------------------|-------------------|----------------------|---------------------|-----------|
| CBD and THC Blood samples  | Screening Visit | Baseline | X               | X                | X                | X                | X                | X                 | X                 | X                 | X                    | X                   | X         |
| AED blood sample            | Screening Visit | Baseline | X               | X                | X                | X                | X                | X                 | X                 | X                 | X                    | X                   | X         |
| Seizure Diary Review       | Screening Visit | Baseline | X               | X                | X                | X                | X                | X                 | X                 | X                 | X                    | X                   | X         |
| Skin Diary Review          | Screening Visit | Baseline | X               | X                | X                | X                | X                | X                 | X                 | X                 | X                    | X                   | X         |
| Skin assessment examination | Screening Visit | Baseline | X               | X                | X                | X                | X                | X                 | X                 | X                 | X                    | X                   | X         |
| Skin irritation examination | Screening Visit | Baseline | X               | X                | X                | X                | X                | X                 | X                 | X                 | X                    | X                   | X         |
| Adverse events             | Screening Visit | Baseline | X               | X                | X                | X                | X                | X                 | X                 | X                 | X                    | X                   | X         |

**Footnotes for Table 3**

a. An 8-week prospective Baseline.
b. All patients will have a follow-up End of Study Visit at Week 15.
c. Complete Physical and Neurological exam including height and weight at Screening. Complete Physical exam at End of Study only if clinically relevant. Targeted Physical examination will include brief Physical and Neurological exam and weight.
d. Epilepsy consortium to review Diagnostic Interview for Seizure Classification Outside of Video EEG Recording (Discover), Seizure Identification Form and Diagnostic Review Form (SIF-DRF) and Seizure Diary to confirm diagnosis.
e. Vital signs (including blood pressure, heart rate, respiratory rate, and oral or tympanic temperature) will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be taken prior to blood draws on Day 1 and Weeks 4, 8, 12 and End of Study.
f. Fasting laboratory tests will be completed at approximately the same time of day each time.
g. A serum pregnancy test will be completed at Screening for all women of childbearing potential.
h. A urine pregnancy test will be performed before randomization on Day 1 and at Weeks 4, 8, and End of Study Visit for all women of childbearing potential.
i. Patients will dose with Treatment A, Treatment B or Treatment C every day. During visits on Day 1, Week 4, 8 and 12, patients will administer the dose in the clinic after they have their blood drawn.
j. Patients will assess their dosing site daily for 14 weeks and record all irritations in their daily skin irritation diary. When irritation exists, efforts will be made to apply the gel to a non-irritated area of the shoulders and/or upper arms. If the skin irritation score is “1”, the patient will contact the Investigator to determine if an Un-scheduled Visit is required.
k. 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. AED blood samples will be taken at screening and Week 4 (Day -28± 3 days) of the baseline period.
l. Shoulders and upper arms will be examined to determine there are no imperfections, lesions, tattoos, or discolorations where study drug could be applied.
m. A skin irritation examination will be completed by the Investigator at Day 1 pre-dose, at visits at Weeks 4, 8, 12, at any unscheduled visits and End of Study visit.
6.6.2. **Informed Consent**

Signed informed consent will be obtained at the Screening Visit for all patients. The informed consent form (ICF) will be signed before any study procedures are undertaken, or before any medications are withheld from the patient, in order to participate in this study. Details about how the ICF will be obtained and documented are provided in Section 15.3 Patient Information and Informed Consent.

6.6.3. **Demographics**

At the Screening Visit, patient demographic information will be collected and recorded in the eCRF and IWRS.

6.6.4. **Vital Signs**

Vital sign determinations include sitting blood pressure, heart rate, respiratory rate, and oral or tympanic body temperature will be recorded. Vital signs will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be assessed during the Screening Visit, on Day 1 prior to dosing, and will be taken prior to plasma blood sample collection at pre-dose, at Weeks 4, 8, 12, and End of Study.

6.6.5. **Medical History**

A complete medical history, including neurological exam, will be obtained from each patient during the Screening Visit.

6.6.6. **Epilepsy Diagnosis/Seizure Diary**

At screening, patients will have their epilepsy diagnosis and seizure classification confirmed. The monthly seizure frequency for each type of partial seizure will be recorded. A seizure diary will be distributed to patients with instructions on how to record daily seizure counts for each type of POS during the 8-week prospective Baseline Period (Appendix 19.2).

The Diagnostic Interview for Seizure Classification Outside of Video EEG Recording (Discover) form will be completed for each patient at screening (Appendix 19.3). The seizure identification form/diagnostic review form (SIF/DRF) will also be completed for each patient at screening (Appendix 19.4). This form will be faxed or emailed to the Epilepsy Study Consortium immediately after the Screening Visit. Investigative sites will also send a copy of the seizure diary key from the Screening Visit. This process will ensure consistency between the subject diary key and the seizure classifications approved by the Epilepsy Consortium.

