ZYN002

An Open-Label, Tolerability and Efficacy Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome (INSPIRE)

Original Protocol Number:	ZYN2-CL-031
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Phase:	2
IND Number:	130876
Sponsor:	Zynerba Pharmaceuticals Pty., Ltd. 2 Riverside Quay Southbank, VIC 3006 Australia Zynerba Pharmaceuticals, Inc. 80 W. Lancaster Ave., Suite 300 Devon, PA 19333 United States of America
Medical Monitor:	PPD , MD PPD PPD

CONFIDENTIAL INFORMATION

1. INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure Edition 8 dated 23 October 2020 and the Interim Supplement .01 to the IB dated 23 March 2021 for ZYN002. I have read the ZYN2-CL-031.05 protocol dated 17 August 2021 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Email Address and Telephone Number
Responsible Physician	PPD, MD	PPD

2. SYNOPSIS

Name of Sponsor/Company:
Zynerba Pharmaceuticals Pty. Ltd./Zynerba Pharmaceuticals, Inc.

Name of Investigational Product: ZYN002

Name of Active Ingredient: Cannabidiol (CBD)

Title of Study: An Open-Label Tolerability and Efficacy Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome

Study Centers: Australia and the United States

Children's Health Queensland Hospital and Health Services
Lady Cilento Children's Hospital
501 Stanley St.
South Brisbane, QLD 4101
Australia

And

Genetics Clinics Australia
263 Glen Eira Rd,
Nth Caulfield, VIC 3161

And

Greenwood Genetic Center – Greenville
14 Edgewood, Drive
Greenville, SC 29605

Principal Investigator:

PPD, MBBS, FRACP, MRCPCH, PGCAP, DM
Children's Health Queensland Hospital and Health Services
Lady Cilento Children's Hospital
501 Stanley St.
South Brisbane, QLD 4101
Australia

Study Period:	**Phase of Development:** 2
Estimated date first patient enrolled: February 2020 Estimated date last patient enrolled: October 2021 Estimated date last patient completed: May 2022	

Objectives:

Primary:

To evaluate the safety and tolerability of ZYN002 administered as a transdermal gel formulation, for up to 38 weeks, in patients ages 4 to < 18 years, in the treatment of 22q.11.2 Deletion Syndrome (22qDS).

Secondary:

- To evaluate the efficacy of ZYN002 in the treatment of symptoms of 22qDS
- To evaluate cannabidiol (CBD) and tetrahydrocannabinol (THC) plasma level exposure

Exploratory:

The identification of plasma levels of CBD metabolite(s) may be conducted.

Methodology:

This is an open-label study to assess the safety, tolerability and efficacy of CBD administered as ZYN002, a transdermal gel, for the treatment of child and adolescent patients with 22qDS. Male and female patients with 22qDS will be treated in Period 1 for 14 weeks. Patients with less than a 25% improvement from baseline in the ABC-C irritability subscale, the investigator may increase the total daily dose at Week 6. Patients that have made a ≥35% improvement on the ABC-C irritability sub-scale will be allowed to continue to Period 2 for an additional 24 weeks of treatment. At the end of study, patients taking anti-epileptic drug (AED) medication(s) will have an additional one or two week Taper Period, unless they are transitioning to receive drug through Special Access, if available. Approximately 20 male and female patients, ages 4 to < 18 years, will receive ZYN002.

Study Screening:

Prior to any Screening procedures being performed, the parent/caregiver will provide written informed consent and, if applicable, the patient will provide assent. During the Screening Period, the site staff will review the eligibility criteria, review any medications including over-the-counter (OTC) medications the patient is taking, obtain the patient's medical history including their 22qDS diagnosis, confirm epilepsy diagnosis (if applicable), collect demographic detail, obtain vital signs, perform an electrocardiogram (ECG), perform a physical and neurological exam, skin assessment, obtain blood for safety laboratory tests and presence of ethanol, collect urine for urinalysis and a drug screen, and administer assigned scales. Blood samples will be taken for hematology, serology and chemistry testing, and pregnancy testing (females only, if applicable). At Screening, patients will also have a blood sample drawn for CBD/THC PK exposure and valproic acid levels (for patients receiving valproate or valproic acid).

Note: only one ECG to be collected prior to starting treatment (Screening or Visit 2), provided that ECG is normal or has a finding that is not clinically significant.

The scales administered at Screening include:

- Aberrant Behavior Checklist (ABC-C)
- Autism Diagnostic Observation Schedule®-2 (ADOS®-2) (Note: is not administered at Screening if it has been administered in the prior 6 months and the results are available)
- Clinical Global Impression-Severity (CGI-S)
- Columbia-Suicide Severity Rating Scale – Children's version (C-SSRS)
- Anxiety, Depression and Mood Scale (ADAMS)
- Qualitative Caregiver Reported Behavioral Problems Survey
- Children's Sleep Habits Questionnaire (CSHQ)
- Pediatric Anxiety Rating Scale-Revised (PARS-R)

14-Week and 24-Week Extension Open Label Treatment Period:

Following the Screening Period, eligible patients will receive ZYN002 on Study Day 1 (Visit 2). There must be at least 7 days between Visit 1 (Screening) and Visit 2 (Day 1).

Patients and parents/caregivers will be required to visit the clinic at Day 1/Visit 2, Week 6/Visit 3, and Week 14/Visit 4, for the collection of: vital signs, ECG, concomitant medication review, physical and

neurological exam, pregnancy tests, skin assessment exam (Day 1) and skin irritation examination (Visits 3 and 4), adverse event (AE) review, and questionnaire and scale completion.

Blood samples for laboratory tests, CBD/THC PK exposure, and valproic acid (for patients taking valproate or valproic acid) will be collected at Week 6/Visit 3, Week 14/Visit 4 and Week 38/Visit 7 EOS/ET.

In addition, there will be a follow-up telephone visit at Week 10 for patients who had their dose adjusted at Week 6.

Patients that complete Visit 4 and have made a ≥35% improvement on the ABC C irritability subscale will be allowed to continue to Period 2 for an addition 24 weeks of treatment. Period 2 will have additional Visits at Week 22/Visit 5, Week 30/Visit 6, and Week 38/Visit 7 EOS/ET. Refer to the Schedule of Assessments (Table 5 and Table 6) for all activities to be completed at each study Visit.

Note: only one ECG to be collected prior to starting treatment (Screening or Visit 2), provided that ECG is normal or has a finding that is not clinically significant.

At Visit 2, parents/caregivers will be instructed on proper application of the study drug. Patients will be permitted to shower or clean the arm area up to 30 minutes prior to the study dose.

Parents/caregivers will use gloves supplied by the Sponsor to apply the study drug. Parents/caregivers will apply all study drug to clean, dry, intact skin, thoroughly massaging it into the right and/or left upper arms and shoulders until the area is dry. The study drug will be rubbed in completely and must be dry prior to dressing.

Patients should keep the application site dry for six hours but may apply an approved moisturizing lotion (Cetaphil), provided by the Sponsor, two hours after dosing. The application site should be covered to minimize sun exposure when going outside during the day. Sunscreen at the application site may be used two hours after dosing. If excessive skin irritation occurs at the application site, the parent (after consultation with the Investigator) may switch the application site temporarily to the upper thighs.

Patients who weigh ≤ 35 kg will receive 125 mg CBD Q12H (every 12 hours) (± 2 hours); for a total daily dose of 250 mg CBD. Patients who weigh > 35 kg will receive 250 mg CBD Q12H (±2 hours); for a total daily dose of 500 mg CBD. All patients will remain on their assigned dose through Week 6. At Week 6, if the patient has less than a 25% improvement from baseline in the ABC-C irritability subscale, the investigator may increase the dose, as follows:

- Patients who weigh ≤ 35 kg receiving a total daily dose of 250 mg CBD may increase to a daily dose of 500 mg.
  Patients who weigh > 35 kg receiving a daily dose of 500 mg CBD may increase the dose to 750 mg/day.

The following questionnaires and scales will be administered at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 EOS/ET, unless an exception is noted:

- ABC-C
- CGI-S
- Clinical Global Impression-Improvement (CGI-I) (not completed on Visit 2, Day 1)
- ADAMS
- C-SSRS
- Qualitative Caregiver Reported Behavioral Problems Survey (not completed at Visit 2)
- Children's Sleep Habit Questionnaire (Visit 4 and Visit 7 EOS/ET only)
- PARS-R

End of Study (EOS) / Early Termination Visit (ET):

Patients not on AEDs who are prematurely discontinued or do not qualify for Period 2, will complete the early termination procedures at Visit 4 EOS/ET.

Patients taking valproate or valproic acid for the treatment of seizures or epilepsy, including patients who prematurely discontinue, will taper their current study dose in the following manner beginning at Visit 7 EOS/ET. Should patients taking AEDs at the EOS continue to receive drug through Special Access (if available) they will not taper their dose.