The above mentioned forms are forwarded to one of the Consortium’s reviewers who are board certified neurologists/epileptologists. If no discrepancies are found, Feedback Forms are completed by the Consortium administrators and returned to the site documenting that the SIF/DRF is approved. Sites will be contacted by the Epilepsy Consortium if there are queries or if additional information is needed in order to approve the patient for participation.

If the seizures reported on the diary key and the SIF differ, the Epilepsy Consortium will query the site. For some patients, revisions to the Seizure Identification Form may be necessary.
If a new seizure occurs during the study, a revised SIF will be submitted to the Epilepsy Consortium for review and approval.

The patient will continue in the 8-week prospective period while the site awaits approval from the Epilepsy Consortium.

The patient will be instructed on completion of the seizure diary at the screening visit. The patient’s daily seizure diary, including the seizure codes used will be reviewed by the Investigator at the Baseline Visit, Day 1, and at Weeks 4, 8 and 12. Data from the diaries will be recorded in the eCRF.

6.6.7. Skin Irritation Diary

Patients will be instructed on completion of the daily skin irritation diary at the screening visit (Appendix 19.5). Before each study dose patients will record the skin irritation score in their daily skin irritation diary. When skin irritation is noted, patients should apply the gel to a non-irritated area of the shoulders and/or upper arms. If the skin irritation score is “1” or Redness, the patient will contact the Investigator to determine if an Unscheduled Visit is required. If an Unscheduled Visit is not required, patients will be instructed to call the Investigator if the skin irritation worsens. The patient’s skin irritation diary will be reviewed by the Investigator. The Investigator will use discretion in suspending dosing for patients with a skin irritation score of 4 but will in all cases immediately (within 24 hours) complete an adverse event report and contact their study Clinical Research Associate (CRA) and the Zynerba Medical Monitor.

6.6.8. Suicidality

The C-SSRS is to be completed at Screening, Day 1 (prior to dosing), study visits at Weeks 4, 8, 12, any unscheduled visits and at the End of Study 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. Note that any completed suicide or suicidal attempt will be collected as a SAE.

6.6.9. Concomitant Medication Review

Medication (prescription and OTC) use will be recorded at the Screening Visit and updated at Day 1 (prior to dosing). A review of patient concomitant medication will be performed at Weeks 4, 8, 12, at any Unscheduled Visits, and at the End of Study Visit.

6.6.10. Review Adverse Events

A review of AEs will be performed at Screening, Day 1, Weeks 4, 8 and 12 and at any unscheduled visits and at the End of Study Visit.

Detailed information regarding AEs can be found in Section 12.2.

6.6.11. Physical Examinations

A complete physical and neurological examination, including height and weight will be performed at the Screening Visit. A complete physical examination will only be performed at the End of Study Visit if considered clinically relevant. Any clinically significant changes from the Screening Visit will be documented.
A targeted physical and neurological examination (including heart, lungs, abdomen, extremities and body weight) will be performed at Day 1, at Weeks 4 and 8, and at the End of Study Visit. Patient weight will be collected with minimal clothing (e.g., no coats, shoes, jumpers or jackets).

6.6.12.  Electrocardiogram

A 12-lead resting ECG will be obtained during the Screening Visit, at Day 1, at Week 8, and at the End of Study Visit. As applicable, ECGs will be conducted pre-dose, within 60 minutes of study drug application. 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.

6.6.13.  Skin Assessment Examination

At the Screening Visit and Day 1 (prior to dosing), the shoulders and upper arms will be examined to determine there are no imperfections, lesions, tattoos, or discolorations where study drug will be applied.

6.6.14.  Skin Irritation Examination

A complete skin irritation examination will be conducted on Day 1 (pre-dose), and pre-dose at Weeks 4, 8, and 12, unscheduled visits for skin irritation follow-up and at the End of Study Visit. When skin irritation is noted, efforts will be made to apply the gel to a non-irritated area of the shoulders and/or upper arms. The Investigator will use discretion in suspending dosing for patients with a skin irritation score of 4 but will in all cases immediately (within 24 hours) complete an adverse event report and contact their study Clinical Research Associate (CRA) and the Zynerba Medical Monitor.

Refer to Table 4 for the Skin Irritation Scale to be used for skin irritation examinations.

Table 4:  Skin Irritation 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 |

6.6.15.  Clinical Laboratory Testing

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.

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 based on Table 3 - Schedule of All Assessments, routine laboratory tests (clinical chemistry and hematology) and urinalysis will be collected at the Screening Visit, at the Day 1, Week 8, and at the End of Study Visit.

6.6.15.1. **Screening (Days -56 to -1)**

- 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.
- Hepatitis B (HBsAg), hepatitis C (HCV-Ab) serology and human immunodeficiency virus (HIV) type 1 and 2.
- Urine drug screen to include cocaine, THC, barbiturates (except as AED medication), amphetamines, benzodiazepines, opiates, and ethanol.
- 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.
- A serum pregnancy test will be performed by the local laboratory for female patients of childbearing potential at the Screening Visit. Urine pregnancy tests will be performed at Day 1 and Weeks 4, 8, and End of Study Visit. Any patient that is pregnant will be excluded or discontinued from the study, as applicable.

6.6.15.2. **Day 1 (+3 days) and Week 8**

- Routine blood chemistry tests will include: glucose, total bilirubin, SGOT/AST, SGPT/ALT, alkaline phosphatase, blood urea nitrogen, creatinine, amylase, total protein, uric acid, sodium, chloride, bicarbonate, potassium, calcium, phosphorous, albumin, triglycerides, cholesterol: LDL and HDL.
- Routine hematology tests will include: WBC with differential count, RBC, hematocrit, hemoglobin, and platelet count.
- Testosterone (males only, total and free). Blood sample for testosterone should be collected at the same time of day throughout the study.
- 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.
6.6.15.3. **End of Study Visit**

- Each patient will have an End of Study Visit completed at Week 15. The clinical laboratory testing will include the following:
  - Routine blood chemistry tests will include: glucose, total bilirubin, SGOT/AST, SGPT/ALT, alkaline phosphatase, blood urea nitrogen, creatinine, amylase, total protein, uric acid, sodium, chloride, bicarbonate, potassium, calcium, phosphorous, albumin, triglycerides, cholesterol: LDL and HDL.
  - Routine hematology tests will include: WBC with differential count, RBC, hematocrit, hemoglobin, and platelet count.
  - Testosterone (males only, total and free). Blood sample for testosterone should be collected at the same time of day throughout the study.
  - 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.

6.6.16. **Hepatitis/HIV Screen**

During the Screening Visit, patients will be screened for HBsAg, HCV-Ab serology and HIV type 1 and 2.

6.6.17. **Pregnancy Test – Females Only**

A serum pregnancy test will be performed for female patients of childbearing potential at the Screening Visit. A urine pregnancy test will be performed on Day 1 and at Weeks 4, 8, at the End of Study. Any patient that is pregnant will be excluded or discontinued from the study, as applicable.

6.6.18. **Urine Toxicology Screen**

A urine toxicology screen to include cocaine, THC, barbiturates (except as AED medication), amphetamines, benzodiazepines, opiates, and ethanol will be done at Screening. A positive urine toxicology screen (except for benzodiazepines prescribed as rescue medication) will result in excluding the patient from the study.

6.6.19 **Blood Samples for AEDs, CBD and THC Levels**

At screening and Week 4 (Day -28 ± 3 days) of the Baseline Period, patients will have blood drawn for plasma level of their AEDs. Prior to the initial dosing on Study Day 1, patients will report to the investigative site to have a pre-dose blood sample drawn for plasma levels of CBD, THC and AEDs. Patients will be required to visit the clinic every 2 weeks through Week 8 and at Week 12 to have a blood sample drawn for plasma levels of their AEDs. At Weeks 4, 8, and 12 patients will have a blood sample drawn for determination of CBD and THC plasma level.
7. SELECTION AND WITHDRAWAL OF PATIENTS

Patients will have a diagnosis of epilepsy with POS. Patients must qualify based on complete inclusion and exclusion criteria to be eligible to enroll.

7.1. Patient Inclusion Criteria

1. Male or female adults, 18-70 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, 12-lead ECG, and clinical laboratory test results. Laboratory results outside of the reference range, but acceptable, must be documented as not clinically significant (NCS) by the Investigator.

3. Patients must have a diagnosis of focal epilepsy (POS) with or without secondary generalization (International League Against Epilepsy Classification) for greater than or equal to 2 years which has been documented by review of the most informative electroencephalogram (EEG), magnetic resonance imaging (MRI) scan, and narrative from the physician who manages the patient’s epilepsy. All patient epilepsy diagnoses and seizure classification will be confirmed by expert review by the Epilepsy Study Consortium.

4. History of previous epilepsy surgery is acceptable provided seizure frequency is stable over the past 3 months prior to screening.

5. Presence of previous vagal nerve stimulator, deep brain stimulator or responsive neurostimulation (RNS) is acceptable if present for one year and settings have remained stable over the past 3 months prior to screening.

6. Based on history, patients have on average at least three (3) observable POS per month and would therefore, likely have at least six (6) POS during the 8-week Baseline Period and not more than 20 or more consecutive POS-free days.