- Participants who weigh 35 kg or less and were receiving 250 mg daily dose of ZYN002, will be reduced to 125 mg daily dose over one week. Only one sachet will be applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 40.
    - If the participant's dose was increased at Week 6 to 500 mg daily dose of ZYN002, the dose will be reduced to 250 mg daily dose over one week with 2 sachets applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 40.
- Participants who weigh 35 kg or more and were receiving 500 mg daily dose of ZYN002, will be reduced over two weeks. During the first week the dose will be reduced to 125 mg two times a day (applied 12 hours apart) which will make the total daily dose 250 mg. This is one sachet in the morning and one sachet in the evening. During the second week, the dose will decrease to 125 mg daily dose, which means one sachet each day for a week applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 41.
  If the participant's dose was increased at Week 6 to 750 mg daily dose of ZYN002, the dose will be reduced to 375 mg daily dose during the first week with one sachet applied in the morning and 2 sachets applied every evening. During the second week, the dose will decrease to 250 mg daily dose, which means 2 sachets each day for a week applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 41.

- Patients tapering their dose will have all Visit 4 EOS/ET assessments completed.
- At Week 38, patients will have their original dose in the morning and will have their evening dose as their new tapered dose.
- Patients will return on Week 40 or 41 and have the following assessments completed:
    - Concomitant medication review
    - Vital signs
    - Targeted physical exam if investigator deems clinically relevant
    - Pregnancy test (females only)
    - C-SSRS administered
    - Collection and review of Skin Irritation Diary
    - Skin irritation examination
    - Adverse event review

Patients having a skin irritation score > '0' at Visit 7, or Weeks 40 or 41 (for patients taking AEDs) will continue to be followed through Unscheduled Visits until the skin irritation score is recorded as '0' (no erythema).

Safety Monitoring:

Patient safety will be monitored at each study visit using standard measures, including physical and neurological exams, examination of skin at application sites for irritation, vital signs (including oral, infrared forehead or tympanic temperature), 12- lead ECGs, the C-SSRS, safety laboratory tests (Screening, Week 6, Week 14, and Week 38), urinalysis (Screening, Week 6, Week 14, and Week 38), and AE monitoring.

In addition, there will be a follow-up telephone visit at Week 10 for patients who had their dose adjusted at Week 6.

At Screening, patients will have an epilepsy diagnosis confirmed by the Investigator, if applicable. The parents/caregivers of patients with a current epilepsy and/or seizure diagnosis will be asked at each study visit if there has been any increase in frequency or severity of the patient's seizures. If an increase in frequency or severity is noted, this will be recorded as an adverse event (AE) in the case report form (CRF).

Parents/caregivers will be provided a diary to complete a daily skin irritation examination. Every evening from Day 1 through discharge from the study, parent/caregivers will record the skin irritation score in the daily skin irritation diary. When skin redness is noted, parents/caregivers should apply the gel to a non-red area of the upper arms and shoulders. If the skin irritation score is higher than '2' (moderate erythema) at any time, the parent/caregiver will contact the study site to determine if an Unscheduled Visit is required.

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. A de-identified photograph of the skin irritation (or area) of interest may be taken after consultation with and approval of the Sponsor. Digital photographs will be retained for information purposes only. In place of suspending the dosing due to skin irritation, the Investigator may instruct the parent/caregiver to temporarily change the application site to the upper thigh.

Plasma Samples for CBD, THC and Valproic Acid:

Blood samples for plasma levels of CBD and THC will be collected at Screening (Visit 1 baseline), Week 6/Visit 3, Week 14/Visit 4, and Week 38/Visit 7 EOS/ET.

In addition, blood samples for valproic acid levels (for patients taking valproate or valproic acid) for treatment of seizures or epilepsy, will be collected at Screening, Week 6/Visit 3, Week 14/Visit 4, and Week 38/Visit 7 EOS/ET. The time of blood sample collection, as well as the time of last valproate/valproic acid dose, if applicable, and study drug dose 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. Plasma samples for valproic acid will be analyzed through a local laboratory.

Number of Patients (Planned):

Approximately 20 male and female patients will be enrolled. Patients who prematurely discontinue after Visit 2 will not be replaced.

Diagnosis and Main Criteria for Inclusion:

Patients must qualify based on meeting all of the inclusion and none of the exclusion criteria to be eligible to enroll.

Inclusion Criteria:

1. Male or female children and adolescents aged 4 to <18 years, at the time of Screening.
2. Judged by the Investigator to be in generally good health at Screening based upon the results of a medical history, physical examination, and clinical laboratory test results. Laboratory results outside of the reference range must be documented as not clinically significant by the Investigator.
3. Patients must have a diagnosis of 22qDS confirmed by genetic testing, with or without autistic features.
4. Patients have a CGI-S score of 4 or higher at Screening and Visit 2.
5. Patients must have a severity score on the PARS-R of 10 or higher at Screening and Visit 2.
6. Patients with a history of seizure disorders must currently be receiving treatment with a stable regimen of one or two AEDs, or must be seizure-free for one year if not currently receiving AEDs.
7. If patients are receiving non-pharmacological behavioral and/or dietary interventions, they must be stable for three months prior to Screening.
8. Patient has demonstrated stable calcium levels for one year prior to Screening.
9. Patients have a body mass index between 12–35 kg / m^2 (inclusive).
10. Females of childbearing potential must have a negative pregnancy test at the Screening Visit and a negative pregnancy test at all designated study visits.
11. Patients and parents/caregivers agree to abide by all study restrictions and comply with all study procedures.
12. Patients and parents/caregivers must be adequately informed of the nature and risks of the study and give written informed consent (and assent if applicable) prior to Screening.
13. Parents/caregiver(s) must provide written consent to assist in study drug administration.
14. In the Investigator's opinion, patients and parents/caregivers are reliable and willing and able to comply with all protocol requirements and procedures.

Exclusion Criteria:

Any of the following is considered criterion for exclusion:

1. Females who are pregnant, nursing, or planning a pregnancy; females of childbearing potential and male patients with a partner of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined below for the duration of therapy and for three months after the last dose of study medication.
    a. Standard acceptable methods of contraception include abstinence or the use of a highly effective method of contraception, including hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, vasectomy, or intrauterine device.
2. History of significant allergic condition, significant drug-related hypersensitivity, or allergic reaction to any compound or chemical class related to ZYN002 or its excipients.
3. Exposure to any investigational drug or device ≤ 30 days prior to Screening or at any time during the study.
4. Patient has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 2 times the upper limit of normal (ULN) or has alkaline phosphatase levels ≥ 3 times the ULN as determined from Screening safety laboratories.
5. Use of cannabis or any THC or CBD-containing product within three months of Screening Visit or during the study.
6. Patient has a positive drug screen for sympathomimetic amines (amphetamines (unless prescribed); benzodiazepines; buprenorphine; cannabinoids; methadone; cocaine (metabolites); and opiates; (excludes barbiturates used as AED medication), including ethanol.
7. Patient is using the following AEDs: clobazam, phenobarbital, ethosuximide, felbamate, carbamazepine, phenytoin or vigabatrin.
8. Patient is using any strong inhibitor/inducer of CYP3A4 or sensitive substrate for CYP3A4 including but not limited to 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, pimozide, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinioin, vincristine, vinorelbine, St. John's Wort, and grapefruit juice/products.
9. Patient with diagnosis of known genetic disorder, other than 22qDS (i.e. Prader-Willi Syndrome, Angelman Syndrome, Fragile X Syndrome, Rett Syndrome etc.).
10. Patient has diagnosis of DiGeorge or Velocardiofacial syndrome without the presence of 22qDS.
11. Patient has a primary psychiatric diagnosis other than 22qDS or anxiety, including bipolar disorder, psychosis, schizophrenia, post-traumatic stress disorder (PTSD) or major depressive disorder.
12. Patients is on stable treatment of >6 months of not more than two psychoactive medications at screening or throughout the study (with the exception of one psychoactive medication prescribed for sleep).
13. Patient has an advanced, severe, or unstable disease that may interfere with the study outcome evaluations.
14. Patient is expected to initiate or change pharmacologic or non-pharmacologic interventions during the course of the study.
15. Patient has an acute or progressive neurological disease, or any psychiatric disorder or severe mental abnormalities that are likely to require changes in drug therapy or interfere with the objectives of the study or ability to adhere to protocol requirements.
16. Patient has a positive result for the presence of HBsAg, HCV, or HIV antibodies.
17. Patients at risk of needing cardiovascular surgical repair within the upcoming 12 months.

18. Patient has unstable cardiovascular disease, such as advanced arteriosclerosis, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, cardiac conduction problems, exercise-related cardiac events including syncope and pre-syncope, risk factors for Torsades de pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT Syndrome), other serious or other clinically unstable cardiac problems as indicated by history, physical examination, or ECG.
19. 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 medication.
20. 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 absorption of the study drug.
21. History of treatment for, or evidence of, drug abuse within the past year.
22. Patient responds "yes" to Question '4' or '5' on the C-SSRS (Children) during Screening or at any time on study.

Investigational Product, Dosage, and Mode of Administration:

Treatment Period:

This study has a 14-Week Treatment Period and a 24-Week Extension Period, dosing is as follows:

- Patients weighing ≤ 35 kg will receive 125 mg CBD applied Q12H (± 2 hours); total daily dose of 250 mg CBD. Each application will consist of **one sachet** of ZYN002 CBD 4.2% concentration, containing 2.98 g of gel. At Week 6, if the patient has less than a 25% improvement from baseline in the ABC-C irritability subscale, the investigator may increase the dose as follows:
    - Patients weighing ≤ 35 kg receiving a total daily dose of 250 mg CBD may increase to a daily dose of 500 mg. Each application will consist of two sachets of ZYN002 CBD 4.2% concentration, containing 2.98 g of gel

  Patients weighing > 35 kg will receive 250 mg CBD applied Q12H (±2 hours); total daily dose of 500 mg CBD. Each application will consist of **two sachets** of ZYN002 CBD 4.2% concentration, each sachet containing 2.98 g of gel. At Week 6, if the patient has less than a 25% improvement from baseline in the ABC-C irritability subscale, the investigator may increase the dose as follows:
    - Patients who weigh > 35 kg receiving a daily dose of 500 mg CBD may increase the daily dose to 750 mg. Each application will consist of three sachets of ZYN002 CBD 4.2% concentration, containing 2.98 g of gel.