7. Patient is currently being treated and maintained with a stable regimen of one, two, or three AEDs.

8. Patient is able and willing to maintain a daily seizure and daily skin irritation diary.

9. Patient has a body mass index between 18-35 kg/m².

10. Females of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy on Day 1 and at Weeks 4, 8, and End of Study Visit. Females of child-bearing potential and male patients with a partner of childbearing potential; must use an acceptable method of contraception, (as outlined below), from at least 21 days prior to the first dose of study drug and for 3 months after the last dose of study drug.

   a. Standard acceptable methods include use of a highly effective method of contraception, including hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, spermicide, vasectomy, intrauterine device.

11. Patient agrees to abide by all study restrictions and comply with all study procedures.

12. Patient must be adequately informed of the nature and risks of the study and give written informed consent prior to screening.
13. In the Investigator’s opinion, the patient is reliable and is willing and able to comply with all protocol requirements and procedures.

7.2. 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 (except clinical study ZYN2-CL-01 or ZYN2-CL-02), 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 four (4) weeks of the Screening Visit or during the study.

4. Patient has change in current tobacco product(s) use within 30 days of screening or plans to change their use during the study.

5. Patient has had a diagnosis of idiopathic (“primary”) generalized (e.g., juvenile myoclonic epilepsy, absence epilepsy), or mixed epilepsy (LGS) or non-epileptic seizures within the last 5 years prior to study entry.

6. Patient is using the following AEDs: clobazam, ethosuximide, felbamate or vigabatrin. If a benzodiazepine (excluding clobazam) is being used as a rescue medication, it will be counted as an AED if used more than two days a week.

7. Patient has had a change in AED regimen in the last 4 weeks.

8. Patient has had epilepsy dietary therapy initiated for < 3 months prior to enrollment.

9. Patient has only simple partial seizures without any observable motor component or has seizures occurring in a non-countable clustered pattern.

10. Patient has an episode of status epilepticus within the 12 months prior to screening.

11. Patient has seizures secondary to illicit drug or alcohol use, infection, neoplasm, demyelinating disease, degenerative neurological disease or CNS disease deemed progressive, metabolic illness or progressive degenerative disease.

12. Patient has acute or progressive neurological disease moderate or severe psychiatric disease, or severe mental abnormalities that are likely to require changes in drug therapy during the Maintenance Period of the study, or interfere with the objectives of the study, or the ability to adhere to protocol requirements.

13. Patient is using the following medications: midazolam, oral ketoconazole, fluconazole, nefazadone, rifampin, alfentanil, alfuzosin, amiodarone, cyclosporine, dasatinib, docetaxol, eplerenone, ergotamine, everolimus, fentanyl, halofantrine, irinotecan, lapatinib, levomethadyl, lumefantrine, nilotinib, pimozone, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinoin, vincristine, vinorelbine and St. John’s Wort.
14. Women who are breast feeding or lactating.
15. Patient has a history of actual suicide attempt in the last 5 years or more than one lifetime suicide attempt.
16. Patient responded “yes” to Question 4 or 5 of C-SSRS at the Screening Visit.
17. Patient has positive result for the presence of Hepatitis B surface antigen (HBsAg), Hepatitis C virus antibodies (HCV-Ab), or human immunodeficiency virus (HIV) antibodies.
18. Patient has positive drug screen, including ethanol, cocaine, THC, barbiturates (except as AED medication), amphetamines, benzodiazepines (except as rescue medication), and opiates.
19. 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.
20. Patient has any skin disease or condition, including eczema, psoriasis, melanoma, acne, contact dermatitis, scarring, imperfections, lesions, tattoos, or discoloration that may affect treatment application, application site assessments, or affect absorption of the study drug.
21. Patient has history of treatment for, or evidence of, alcohol or drug abuse within the past year or regular alcohol consumption exceeding an average of two units of alcohol per day.
22. Patient demonstrates behavior indicating unreliability or inability to comply with the requirements of the protocol.

7.3. Randomization Criteria

After the Baseline Period, qualified patients will be randomized at Day 1 (+ 3 days) if they continue to meet the inclusion criteria and have had at least six (6) POS seizures during the Baseline Period.

All exclusion criteria must be reviewed for eligibility for randomization.

7.4. 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 Baseline Period. After randomization, 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 randomization will not be replaced. All effort will be made to ensure that the End of Study procedures will be completed at the time of discontinuation.
8. **TREATMENT OF PATIENTS**

8.1. **Description of Study Drug**

ZYN002 is a synthetically manufactured CBD in a clear permeation-enhanced gel formulation. The drug product will be supplied as a transdermal gel and will be contained in a foil-lined sachet. The placebo gel formulation is identical to the ZYN002 gel formulation except it has no active ingredient (CBD). The placebo gel and the ZYN002 gel are identical in appearance. Each sachet is nominally filled to dispense 2.32 g of gel. The gel will be applied to clean, dry, intact skin of the shoulders and/or upper arms. The three study drug treatments are as follows:

- Treatment A ZYN002 - CBD 195 mg (2 sachets ZYN002 4.2%) applied Q12 H (± 2 hours); total daily dose of 390 mg.
- Treatment B ZYN002 – CBD 97.5 mg (1 sachet ZYN002 4.2% + 1 sachet placebo) applied Q12 H (± 2 hours); total daily dose of 195 mg
- Treatment C Placebo gel (2 sachets placebo) applied Q12 H (± 2 hours)

8.2. **Concomitant Medications**

8.2.1. **Allowable Medications**

Patients may take hormonal contraception and AEDs (not in the exclusion criteria) during study participation. Other prescription or over-the-counter medications may be taken as approved in advance by the investigator and recorded in the eCRF. The following medications are not allowed: midazolam, oral ketoconazole, fluconazole, nefazadone, rifampin, alfentanil, alfuzosin, amiodarone, cyclosporine, dasatinib, docetaxol, eplerenone, ergotamine, everolimus, fentanyl, halofantrine, irinotecan, lapatinib, levomethadyl, lumefantrine, nilotinib, pimozide, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinioin, vincristine, vinorelbine and St. John’s Wort.

8.3. **Duration of Treatment**

All patients will complete an initial Screening Visit.

After an eight-week Baseline Period, patients will receive daily application of study drug for 12 weeks.

Patients will undergo a two-week blinded dose reduction at the end of Week 12. Patients will have their dose reduced by 50% at Week 13 and another 50% (only patients receiving Treatment A) at Week 14 and then treatment will be discontinued.

Patients will complete an End of Study Visit at Week 15. If the skin irritation score at Week 15 is > 0, the patient will continue to be followed through an Unscheduled Visit until the skin irritation score is recorded as ‘0’. At this time, the patient will be discharged from the study.

8.4. **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.
All patients will be provided with a sufficient supply of study drug during their site visit every 2-weeks for the first 8 weeks and then a one-month supply for the last four weeks. At Week 12, patients will be provided a 2-week supply to complete the tapering period. Patients will bring the used and unused sachets 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 if the patient was compliant for the previous 2-4 weeks.

8.5. Randomization and Blinding

On Day 1 (+ 3 days) patients with epilepsy will be randomized in a 1:1:1 ratio to receive either Treatment A ZYN002 – CBD 195 mg Q12 H, Treatment B ZYN002 – CBD 97.5 mg Q12 H and placebo, or Treatment C placebo Q12 H for 12 weeks.

In order to maintain the study blind, each patient will apply four sachets of study drug per day, two sachets in the morning and two sachets in the evening as shown in Table 5.

Table 5: Blinded Study Drug Assignment

| Treatment Group Assignment | Morning Applicationa | Evening Applicationa |
|----------------------------|----------------------|---------------------|
| Treatment A (ZYN002 390 mg) | 2 sachets ZYN002 97.5 mg | 2 sachets ZYN002 97.5 mg |
| Treatment B (ZYN002 195 mg) | 1 sachet ZYN002 97.5 mg + 1 sachet placebo | 1 sachet ZYN002 97.5 mg + 1 sachet placebo |
| Treatment C (Placebo)       | 2 sachets placebo     | 2 sachets placebo   |

aApplications are Q12 H (± 2 hours)

A randomization scheme will be generated prior to study initiation.

Once a patient qualifies to participate in the study, the respective site will receive the randomization number for the participant.

The un-blinded randomization schedule will be maintained within the IWRS system. The research facility must contact [contact information] prior to contacting the IWRS system about breaking the blind.
9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

ZYN002 Transdermal Synthetic Cannabidiol Gel is a clear transdermal gel containing CBD for topical application. It is available as ZYN002 4.2% w/w.

9.2. Study Drug Packaging and Labeling

ZYN002 drug product and placebo will be packaged in aluminum sachets.

Study supplies will be double-blind 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
- Manufacturer/Sponsor Identification

9.3. Study Drug Storage

Study drug is to be stored

9.4. Study Drug Preparation

Study drug will be applied directly from the sachets as received.

9.5. Administration

Treatments A, B, and C will be supplied in sachets. Patients will be permitted to shower 30 minutes prior to each morning’s dosing. The entire contents of one sachet will be applied by the patient to clean, dry, intact skin of the left or right shoulder and/or upper arms and will be thoroughly massaged into the shoulders and/or upper arms by the patient. The other sachet will be similarly applied to the other shoulder/arm (Appendix 19.1). The application site will dry completely prior to dressing. Once the patient has completed their treatment application they will wash their hands thoroughly with soap and water to remove any residual gel. Patients may get dressed after the dose completely dries. Treatment with 2 sachets of study drug will be applied twice daily, Q12 H (± 2 hours) for 12 weeks.

The first dose of study drug will be applied by the patient at the Day 1 study visit and at visits at Weeks 4, 8 and 12.