Should the weight of the patient change from visit to visit the dose may be adjusted, at the discretion of the investigator.

Duration of Treatment:

Parents/caregivers will apply study drug twice daily for 14 weeks in Period 1 and up to 24 weeks in the extension Period 2. Patients on AEDs will have an additional one or two weeks of treatment to taper off study drug, unless they transition to receive drug through Special Access at the EOS.

Reference Therapy, Dosage and Mode of Administration:

N/A Open-Label Study

Safety and Pharmacokinetic Analyses:

Safety Analyses:

Safety assessments will include collection of AEs including seizure assessment if applicable, physical and neurological examination, 12-lead ECG, clinical laboratory assessments (hematology, chemistry, and urinalysis), vital signs, C-SSRS, and findings from the skin irritation examinations following treatment. All patients who receive at least one dose of study drug will be included in the safety analysis.

Plasma Concentrations of CBD/THC:

Plasma concentrations for CBD and THC will be summarized by treatment group and by Screening and treatment time points. As only sparse samples will be collected, pharmacokinetic (PK) parameters for CBD will not be calculated; however, observed plasma concentrations will be compared to simulated exposures based on population PK modeling.

Plasma Concentrations - Valproic Acid:

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

- Plasma concentration at Screening, pre-dose Week 6, Week 14 and Week 38 EOS/ET.
- Elapsed time between last valproate/valproic acid 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 valproic acid plasma trough concentrations and elapse time will be presented at each nominal PK sampling time.

Statistical Methods:

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) for continuous data and number (n) and percentage (%) for categorical data will be presented for all efficacy and safety parameters.

All efficacy assessments will be summarized at Weeks 6, 14, 22, 30, and 38 EOS/ET.

Vital sign assessments (actual and change from screening) taken at study Day 1, Weeks 6, 14, 22, 30 and 38 and will be summarized using descriptive statistics and presented by maintenance dose.

ECGs (actual and change from Screening) will be summarized by actual treatment group. ECG results including any clinically significant findings will be summarized at each study visit.

Safety laboratory and urinalysis assessments taken at Week 6, Week 14, and Week 38 EOS/ET (actual and change from Screening) will be summarized by treatment at the time of the assessment.

Application site irritation will be summarized using counts and percentages at each respective site irritation score (0, 1, 2, 3, or 4) by dose at the time of assessment.

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

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation	Definition
2-AG	Arachidonoylclycerol
22q11.1 or 22qDS	22q11.2 Deletion Syndrome
5-HT	Serotonin
ADAMS	Anxiety, Depression and Mood Scale
ADOS®-2	Autism Diagnostic Observation Schedule®-2
AE	Adverse event
AEA	Anandamide
AED	Anti-epileptic drug
AIM	Autism Impact Measure
ALT	Alanine transaminase
API	Active Pharmaceutical Ingredient
ASD	Autism Spectrum Disorder
AST	Aspartate transaminase
AUC	Area under the curve
BID	Twice daily
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBD	Cannabidiol
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CFR	Code of Federal Regulations
C_{max}	Maximum observed concentration
CNS	Central nervous system
CRA	Clinical Research Associate
CRF	Case Report Form
CSHQ	Children's Sleep Habit Questionnaire
C-SSRS	Columbia Suicide Severity Rating Scale
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
e.g.	For example
FDA	Food and Drug Administration
GCP	Good clinical practice
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibodies
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HREC	Human Rights Ethics Committee
ICF	Informed consent form
ITT	Intent-to-treat
IV	Intravenous

Table 2: Abbreviations and Specialist Terms

Abbreviation	Definition
Kg	Kilogram
LDL	Low density lipoprotein
MAPK1	Mitogen-activated protein kinase 1
MedDRA	Medical Dictionary for Regulatory Affairs
Mg	Milligram
MS/MS	Tandem mass spectrometry
N	Number
Ng	Nanogram
NOAEL	No-observed-adverse-effect-level
NONMEM	Nonlinear mixed effects model
OA	Osteoarthritis
OTC	Over-the-counter
PARS-R	Pediatric Anxiety Rating Scale-Revised
PK	Pharmacokinetic
PND	Post-natal day
PTSD	Post traumatic stress disorder
Q12 H	Every 12 hours
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TBX1	T-Box Protein 1
TdP	Torsades de pointes
THC	Δ^9-tetrahydrocannabinol
ULN	Upper limit of normal
UV	Ultraviolet
WBC	White blood cell
w/w	Weight/weight

5. INTRODUCTION

5.1. Background Information

The Drug Product ZYN002 is a transdermal cannabidiol (CBD) gel. CBD is the primary non-euphoric cannabinoid contained in the *Cannabis sativa L* plant. The CBD contained within ZYN002 is a pharmaceutically produced Active Pharmaceutical Ingredient (API) that is chemically identical to the CBD present in Cannabis.

Cannabis has low affinity for CB_1 and CB_2 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 was founded on the results of well-controlled studies in which CBD has exhibited high tolerability across several modes of administration.

ZYN002 is being developed as a clear, transdermal gel to provide consistent, controlled cannabidiol (CBD) delivery with twice daily (every 12 hours [Q12 H]) dosing. Because CBD is virtually insoluble in water, ethanol and propylene glycol are used as solubilizing agents and diethylene glycol monoethyl ether (brand name: Transcutol® HP) is used as a permeation enhancer.

22q11.2 deletion syndrome, (also referred to as 22qDS) is the most common (yet under-diagnosed) microdeletion syndrome affecting 1 in 2,000 to 1 in 4,000 live births. Approximately 50 genes are affected resulting in effects on multiple body systems. 22q11.1DS is inherited as autosomal dominant but 90-95% cases are spontaneous (McDonald-McGinn et al, 2015). Patients usually harbor a 1.5 to 3 Mb hemizygous deletion at chromosome 22q11.2, resulting in pathognomonic T-Box Protein 1(TBX1), adaptor protein CRKL and/or mitogen-activated protein kinase 1 (MAPK1) haplo-insufficiency.

The TBX1 gene provides instructions for making a protein called T-box 1. Genes in the T-box family play important roles in the formation of tissues and organs during embryonic development. To carry out these roles, proteins produced from these genes bind to specific areas of DNA. The proteins attach to critical regions near genes and help control the activity of those genes. T-box proteins are called transcription factors on the basis of this action. The T-box 1 protein appears to be necessary for the normal development of muscles and bones of the face and neck, large arteries that carry blood out of the heart, structures in the ear, and glands such as the thymus and parathyroid. Although the T-box 1 protein acts as a transcription factor, researchers have not determined which genes are regulated by this protein (Antshel, et al., 2018). Mortality in infancy is 5% mostly due to severe cardiac abnormalities.

DiGeorge syndrome was initially described in the 1960's in patients with cardiac defects, immunodeficiency, cleft lip/plate and hypoparathyroidism without knowledge of the chromosomal defect. In the 1980's the link of these findings to a chromosome defect was identified. Velocardiofacial syndrome was independently described in the 1970's as abnormal development of the parathyroid glands, thymus, and conotruncal region of the heart. "DiGeorge" now applies only to those with DiGeorge syndrome who do not have the 22q deletion. Thirty

five to 90% of patients diagnosed as DiGeorge syndrome and 80 to100% of patients diagnosed with velocardiofacial syndrome have 22qDS (Sullivan, K E, 2011).

The clinical presentations of 22qDS are highly variable within and between families, even in identical twins. Each patient presents their own unique profile of symptoms and signs. Males and females are equally affected. Undiagnosed older children and adults are often only ascertained due to behavioral problems or school performance. In some cases, adults are only diagnosed when they have an affected child. Over 180 clinical features have been described in association with 22qDS, none of which in isolation is considered pathognomonic for the condition (Koczkowska et al, 2017).

The most common medical problems include congenital heart defects (primarily conotruncal abnormalities such as Tetralogy of Fallot), facial and palatal abnormalities, immunodeficiency, and hypocalcemia. There is a very wide range in the severity of these effects from life threatening to very minimal or symptomatic and undiagnosed. The neurocognitive profile is highly variable (both inter- and intra-individual). Typically, early in infancy motor delays (hypotonia) and speech and language delays are evident. The majority of patients fall into an IQ range of 70 to 84. These patients are also at an increased risk to develop ADHD, autism spectrum disorder (ASD), anxiety and mood disorders as well as psychotic disorders and schizophrenia. This complex behavioral/psychiatric phenotype changes across ages particularly with the risk of development of schizophrenia as seen in Figure 1 (Swillen, 2015).