9.6. Study Drug Accountability

Patients will bring the unused and used sachets 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 if the patient was compliant since the previous visit.
9.7. **Study Drug Handling and Disposal**

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

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.
10. **EFFICACY ASSESSMENTS**

The primary efficacy parameter is the number of POS per 28-day period. Seizure frequency per 28-day period (SF28) will be calculated for the 8-week Baseline Period and for the 12-week double-blind Maintenance Period. The seizure frequency is calculated as follows, where D=total number of days for which seizure information is collected for a specific time interval (approximately 56 days for Baseline and 84 days for the double-blind Maintenance period):

\[ SF28 = \frac{(\text{Total Number of Seizures in D days})}{D} \times 28 \]

In addition, the seizure frequency will also be calculated for the initial 14-day period of the Maintenance Period and for the time-period beyond the initial 14 days of the Maintenance Period.

The reduction from Baseline in seizure frequency (RedSF) during the Maintenance Period is defined as:

\[ \text{RedSF(Maintenance)} = \text{SF28(Baseline)} - \text{SF28(Maintenance)} \]

The percent reduction from Baseline in seizure frequency during the Maintenance Period is defined as:

\[ \%\text{RedSF(Maintenance)} = \frac{\text{SF28(Baseline)} - \text{SF28(Maintenance)}}{\text{SF28(Baseline)}} \times 100 \]

In addition, RedSF(Initial 14d), RedSF(After Initial 14d), %RedSF(Initial 14d), and %RedSF(After Initial 14d) will be computed for the initial 14-day period of the Maintenance period(Initial 14d) and for the time period beyond the initial 14 days (After Initial 14d).

**Primary Endpoint:**

The primary efficacy analysis is based on the reduction in SF28 from Baseline Period throughout the Maintenance Period (RedSF(Maintenance)). See Section 13 for further details.

**Secondary Endpoints:**

a) 50% responder rate (defined as the proportion of patients with a ≥ 50% reduction from Baseline in POS frequency per 28-day period during the treatment period compared with Baseline Period, i.e., proportion of patients with %RedSF(Maintenance) ≥ 50%)

b) RedSF(Initial 14d) and RedSF(After Initial 14d)

c) Percent change from Baseline in seizure frequency per 28 days: %RedSF(Maintenance), %RedSF(Initial 14d), and %RedSF(After Initial 14d).

d) Change from Baseline in seizure frequency per 28 days: RedSF.

e) Freedom from POS (seizure-free days) over the treatment period (for patients who complete the study and have no missing data).

f) 100% seizure-free during the treatment period.
11. PHARMACOKINETIC ASSESSMENTS

11.1. Blood Sample Collection

A 4-mL blood sample (trough) for PK analysis of CBD and THC will be collected into heparin collection sachets at pre-dose on Study Day 1 and pre-dose every 4 weeks through Week 12. In addition, a blood sample for AED blood levels will be collected at screening, Week 4 of the Baseline Period, pre-dose on Study Day 1, and every 2 weeks through Week 8 and at Week 12. Where possible, effort should be made to get a trough sample for the AED. If not, the times of blood sample collection, as well as the times of dosing, should be recorded. The times of the first dose of study drug on Day 1 and the previous dose of study drug for each blood draw at Weeks 2, 4, 6, 8, and 12 should be recorded. AED samples will be analyzed by a central laboratory.

Blood samples for CBD and THC analysis will be placed on ice until centrifuged. The blood samples will be placed in a refrigerated centrifuge within 60 minutes of collection and spun at high speed (2500 revolutions per minute) for 10 minutes at 4°C. Plasma samples will be split in half and transferred into appropriately labeled tubes. The plasma samples will be frozen at a freezer temperature of -80°C or below (±10°C), within two hours after collection and will remain frozen until shipped. Half of the plasma sample will be retained at the investigative site as a back-up sample. Half of the frozen samples will be packed in dry ice sufficient to last the number of days applicable to transport. Plasma samples will be shipped to the central laboratory who will ship these samples to the laboratory chosen by the Sponsor, as follows:

An inventory of the samples shipped will accompany the package.

11.2. Sample Analysis

Plasma samples will be analyzed by a validated high-performance liquid chromatography (HPLC), with tandem mass spectrometry (MS/MS) detection for the determination of CBD and THC in plasma.

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. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Patient safety will be monitored during the treatment visits using standard measures, including physical exams, neurological exams, examination of skin at application site, vital signs (including oral temperature), 12-lead ECGs, clinical laboratory tests (hematology, chemistry, urinalysis), testosterone (males only), urine pregnancy test (females only), C-SSRS and AE monitoring.