Figure 1: Phenotypic Manifestations of 22qDS by Age Range

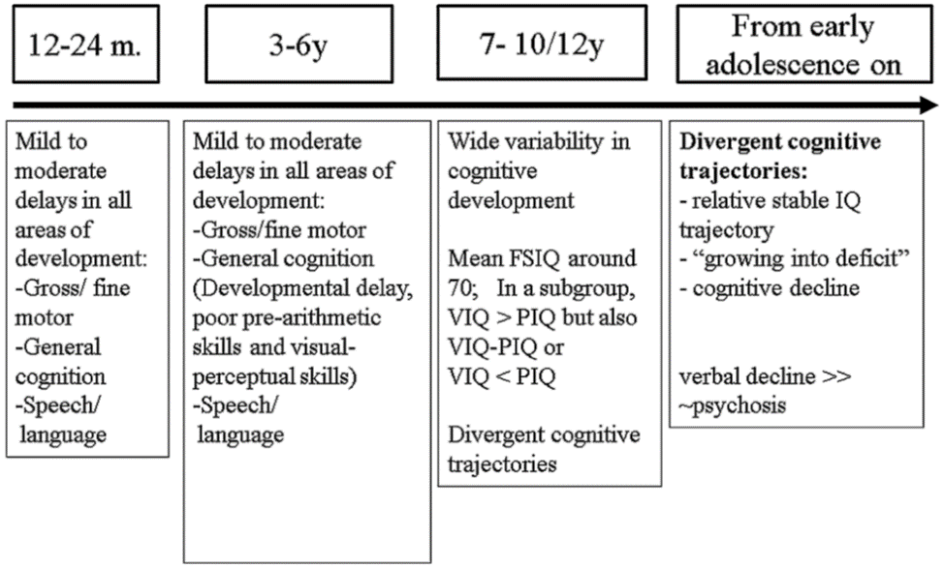

Table 3 summarizes phenotypic features from a large cohort of 22qDS patients (n=906) (McDonald-McGinn, 2011). The incidence of autism in this analysis is lower than that reported by others in which rates over 40% have been found (Antshel, 2007).

Table 3: Summary of 22qDS Patient Phenotypic Features

System	Percent (%)
Cardiac	77
Immune	77
Velopharyngeal	43
Submucous Cleft Palate	16
Overt Cleft Palate	11
Cleft Lip and Palate	2
Esophageal Dysmotility	36
Hypocalcemia	49
Feeding/Swallowing Issues	35
Generalized Anxiety	8
Phobias	42
ADHD	54
Autism	14

Behavioral Effects

The most common behavioral/psychiatric diagnoses in children with 22qDS are attention deficit hyperactivity disorder (ADHD), ASD and anxiety. These behaviors each occur in approximately 40% of patients. Cross-sectional studies have shown that children with 22qDS are withdrawn, have problems with social interaction, attention and anxiety in comparison to patients with speech/language delays or children with simple clefts (Swillen, 2015). The presence of autism in children with 22qDS is not linked to the subsequent risk of developing schizophrenia. These two conditions are independent phenotypic expressions of 22qDS (pleiotropy) (Vorstman, et al, 2013). However, there is a link between ADHD, particularly with inattentive symptoms, in childhood and an increased risk for later development of psychotic disorder (Niarchou, et al, 2018. Cognitive decline in childhood also is associated with an increased risk of schizophrenia.

Psychosis

The incidence of psychiatric disorders in children with 22qDS is similar to that in children with other developmental disorders but this changes as the children age (Swillen, 2015). One percent of patients with schizophrenia carry the 22qDS gene. Up to 30% of the patients with 22q11.2DS will develop schizophrenia or schizo-affective disorder. Schizophrenia is the most common psychiatric disorder in adults with 22qDS. The relative risk for the development of schizophrenia in patients with 22qDS is 20 to 25 times that of the normal population. The only patients with a higher relative risk for schizophrenia are children of parents who both have schizophrenia or monozygotic twins of an affected individual (Basset, 2008). The major

symptoms of schizophrenia seen in patients with 22qDS are essentially the same as those in patients without the deletion. These two groups do differ on intelligence quotient (IQ), however with those with 22qs having lower IQ (70 to 84) compared with patients without the 22qDS. Niarchou et al., (2018) compared the emergence of psychotic symptoms and psychotic disorders in patients with 22qDS with and without inattention symptoms or diagnosed ADHD. Patients with inattention symptoms at the mean age of 11 had a relative risk of 1.2 for the development of psychotic symptoms at 14 years. Patients diagnosed with ADHD at age 11 had a relative risk of 4.5 for having a psychotic disorder at age 14. There is no increased risk for psychotic symptoms or disorder with the presence of hyperactivity-impulsiveness symptoms.

Intelligence

There is a wide range in the effect of 22qDS on intelligence. The effect has been summarized as a 30- point leftward shift in the normal distribution of IQ scores (Swillen, 2015). Approximately 55% have borderline to normal intelligence (FSIQ > 70), approximately 45% have mild to moderate intellectual disability (FSIQ 55 to 70) and a minority experience moderate to severe intellectual disability (Swillen, 2015). There is considerable variability in changes in IQ scores as children age. In a recent longitudinal study, average children with 22qDS showed a cognitive decline of 7 FSIQ-points or 9 VIQ-points with increasing age (Vorstman et al., 2015). In the subgroup that developed psychotic symptoms, this decline was significantly steeper. A relatively low initial IQ (below 75) measured at or before the onset of adolescence was found to be an independent risk factor for psychosis in 22qDS. The association between the decline in VIQ and increased risk of schizophrenia is consistent with what has been described in the general population (Vorstman et al., 2015). By late adolescence and early adulthood approximately 30% of patients with 22qDS will develop psychotic disorders, most often schizophrenia or schizo-effective disorders.

5.2. Nonclinical Summary

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

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

Published nonclinical studies with CBD indicate that it does not produce adverse effects on nervous system, respiratory, or gastrointestinal function, although it does exhibit beneficial activity in some nervous system disorders (e.g., anti-convulsant and anxiolytic activity) and gastrointestinal disorders (e.g., anti-inflammatory activity). In a GLP-compliant study conducted by Zynerba, CBD did not affect cardiovascular system function even at an estimated plasma concentration (4350 ng/mL) that is 256 times greater than the expected plasma C_{max} in patients over a 14-day period (17 ng/mL). Based on this information, human subjects using ZYN002 are unlikely to experience adverse effects on nervous system, cardiovascular, respiratory, or gastrointestinal function.

ZYN002 was devoid of systemic toxicity in animals given topical doses applied to 10% of their body surface area daily for up to 26 weeks (rats) or twice a day for up to 13 weeks (minipigs). These studies identified CBD no-observed-adverse-effect-levels (NOAELs) of 100 and 17 mg/kg/day, respectively, which are both equivalent to approximately 970 mg/day in a 60-kg human subject. After the last dose at these NOAELs, plasma CBD exposure was much greater in rats than minipigs. C_{max} values were 584 ng/mL in male rats and 2680 ng/mL in female rats but only 8 ng/mL in minipigs of both sexes. $AUC_{0\text{-}24h}$ values were 8790 h*ng/mL in male rats and 38900 h*ng/mL in female rats but only 140 h*ng/mL in minipigs of both sexes.

In 26- and 13-week, repeat-dose studies, ZYN002 produced evidence of local irritation at the application site in both rats and minipigs that was CBD concentration-related, and rats were more sensitive than minipigs. For rats, the 26-week NOAEL for local irritation was considered to be the low dose level, where the CBD concentration was 1.0% (10 mg/mL) and the local CBD dose was 0.15 to 0.18 mg/cm^2/day. Local irritation was reversible when dosing stopped. In minipigs, local irritation was transient, limited to erythema, and resolved despite continued twice daily application of ZYN002. Therefore, the 13-week NOAEL for local irritation was considered to be the high-dose level, where CBD concentration was 7.5% (75 mg/mL) and the local CBD dose was approximately 0.62 mg/cm^2 twice daily (BID).

Zynerba has conducted studies of daily administration of ZYN002 to rabbits and rats (up to the highest dose of 100 mg/kg/day) to evaluate the effects of CBD on reproductive function and developmental toxicity, as follows:

- Male rat fertility study (ZYN2-NC-37) concluded reproductive function was not affected at any dose level; there were no effects on the fertility/conception rate, number of days to mating, or the number of corpora lutea, implantation sites, live and dead embryos, resorptions, pre- or post-implantation losses or live embryos index. There also were no effects on sperm concentration, motility, or quality and no histopathologic findings in the testis at any dose level.
- Results from a pregnant rabbit embryo-fetal development study (ZYN2-NC-40) indicated that ZYN002 did not affect the number of corpora lutea, implantation sites, live and dead fetuses, sex ratio, resorptions, pre- and post-implantation losses, or gravid uterus weight. There were also no major malformations or minor external or internal anomalies, skeletal anomalies or skeletal variants that were considered related to study treatment. ZYN002 was considered to have had no effect on embryo-fetal development.
- A female rat fertility study (ZYN2-NC-36) concluded reproductive function was not affected at any dose level; there were no effects on estrous cycling, mating, the fertility/conception rate, number of days to mating, or the number of corpora lutea, implantation sites, live and dead embryos, resorptions, pre- or post-implantation losses, or live embryos index. There also were no effects on ovarian or uterine weight at any dose level.
- A pregnant rat embryo-fetal development study (ZYN2-NC-38) executed during the period of major organogenesis did not affect maintenance of pregnancy or fetal survival, growth.

Zynerba has also conducted a 10-week juvenile rat toxicity study (ZYN2-NC-34) where rats tolerated daily doses of CBD up to 80 mg/kg/day for 10 weeks, administered by SC injection in

sesame oil from post-natal day (PND) 12 to 20 (study Days 1-9) and then by transdermal application of ZYN002 from PND 21 to 81 or 82 (study Days 10-70/71). The only adverse effect was on retinal development:

- Chorioretinal dysplasia was identified at a higher rate in ZYN002 rats (18/298 or 6%) compared to the control group (1/200 rats or 0.5%). The finding was not clearly dose related and was higher than historical background incidence (0.4%). (Tanaka et al. 1993: Hubert et al. 1994; Stein et al. 2017).
- Based on the results of the study, pregnant women or women planning to become pregnant should not receive CBD due to the CBD-related increase in the incidence of chorioretinal dysplasia found in juvenile rats. The chorioretinal dysplasia seen in rats would be irrelevant for human subjects exposed after birth because of species differences in ocular development. Briefly, in humans, the eyelids fuse during the third month of gestation and open during the sixth month of gestation. The human retina is largely morphologically mature at birth. In contrast, in rats the eyelids fuse by pre-natal Day 17 (third trimester) and open at approximately post-natal Day 14; consequently, rats are born with fused eyelids and eyes that are not fully developed. In other words, the CBD-related increase in the incidence of chorioretinal dysplasia in juvenile rats was a consequence of exposure to CBD during a period of choroid and retinal development that occurs prior to birth in humans.

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

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

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

ZYN002 did not induce contact hypersensitivity in a mouse local lymph node assay and so is considered not to pose a risk of inducing contact sensitization in human subjects.

Because of its high ethanol content (> 50%), ZYN002 caused irritation when placed into the eyes of rabbits and would be expected to do so if it accidentally contacts the conjunctiva or cornea of human subjects. Irritation was reversible within 7 days.

In the completed clinical pharmacology studies, ZYN002 was not associated with any impairment in critical areas of cognitive functioning often impacted by CNS drugs, including divided attention and working memory and focused attention after single or repeat doses of ZYN002 at doses up to 250 mg as a single or BID dose. Assessments of psychological health also demonstrated no changes in depression and anxiety symptoms, or positive and negative affect, following administration of ZYN002. Results from three completed Phase 1 studies, along with a population pharmacokinetic (PK) model, which includes results from ZYN2-CL-03, ZYN2-CL-004 and ZYN2-CL-005, have adequately described the PK of CBD following

application of ZYN002 transdermal gel. Pharmacokinetic conclusions for these studies are as follows:

- The plasma CBD concentration-time profiles after transdermal administration of ZYN002 were consistent with slow transcutaneous absorption, extensive distribution (with volume of distribution >20 L/kg), extensive metabolism, and a slow terminal phase half-life ($t_{1/2}$) of approximately 4-12 days.
- THC was not quantifiable in either plasma or urine.
- There is adequate animal NOAEL:human exposure ratios for AUC and C_{max}.

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

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

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

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

5.3. Clinical Summary

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

5.3.1. ZYN002 Phase 1 Studies

Five Phase 1 studies (ZYN2-CL-01, ZYN2-CL-02, ZYN2-CL-008, ZYN2-CL-011, and ZYN2-CL-014) of ZYN002 (CBD) administered via a transdermal delivery system have been conducted in healthy subjects and patients with epilepsy. In addition, one placebo study (ZYN2-CL-06) was conducted to evaluate the skin tolerability of the excipients in the ZYN002 formulation.

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 22qDS, ASD, FXS, and epilepsy.

A summary of the safety results from the Zynerba studies further supports the development of ZYN002. Five Phase 1 safety and tolerability study results are as follows:

- ZYN2-CL-01, a single rising-dose study in healthy subjects (n=32) and patients with epilepsy (n=10) receiving ZYN002 (50, 100, 125, and 250 mg) or placebo showed that ZYN002 was safe and well tolerated at all doses. The incidence of treatment-emergent adverse events (TEAEs) associated with ZYN002 was similar to placebo in healthy volunteers. There were no serious adverse events (SAEs), no clinically significant changes in ECGs, vital signs or clinical laboratory results. ZYN002 had good skin tolerability, and there was no post-dosing erythema at 24, 48, 72, and 96 hours.
- ZYN2-CL-02, a seven-day repeat application, multiple rising dose study of healthy subjects (n=24) receiving ZYN002 (200, 250, 500 mg/day), and patients with epilepsy (n=12), receiving 500 mg/day showed that ZYN002 was safe and well tolerated at all doses. One subject receiving placebo discontinued due to an SAE, a device related infection (catheter) not related to study drug. Most TEAEs were mild in intensity and there was only one severe TEAE of back pain in a healthy subject administered ZYN002 500 mg. Most TEAEs were considered related to study drug and either resolved or were resolving. Application site disorders were the most frequently reported TEAEs for both healthy subjects and epilepsy patients. The most frequently reported TEAEs were application site dryness and application site pruritus. Headache was the most frequently reported TEAE that was not associated with the application site. There were no clinically significant changes in ECGs or vital signs.
- ZYN2-CL-06, a 14-day repeat application study in healthy subjects (n=5) receiving placebo which tested the skin tolerability of the excipients used in the ZYN002 formulation but did not contain the active ingredient of CBD. There were no AEs or SAEs reported in this study. The majority of skin irritation erythema scores were ‘0’ (no erythema), and when erythema was recorded it was scored as a ‘1’ (minimal erythema). There were no clinically significant changes in ECGs, laboratory testing, physical examinations, or vital signs.

- ZYN2-CL-008, a 14-day repeat application study in healthy subjects (n=42) receiving ZYN002 (394.8, 500, and 504 mg/day) or placebo showed that ZYN002 was safe and well tolerated at all doses. Most TEAEs were mild in intensity. Most TEAEs were considered not related to study drug and either resolved or were resolving at the time of database lock. No SAEs were reported and no subjects discontinued from the study due to a TEAE. Headache and upper respiratory tract infection were the most frequently reported TEAEs and occurred in similar incidence for both ZYN002 and placebo. Application site dryness, application site pain, and application site pruritus were the next frequently reported TEAEs.
- ZYN2-CL-011, a 14-day repeat application study in 39 healthy male and female subjects. This study was an open-label study where subjects were all administered 250 mg BID for a total daily dose of 500 mg/day. Three application sites were evaluated; upper thighs (Treatment A), upper back (Treatment B) and the upper arms/shoulders (Treatment C). Twenty-nine of the 29 (74.4%) treated subjects had at least one TEAE. There were no deaths reported in the study. The majority of the events were mild (95.3%) in severity and none were reported as severe. Most TEAEs were reported as related to study treatment (91.9%). One subject PPD discontinued treatment on Day 5 due to an AE of an allergic reaction of skin rash to the upper arms, chest, and forearms. This AE was considered probably related to study treatment. There were no serious adverse events reported.
- ZYN2-CL-014 was a randomized, placebo-controlled, double-blind, multiple-dose, parallel-group, relative bioavailability study to evaluate the relative bioavailability of ZYN02 CBD gel applied to the right and left upper arms/shoulders and the right and left upper arms/shoulders and right and left upper thighs. Treatment was administered BID for 13 consecutive days with only a morning dose on Day 14, to healthy male and female subjects.

  This study evaluated the safety and tolerability of a daily dose of 780 mg where the CBD concentration administered was either 7.5% or 4.2% in healthy subjects.

  Safety results from this 14-day repeat application study in healthy subjects receiving ZYN002 780 mg/day with two CBD concentrations (4.2% and 7.5%) showed that ZYN002 was safe and well tolerated at all application sites (upper right and left thighs and upper arms/shoulders). Thirty five (88%) of the treated subjects had at least one TEAE. There were no deaths due to adverse events. The majority of the events were mild (81%), 18% were considered moderate and one (1%) was reported as severe (subject R011 reporting increased lipase). Most TEAEs were reported as probably related to study treatment (60%). There were no serious adverse events reported. The most frequently reported treatment related TEAE was application site dryness reported by 21 (53%) subjects. All application site TEAEs were considered related to study drug. ZYN002 was well tolerated at all application sites with most erythema being recorded as a score of ‘0’ (no erythema) or ‘1’ (minimal erythema). There were no clinically significant changes in ECGs or vital signs. There were no clinically significant abnormalities observed in group laboratory parameters.

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

5.3.2. ZYN002 Phase 2 Studies

Seven Phase 2 studies have been completed in patients with epilepsy (ZYN2-CL-03, ZYN2-CL-004), osteoarthritis (OA) (ZYN-CL-005), FXS (ZYN2-CL-009, ZYN2-CL-016), DEE (ZYN2-CL-025), and Autism Spectrum Disorder (ASD) (ZYN2-CL-030).