Before each study dose, patients will record the skin irritation score in their daily skin irritation diary. When skin irritation is noted, patients will be instructed to apply the gel to a non-irritated area of the shoulders and/or upper arms. If the skin irritation score is “1”, the patient will contact the Investigator to determine if an Unscheduled Visit is required. If an Unscheduled Visit is not required, patients will be instructed to call the Investigator if the skin irritation worsens. The Investigator will use discretion in suspending dosing for patients with a skin irritation score of 4 but will in all cases immediately (within 24 hours) complete an adverse event report and contact their study Clinical Research Associate (CRA) and the Zynerba Medical Monitor.

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 and at each post-treatment evaluation. 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.

All AEs that occur during the course of 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 efforts will be made to follow-up events until resolution.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

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 or not 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. Patients having clinically significant AEs will be followed until they return to normal or become stabilized.

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. All AEs must be followed to a satisfactory resolution.

All AEs will be collected from study screening until completion of last study visit.

Application site irritation scores (Table 4) of 1, 2, or 3 should not be recorded as AEs but will be assessed and recorded as part of the skin irritation score examinations. Skin irritation recorded with a score of 4 (as assessed by the Investigator) will be recorded as part of the skin irritation examination, and will also be recorded by the Investigator as an AE. The Investigator should report as an expedited AE (within 24 hours of assessment) to the Sponsor.

If a patient reports a worsening of skin irritation 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. 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 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.

The date and time of onset of the adverse event will be collected. Also, the date and time of the resolution of the adverse event will be collected.
12.2.1.2. **Serious Adverse Event**

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

- Death
- 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
- In-patient hospitalization (admission or prolongation of existing hospitalization)
- 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.
- Congenital abnormality or birth defect - Any structural abnormality in patient offspring that occurs after intrauterine exposure to treatment.
- 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.

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:

- **Probable** - An adverse event has a strong temporal relationship to study drug or recurs on re-challenge, and another etiology is unlikely or significantly less likely.
- **Possible** - An adverse event has a strong temporal relationship to the study drug, and an alternative etiology is equally or less likely compared to the potential relationship to study drug. The alternative etiology will be recorded in the eCRF.
- **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. **Adverse Event Severity**

The severity/intensity of the adverse event will be graded using the following definitions:

- **Mild** - The AE is transient and easily tolerated by the patient.
- **Moderate** - The AE causes the patient discomfort and interrupts the patient’s usual activities.
- **Severe** - The AE causes considerable interference with the patient’s usual activities and may be incapacitating or life-threatening.
12.5. Reporting Adverse 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.

24 Hour SAE Telephone: [redacted]
email: [redacted]

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.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator’s responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) 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 IRB or IEC of these additional SAEs.
13. STATISTICS

13.1. Determination of Sample Size

The sample size of 60 subjects per treatment group is sufficient to have a power of 88% to detect a difference between active and placebo if the 50% responder rate is 40% for the active group and 15% for the placebo group. To account for a possible screening failure rate of 15%, a total of 210 subjects should be enrolled to ensure there will be 180 subjects to randomize.

There will be one planned interim analysis when approximately 120 subjects (67% of planned sample size) have completed the trial. The primary objective of the interim analysis is to re-estimate the sample size if the placebo 50% responder rate is higher than what is expected.

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 seizure assessment. The ITT population will be used for all efficacy analyses.

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

The PK population will consist of all patients who have received at least one application of study drug and have plasma concentration obtained from at least one of the three Maintenance Period evaluations.

13.3. Efficacy Analyses

13.3.1. Primary Efficacy Analysis

The primary inferential analysis, based on an analysis of covariance (ANCOVA) model with factors for treatment group and center, will be performed on the log transformed seizure frequency using the transformation ln(SF28 + 1). Log transformed average seizure frequency during the Baseline Period will be used as the covariate. Pairwise comparisons of the two active treatments (Treatment A and Treatment B) to placebo (Treatment C) will be made using least squares (LS) means. The percent reduction over placebo will be estimated as:

\[ 100 \times (1 - \text{exponentiated difference of LS means between active treatment (A or B) and placebo}) \]
13.3.2. Secondary Efficacy Analyses

The secondary analyses will include:

- g) \( \ln(SF28(\text{Initial 14d}) \) and \( \ln(SF28(\text{After Initial 14d}) \) will be analyzed in same manner as the primary efficacy analysis.

- h) 50% responder rate based on the Maintenance Period: Logistic regression with factors for treatment and center will be used to compare the two active treatment groups to placebo.

- i) Percent change from baseline in seizure frequency per 28 days: \%RedSF(Maintenance), \%RedSF(Initial 14d), \%RedSF(After Initial 14d). Descriptive statistics including number (N), mean, median, standard deviation (SD), minimum, and maximum will be presented by treatment group. Graphs of cumulative distribution functions for \%REDSF will be presented by treatment group.

- j) Change from baseline in seizure frequency per 28 days: RedSF(Maintenance), RedSF(Initial 14d), RedSF(After Initial 14d). Descriptive statistics including N, mean, median, SD, minimum, and maximum will be presented by treatment group.

- k) Freedom from POS (seizure-free days) over the treatment period (for patients who complete the study and have no missing data). Descriptive statistics including N, mean, median, SD, minimum, and maximum will be presented by treatment group.

- l) 100% seizure free during the treatment period. Proportion of patient in each treatment group will be presented.

13.4. Pharmacokinetic Analyses

13.4.1. CBD

The following PK parameters 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 by treatment group at each nominal blood sampling time (pre-dose Day 1, pre-dose Week 4, pre-dose Week 8, and pre-dose Week 12). Exploratory analyses on the effect of CBD on plasma levels of AEDs, or vice versa, may be explored.

13.4.2. AED Medications

The following data will be summarized separately for each AED medication:
Plasma concentration occurring at screening, Week 4 of the Baseline Period, Day 1 before dosing with ZYN002 and every 2 weeks through Week 8 and at Week 12.

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 by treatment group at each nominal PK sampling time (Screening, Week 4 of the Baseline Period, pre-dose Day 1, and every 2 weeks through Week 8 and at Week 12).

13.5. Safety Analyses

AEs will be tabulated by treatment group and classified by system organ class and preferred term using the Medical Dictionary for Regulatory Affairs (MedDRA). For each preferred term, the two active groups will each be compared to the placebo group with a Fisher Exact test. Additionally, AEs will be tabulated overall (total number of AEs and total number of patients with AEs).

Descriptive statistics (count, percentage of yes/no responses) will be provided by treatment for Questions 4 and 5 of C-SSRS at each time point.

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

Safety laboratory test results and change from Baseline will be summarized by treatment group and time point with descriptive statistics.

Application site irritation scoring as determined by Investigator will be summarized for each treatment group at Weeks 4, 8, 12 and any unscheduled visits using counts and percentages at each respective site irritation score (0, 1, 2, 3, or 4).
14. DATA 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.
15. ETHICS

15.1. Independent Ethics Committee or Institutional Review Board

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 an IEC/IRB. IEC/IRB 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 IEC/IRB approval prior to implementation of any changes made to the study design.

15.2. 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 IEC/IRB modifications, safety updates, amendments, and deviations of the protocol that impact on patient safety.

At appropriate intervals, the clinical monitor 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 for a minimum of 15 years. These records include the Confidential Follow-up Forms and other documents such as ICFs, laboratory reports, and other source documents, drug accountability forms, IEC/IRB approvals, protocols, and eCRFs.

15.3. Patient Information and Informed Consent

The study protocol and ICF must be approved by the investigator’s IEC/IRB and a copy of the approved ICF must be supplied to the Sponsor. The patient will be asked to read the consent form. If the patient decides to participate in the study, the patient will be asked to sign and date the form as evidence of consent. Each patient 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. The physician will document in the patient’s medical chart that the patient has signed an ICF to participate in an investigational trial, a copy of the ICF will be given to the patient, 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 patients will give explicit permission for representatives of the regulatory authorities and the IRB/IEC to inspect their medical records to verify the information collected. Patients 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, including, without limitation, the Health Insurance Portability and Accountability Act (HIPAA).

All participants in the United States will provide written authorization to disclose protected health information either as a part of the written ICF or as a separate authorization form. The
authorization will contain all required elements specified by the Food and Drug Association (FDA) 45 Code of Federal Regulations (CFR) 164. The patient will be informed that the authorization does not expire. The patient will be informed they can revoke this authorization at any time by giving written notice. If the patient revokes authorization they will not be permitted to continue in the study. The revoking of authorization cannot be considered retroactive to data already collected under an existing authorization. Individual patient medical information obtained during this study is confidential and its disclosure to third parties, other than those mentioned in this section, is strictly prohibited. In addition, medical information obtained during this study may be provided to the patient’s personal physician or to other appropriate medical personnel when required in connection with the patient’s continued health and welfare.

The investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.
16. DATA HANDLING AND RECORDKEEPING

16.1. 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, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

16.2. 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.
17. 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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19. APPENDICES
19.1. Application of ZYN02 Gel Instructions
19.2. **Seizure Diary**

The Seizure Diary is attached:

![Seizure Diary](19.2_Seizure Diary_23May2016.pdf)
19.3. Diagnostic Interview for Seizure Classification Outside of Video EEG Recording Form (Discover)

The Discover Form is attached:
19.4. Seizure Identification Form/Diagnostic Review Form (SIF/DRF)

The SIF/DRF is attached:

[PDF]

19.4_SIFandDRF_Template_23May2016
19.5. Skin Irritation Diary

The Skin Irritation Diary is attached:

[Attached file: Skin Irritation Diary_V3_18 Feb 2016]