1. ZYN2-CL-03, a randomized, double-blind, placebo-controlled, multiple-dose study was conducted at 10 sites in Australia and 4 sites in New Zealand, to assess the efficacy and safety of ZYN002 administered as a transdermal gel to patients with focal epilepsy. The results showed ZYN002 to be safe and well tolerated with a safety profile consistent with previous studies. A total of 188 patients were randomized to receive either 195 or 390 mg/day of ZYN002 or placebo for 12 weeks. AEs were reported by 26 of 63 (41.3%) of placebo-treated patients, 31 of 63 (49.2%) of patients randomized to 195 mg/day of ZYN002 and 32 of 62 (51.6%) of patients randomized to 390 mg/day of ZYN002. For each dosing group, the majority of AEs were mild to moderate in intensity. The TEAE that occurred more frequently in patients on drug than those on placebo and occurred in at least 2% of patients included: fatigue, headache, nausea, application site dryness, anxiety, urinary tract infection, diarrhea, application site pruritus, thermal burn (secondary to seizure related accident), ataxia, oropharyngeal pain and erythema.
2. ZYN2-CL-005, a randomized, double-blind, placebo-controlled, multiple center, multiple dose study, was conducted at 10 sites in Australia, to assess the efficacy and safety of a 12 week repeat application in patients diagnosed with OA of the knee. The results showed ZYN002 to be safe and well tolerated with a safety profile consistent with previous studies. A total of 320 patients were randomized to receive ZYN002 at 250 or 500 mg/day or placebo for 12 weeks. Patients experiencing at least one treatment-emergent adverse event were similar between those on study drug (n=106, 50%) and those on placebo (n=45, 42%). The TEAEs that occurred more frequently in patients on drug than those on placebo and occurred in at least at 2% of patients included: headache, dizziness, application site dryness, application site reaction, and application site pain.
3. ZYN2-CL-009 was an ongoing open-label study to assess the safety and efficacy of ZYN002 administered as a transdermal gel to children and adolescents (age range 6 to <18) with Fragile X Syndrome (FXS). The study was conducted at three investigative sites in Australia. The 12-week treatment period included a 6-week titration period, after which the patient was to remain on their maintenance dose over the next 6 weeks of treatment. Following completion of the first 12 weeks of treatment, patients had the option of continuing into an extension phase of the study, which allowed for them to receive study drug for up to 24 additional months. The extension phase of the study has concluded and is in the process of preparing results.

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

12-week treatment period results include:

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

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

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

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

Study results for Week 51 of the extension period include:

Through Week 51 there were no clinically significant changes in vital signs, ECGs, or clinical laboratory results. Through Week 51 there were a total of 66 TEAEs reported in the study, all mild to moderate in severity, with the majority judged by the Investigator as not related to study drug. No SAEs have been reported. Gastroenteritis and upper respiratory tract infections continue to be the most commonly reported adverse events.

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

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

Data from the extension phase of the study highlight continued gains in the primary and key secondary efficacy outcomes. The improvement observed during the initial 12-week treatment period has been sustained through 12 months. A 54.4% reduction in ADAMS

Total Score was observed between Screening and Month 12, relative to a 48.6% reduction from Screening to Week 12 (among the 12 patients enrolled through Month 12 of the extension phase). Similar changes were observed for Social Avoidance as measured by both the ADAMS (52.5% [n = 12] at Week 12 vs. 55.6% [n = 12] at Month 12) and ABC-C_{FXS} (57.9% [n = 12] at Week 12 vs. 77.2% [n = 9] at Month 12).

4. ZYN2-CL-004 was an open-label extension study to allow patients with focal epilepsy who completed ZYN2-CL-03 to continue to receive ZYN002. The primary objective was to assess the long-term safety and tolerability of ZYN002 in adult epilepsy patients over an 18-month period. The secondary objective was to evaluate efficacy in this population. Patients had to complete the 12 weeks of study treatment on protocol ZYN2-CL-03. ZYN002 was administered as a transdermal gel with all patients starting on ZYN002 at doses equal to or higher than those used in the blinded study – CBD 195 mg every 12 hours (Q12 H) (±2 hours) (390 mg daily), with the option that after Month 1 to either increase or reduce the dose of ZYN002. The dose could be increased to 292.5 mg Q12H (±2 hours) (585 mg daily). After one month at the 585 mg daily dose, the Investigator had the option to increase the dose to 390 mg Q12H (±2 hours) (780 mg daily). Of the patients who completed the blinded 12-week phase, 171 (98%) enrolled in the open-label extension study. Seizure control was evaluated as a function of duration on ZYN002, regardless of initial randomization group or dose. Longer exposure to ZYN002 resulted in greater improvements in seizure frequency, with median percent change in seizures from -25% at 3 months (n=171), -40% at 6 months (n=130), -48% at 9 months (n=107), -52% at 12 months (n=94), -57% at 15 months (n=84) and -55% at 18 months (n=63).

   ZYN002 was well tolerated, with excellent skin tolerability. The most common adverse events were upper respiratory tract infection (viral and bacterial; 20.4%), headache (11.7%), laceration (8.8%) and fatigue (5.8%). One patient died following the Month 15 visit; the causality is suspected Sudden Unexplained Death in Epilepsy. There have been no abnormal liver adverse events, defined as alanine aminotransferase or aspartate aminotransferase levels > 3 times the upper limit of normal.

5. ZYN2-CL-025 was an open-label study to evaluate over a 26-week treatment period, (Period A) the safety and tolerability of ZYN002 in 48 children and adolescent patients (age range 3 to <18 years) with developmental and epileptic encephalopathies (DEE). Patients weighing ≤ 25 kg received 125 mg CBD Q12H (±2 hours), for a total daily dose of 250 mg CBD (2 sachets) for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose could remain at 250 mg CBD daily or be increased to 250 mg CBD Q12H (±2 hours), for a total daily dose of 500 mg CBD (4 sachets) for the remaining 22 weeks of the treatment period. Patients weighing > 25 kg received 250 mg CBD Q12H (±2 hours), for a total daily dose of 500 mg CBD (4 sachets) for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose could remain at 500 mg CBD daily or be increased to 375 mg CBD Q12H (±2 hours), for a total daily dose 750 mg CBD (6 sachets) for the remaining 22 weeks of the treatment period. No sooner than Week 10, after evaluation of the patient's seizure diary and CBD plasma concentration from Weeks 4 and/or 6 the Investigator in conjunction with the Zynerba Medical Monitor, may determine that the patient's dose could be increased. An unscheduled visit was required in order to increase the dose. Patients taking 500 mg CBD daily may be increased to 750 mg CBD daily (6 sachets) and patients taking 750 mg CBD daily could be

increased to 1000 mg CBD (8 sachets) daily for the remainder of the treatment period. In Period B patients continued to receive ZYN002 for up to an additional 46 weeks at the same maintenance dose they were receiving at Week 26.

6. ZYN2-CL-016 was a randomized, double-blind, placebo-controlled, multiple-center study to assess the efficacy and safety of ZYN002 for the treatment of child and adolescent (age range 3 to <18 years) patients with FXS. Male and female patients with FXS were treated for 12 weeks with a two-week single-blind placebo lead-in preceding the 12-week double-blind treatment period. Approximately 204 male and female patients, ages 3 to < 18 years, were be randomized 1:1 to either study drug or placebo. Randomization was stratified by gender, weight category and region. In a blinded fashion, ZYN002-treated patients who weigh ≤ 35 kg received 125 mg CBD Q12H (every 12 hours) (± 2 hours); for a total daily dose of 250 mg CBD. Patients who weighed > 35 kg received 250 mg CBD Q12H (±2 hours); for a total daily dose of 500 mg CBD. All patients remained on their assigned dose during the 12-week treatment phase of the study.
7. ZYN2-CL-030 was an open-label study of patients aged 4 to < 18 years diagnosed with autism spectrum disorder (ASD). Treatment duration was 14 weeks with a 6-month extension. The study has concluded and is in the process of preparing results.

5.3.3. Ongoing ZYN002 Clinical Studies

Two clinical ZYN002 studies are ongoing as follows:

- ZYN2-CL-017 is a 52-week, ongoing, open label study for those patients that complete the treatment phase of studies ZYN2-CL-009, ZYN2-CL-016, and ZYN2-CL-033.
- ZYN2-CL-031 is an open-label study of patients aged 4 to < 18 years diagnosed with 22q.11.2 Deletion Syndrome. Treatment duration is 14 weeks with a 6-month extension. The study is currently enrolling.

5.3.4. Completed Clinical Studies in Literature

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

- Most assessments have used a 600 mg oral dose of CBD, but subjects in several trials have been treated with oral CBD doses of 1200 mg or more (Zuardi et al, 2010; Matsuyama and Fu 1981), and one study employed a 1500 mg dose (Zuardi et al. 2006). More recent epilepsy studies have titrated doses up to 25 – 50 mg/kg of oral doses in patients (age 1-30 years) (Devinsky et al. 2016, Devinsky et al. 2017). The mean CBD dose at 12 weeks was 22.9 mg/kg corresponding to a 732 mg oral dose for an average 10-year old patient. At the highest dose, Zynerba has studied a 1000 mg daily dose of CBD (ZYN002 4.2%). This study will investigate ZYN002 at the daily dose of 250 or 500 mg ZYN002 (4.2% concentration).
- Because the zero-order delivery from ZYN002 should provide a lower C_{max} than oral or buccal routes of delivery, ZYN002 usage may result in less systemic exposure, placing it well below the threshold of safety in humans that has been established at higher systemic doses with oral, inhalation and injectable formulations.
- The 600 mg oral dose of CBD has been monitored in multiple long-term treatment situations. In at least six studies, study periods of 3 months have been used (Martin-Santos et al. 2012; Bhattacharyya et al. 2012; Winton-Brown et al. 2011; Fusar-Poli et al. 2010; Bhattacharyya et al. 2010; Fusar-Poli et al. 2009; Borgwardt et al. 2008), and several patients have taken CBD for 4.5 months (Cunha et al. 1980).
- Psychoactive effects associated with CBD have not been widely reported until recently. Previous reports suggest the absence of psychoactive effects whether CBD is administered intravenously (Perez-Reyes et al. 1973) or orally (Englund et al. 2013; Martin-Santos et al. 2012, Bhattacharyya et al. 2012; Bhattacharyya et al. 2010; Zuardi et al. 2009), and pre-treatment with oral CBD 600 mg has been shown to inhibit the psychosis and cognitive impairment associated with intravenous THC 1.5 mg (Englund et al. 2013 and Bhattacharyya et al. 2010). Recent studies with Epidiolex (5 to 20 mg/kg/day)show high rates of somnolence (36%) and fatigue (20%) (Devinsky et al. 2017). These effects could be due to drug, underlying disease, potential conversion of oral CBD to THC or a combination of these factors. Previous work has shown that in the presence of acidic reagents, CBD isomerizes to tetrahydrocannabinol (Ganoi and Mecoulam, 1966). In simulated gastric fluid, cannabidiol converts to Δ^9-tetrahydrocannabinol, 9-α-hydroxy-hexahydrocannabinol and 8-hydroxy-iso-hexahydrocannabinol. All have psychoactive activity (Merrick et al. 2016; Watanabe et al. 2007).
- CBD-treated subjects in clinical studies have shown no treatment-related effects on key vital sign indicators, including blood pressure and heart rate (Perez-Reyes et al. 1973; Martin-Santos et al. 2012; Hallak et al. 2011; Fusar-Poli et al. 2009; Borgwardt et al. 2008; Zuardi et al. 1993; Consroe et al. 1991; Zuardi et al. 1982), as well as electrocardiography (Guy and Flint 2003; Carlini and Cunha 1981; Cunha et al. 1980).

- Findings from functional magnetic resonance imaging and behavioral studies show that CBD modulates function in regions not usually implicated in response inhibition. In terms of clinical sequelae, these data help to explain why CBD does not impair motor or cognitive performance and has anxiolytic effects (Borgwardt et al. 2008).

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

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

Primary:

To evaluate the safety and tolerability of ZYN002 administered as a transdermal gel formulation, for up to 38weeks, in patients ages 4 to < 18 years, in the treatment of symptoms of 22q.11.2 Deletion Syndrome (22qDS).

Secondary:

- To evaluate the efficacy of ZYN002 in the treatment of symptoms of 22qDS.
- To evaluate CBD and THC plasma level exposure.

Exploratory:

The identification of plasma levels of CBD metabolite(s) may be conducted.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label study, to assess the tolerability and efficacy of CBD administered as ZYN002, a transdermal gel, for the treatment of child and adolescent patients with 22qDS. Male and female patients with 22qDS will be treated in Period 1 for 14 weeks. Patients with less than a 25% improvement from baseline in the ABC-C irritability subscale, the investigator may increase the total daily dose at Week 6. Patients that have made a ≥35% improvement on the ABC-C irritability sub-scale will be allowed to continue to Period 2 for an additional 24 weeks of treatment. Patients taking AED medications for treatment of seizures or epilepsy, will have an additional one or two week Taper Period unless they transition to receiving drug through Special Access. Approximately 20 male and female patients, ages 4 to < 18 years, will receive ZYN002. ZYN002, with a 4.2% concentration of CBD, will be administered as a transdermal gel according to the dosing schedule outlined in Section 7.4.

Prior to any Screening procedures being performed, the parent/caregiver will provide written informed consent and, if applicable, the patient will provide assent.

7.2. Number of Patients

Approximately 20 male and female patients will be enrolled. Patients who prematurely discontinue after Visit 2 will not be replaced.

7.3. Dose Rationale

Steady-state CBD concentrations were simulated, using a nonlinear mixed effects model (NONMEM, n=1000), for pediatric subjects by age group and by body weight. Simulated exposures were compared, for each pediatric age group receiving ZYN002 at either 125 or 250 mg CBD BID, to adults receiving ZYN002 250 mg CBD BID (a ZYN002 dose that has been demonstrated to be safe and well tolerated; Section 5.3), assuming dose proportionality. The simulations suggest that dosing 125 mg CBD BID in subjects weighing ≤ 35 kg results in relatively similar mean AUCs (85-140%) compared to adults receiving 250 mg CBD BID and that dosing pediatric age groups weighing > 35 kg with 250 mg CBD BID also results in similar mean AUCs (96 to 123%) compared to adults.

Therefore, a total daily dose of 250 or 500 mg CBD will be applied to patients that weigh ≤ 35 kg and a total daily dose of 500 or 750 mg will be applied to patients that weigh > 35 kg.

ZYN002 studies have been conducted in healthy subjects and patients using the CBD 4.2% concentration at similar daily dose levels as this study (250, 500 and 1000 mg/day). ZYN002 has shown to be safe and well tolerated in all studies (Refer to Section 5.3).

7.4. Treatment Assignment

The last date of study treatment will be collected and recorded in the CRF. This study has a 14-week treatment period as follows:

- Patients weighing ≤ 35 kg will receive 125 mg CBD applied Q12H (± 2 hours); total daily dose of 250 mg CBD. Each application will consist of **one sachet** of ZYN002 CBD 4.2% concentration, containing 2.98 g of gel. At Week 6, if the patient has less than a 25% improvement from baseline in the ABC-C irritability sub-scale, the investigator may increase the dose as follows:
    - Patients weighing ≤ 35 kg receiving a total daily dose of 250 mg CBD may increase to a daily dose of 500 mg. Each application will consist of **two sachets** of ZYN002 CBD 4.2% concentration, containing 2.98 g of gel.
- Patients weighing > 35 kg will receive 250 mg CBD applied Q12H (±2 hours); for a total daily dose of 500 mg CBD. Each application will consist of **two sachets** of ZYN002 CBD 4.2% concentration, each sachet containing 2.98 g of gel. At Week 6, if the patient has less than a 25% improvement from baseline in the ABC-C irritability sub-scale, the investigator may increase the dose as follows:
    - Patients weighing > 35 kg receiving a total daily dose of 500 mg CBD may increase the daily dose to 750 mg. Each application will consist of **three sachets** of ZYN002 CBD 4.2% concentration, containing 2.98 g of gel.

Should the weight of the patient change from visit to visit the dose may be adjusted, at the discretion of the investigator.

7.5. Dose Adjustment Criteria

Patients will receive their assigned dose of ZYN002 as described in Section 7.4. Dose adjustments will be made for patients on AEDs for treatment of seizures or epilepsy, who will have a Taper Period at the end of the study, unless they are transitioning to receive drug through Special Access, if available (Section 7.8).

Should the weight of the patient change from visit to visit the dose may be adjusted, at the discretion of the investigator.

In addition, at Week 6 if the patient has less than a 25% improvement from baseline in the ABC-C irritability subscale, the investigator may increase the total daily dose.

7.6. Study Assessments

7.6.1. Screening Period

During the Screening Period, the site staff will review the eligibility criteria, review any medications including OTC medications the patient is taking, obtain the patient's medical history including their 22qDS diagnosis, confirm epilepsy diagnosis (if applicable), collect demographic details, obtain vital signs, perform an ECG, perform a physical and neurological exam, skin assessment, obtain blood for safety laboratory tests, and presence of ethanol collect urine for urinalysis and a drug screen, and administer assigned scales. Blood samples will be taken for

hematology and chemistry testing, and pregnancy testing (females only, if applicable). Patients will also have a blood sample drawn CBD/THC PK exposure and for valproic acid levels (for patients receiving valproate or valproic acid). Refer to Table 4 for all Screening assessments. Note: only one ECG to be collected prior to starting treatment (Screening or Visit 2), provided that the ECG is normal or has a finding that is not clinically significant. The scales administered at Screening include:

- Aberrant Behavior Checklist (ABC-C)
- Autism Diagnostic Observation Schedule®-2 (ADOS®-2) (Note: is not administered at Screening if it has been administered in the prior 6 months and the results are available)
- Clinical Global Impression-Severity (CGI-S)
- Columbia-Suicide Severity Rating Scale – Children's version (C-SSRS)
- Anxiety, Depression and Mood Scale (ADAMS)
- Qualitative Caregiver Reported Behavioral Problems Survey
- Children's Sleep Habit Questionnaire (CSHQ)
- Pediatric Anxiety Rating Scale – Revised (PARS-R)

In addition, an optional blood sample may be collected at the Screening Visit for analysis of the features of the 22qDS gene.

7.6.1.1. 14-Week and 24-Week Extension Open Label Treatment Period

Following the Screening Period, eligible patients will receive ZYN002 on study Day 1 (Visit 2). There must be at least 7 days between Visit 1 (Screening) and Visit 2 (Day 1).

Patients and parents/caregivers will be required to visit the clinic at Day 1/Visit 2, Week 6/Visit 3, and Week 14/Visit 4 End of Study (EOS)/Early Termination (ET), for the collection of: vital signs, ECG, concomitant medication review, physical and neurological exam, pregnancy tests, skin assessment examination (Day 1) and skin irritation examination (Visit 3 and 4), adverse AE review, and questionnaire's and scale completion. Blood samples for laboratory tests, CBD/THC PK exposure, and valproic acid (for patients taking valproate or valproic acid) levels will be collected at Week 6/Visit 3 Week 14/Visit 4, and Week 38/Visit 7 EOS/ET.

In addition, there will be a follow-up telephone visit at Week 10 for patients who had their dose adjusted at Week 6. Patients that complete Visit 4 and have made a ≥35% improvement on the ABC C irritability subscale will be allowed to continue to Period 2 for an addition 24 weeks of treatment. Period 2 will have additional Visits at Week 22/Visit 5, Week 30/Visit 6, and Week 38/Visit 7 EOS/ET. Refer to the Schedule of Assessments (Table 5 and Table 6) for the activities to be completed at each study Visit.

Note: only one ECG to be collected prior to starting treatment (Screening or Visit 2), provided that ECG is normal or has a finding that is not clinically significant.

At Visit 2, parents/caregivers will be instructed on proper application of the study drug (Section 20.1). Patients will be permitted to shower or clean the arm area up to 30 minutes prior to the study dose.

Parents/caregivers will use gloves supplied by the Sponsor to apply the study drug. Parents/caregivers will apply all study drug to clean, dry, intact skin, thoroughly massaging it

into the right and/or left upper arms and shoulders until the area is dry. The study drug will be rubbed in completely and must be dry prior to dressing.

Patients should keep the application site dry for six hours but may apply an approved moisturizing lotion (Cetaphil), provided by the Sponsor, two hours after dosing. The application site should be covered to minimize sun exposure when going outside during the day. If redness occurs at the application site, the parent (after consultation with the Investigator) may switch the application site temporarily to the upper thighs. The following questionnaires and scales will be administered at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 EOS/ET:

- ABC-C
- CGI-S
- Clinical Global Impression-Improvement (CGI-I) (not completed on Visit 2, Day 1)
- ADAMS
- C-SSRS
- Qualitative Caregiver Reported Behavioral Problems Survey (not completed at Visit 2)
- Children's Sleep Habit Questionnaire (Visit 4 and Visit 7 EOS/ET only)
- PARS-R

Study procedures will be performed as summarized in the study schematic presented in Tables 4, 5, and Table 6.

Table 4: Schedule of Assessments – Screening (Visit 1)

Study Procedures	Screening Visit Days -28 to Day -8
Informed Consent	X
Review Eligibility Criteria	X
Medical History	X
Demographics	X
Concomitant Medications	X
Complete Physical / Neurological Exam[a]	X
Confirm 22qDS Diagnosis	X
Confirm Epilepsy Diagnosis	X
Vital Signs	X
12-lead ECG[b]	X
HIV-Ab 1+2 + Hepatitis B+C	X
Laboratory Tests and Urinalysis	X
Pregnancy Test (females)	X
Drug Screen (Urine and Blood)	X
Aberrant Behavior Checklist-Community (ABC-C)	X
Autism Diagnostic Observation Schedule®-2 (ADOS®-2)[c]	X
Clinical Global Impression-Severity (CGI-S)	X
Columbia-Suicide Severity Rating Scale – Children's version (C-SSRS)	X
Anxiety, Depression and Mood Scale (ADAMS)	X
Qualitative Caregiver Reported Behavioral Problems Survey	X
Children's Sleep Habit Questionnaire (CSHQ)	X
Pediatric Anxiety Rating Scale (PARS-R)	X
CBD/THC PK Sample	X
AED Blood Sample[d]	X
Skin Assessment Exam[e]	X
Adverse Event Review	X
Optional: DNA for genomic screening	Optional

a. Complete Physical and Neurological exam including height and weight at Screening.
b. One ECG to be collected prior to starting treatment (Screening or Visit 2), provided that ECG is normal or has a finding that is not clinically significant.
c. ADOS®-2 will not be administered at Screening if it has been administered in the prior 6 months and the results are available.
d. Applicable to only those patients taking AED medications.
e. Shoulders and upper arms will be examined to determine there are no 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 where study drug could be applied.

Note: There must be at least 7 days between Visit 1 (Screening) and Visit 2 (Day 1).

Table 5: Period 1 Schedule of Assessments – 14-Week Treatment Period

Study Procedures	14-Week Treatment Period 1 Visit Schedule			Taper Period, If Applicable		Study Visit Week 16 or Week 17 for AED Patients Tapering Study Drug[a]	Un-scheduled Visit(s)	Week 10 Telephone Follow-up
	Visit 2 Day 1	Visit 3 Week 6 (± 3 days)	Visit 4 Week 14 EOS/ET[a] (± 3 days)	Week 15 (± 3 days)	Week 16 (± 3 days)			
	Study Drug Dosing			Tapered 50% each week. No Study Visit				
Review Eligibility Criteria	X							
Concomitant Medications	X	X	X			X	X	X
Physical/Neurological Exam[b]	X	X	X			X		
Vital Signs[c]	X	X	X			X	X	
12-lead ECG[d]	X	X	X					
Laboratory Tests and Urinalysis		X	X					
Pregnancy Test[e]		X	X			X		
CBD/THC PK Blood Sample		X	X					
Blood Sample Valproic Acid[f]		X	X					
ABC-C	X	X	X					
CGI-S	X	X	X					
CGI-I		X	X					
ADAMS	X	X	X					

Table 5: Period 1 Schedule of Assessments – 14-Week Treatment Period, cont'd								
Study Procedures	**14-Week Treatment Period – Visit Schedule**			**Taper Period, If Applicable**		**Study Visit Week 16 or Week 17 for AED Patients Tapering Study Drug[a] Visit[a]**	**Un-scheduled Visit(s)**	**Week 10 Telephone Follow-up[l]**
	Visit 2 Day 1	**Visit 3 Week 6 (± 3 days)**	**Visit 4 Week 14 EOS/ET[a] (± 3 days)**	**Week 15 (± 3 days)**	**Week 16 (± 3 days)**			
	Study Drug Dosing			**Tapered 50% each week. No Study Visit**				
C-SSRS	X	X	X			X	X	
Qualitative Caregiver Behavioral Problems/Improvements Survey		X	X					
Children's Sleep Habit Questionnaire			X					
Pediatric Anxiety Rating Scale - Revised	X	X	X					
Instruct Parent/caregiver on Study Drug Application[g]	X							
Daily Study Drug Application[h]	X	X	X	X	X			
Skin Assessment Exam[i]	X							
Parent/caregiver Completes Daily Skin Irritation Diary[j]	X	X	X	X	X	X	X	
Review Patient Skin Irritation Diary		X	X			X	X	
Skin Irritation Exam[k]		X	X			X	X	X
Adverse Event Review	X	X	X			X	X	X

Table 5 Footnotes - <u>Period 1</u>:

a. All patients will have a Week 14 Visit/ET. All patients that do not qualify for Period 2 will have an End of Study Visit at Week 14. AED patients will taper study drug for 1 or 2 weeks after the EOS Visit and return on Week 16 or 17 for final discharge from the study.
b. For patients that do not qualify for Period 2, Week 14/Visit 4 EOS/ET patients will have both weight and height taken. For patients taking AEDs and returning on Week 16 or 17 to be discharged from the study, a targeted physical examination (heart, lungs, abdomen and extremities) may be performed, if the investigator deems clinically relevant.
c. Vital signs (including blood pressure, heart rate, respiratory rate, and infrared forehead or oral or tympanic temperature) will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be assessed at each study visit pre-dose.
d. One ECG to be collected prior to starting treatment (Screening or Visit 2), provided that ECG is normal or has a finding that is not clinically significant.
e. A pregnancy test will be completed at Week 6, and Week 14/EOS/ET for all females of childbearing potential. Pregnancy tests can be plasma or urine.
f. Patients receiving valproate or valproic acid will have a blood sample drawn for plasma level of valproic acid. Where possible, effort should be made to get a trough sample. If not, the AED morning dose may be administered prior to the clinic visit. The time of the prior dose of study drug and valproate/valproic acid, if applicable in addition to the time of each blood sample collection will be recorded. During the Treatment Period valproic acid (for patients receiving valproate or valproic acid) blood samples will be taken at Week 6, and Week 14.
g. On Day 1 the parent/caregiver will be instructed on how to complete the daily skin irritation diary. Scoring of skin irritation will start the evening of Day 1 through discharge from the study by the parent/caregiver. The site will evaluate the parent/caregiver applying the study treatment at each study visit and provide feedback/additional instruction as applicable.
h. At Weeks 6, and 14 parents/caregivers will administer the dose in the clinic after they have their PK and valproic acid (for patients taking valproate/valproic acid) blood drawn. At Week 14 patients who require a tapering period will be provided a 1 or 2-week supply of study treatment.
i. A skin assessment examination will be completed by the Investigator at Day 1 pre-dose. Shoulders and upper arms will be examined to determine there are no 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 where study drug could be applied.
j. Parents/caregivers will assess the application site daily and record all irritation scores in their daily skin irritation diary, starting with the PM dose on Day 1. When irritation exists, efforts will be made to apply the gel to a non-irritated area of the upper arms/shoulders and/or right and left upper thighs. Temporary application to the upper thighs can only be used after consultation with the investigator. If the skin irritation score is greater than “2”, the patient will contact the Investigator to determine if an Unscheduled Visit is required.
k. The investigator will perform a skin irritation examination pre-dose at study Visits 3, Visit 4/EOS/ET and Unscheduled Visits. The parent/caregiver will also be asked about the patients skin irritation at the Week 10 Telephone Follow-up call.
l. A Telephone Follow-Up with occur for those patients whose dose was increased at Week 6.

Table 6: Period 2 Schedule of Assessments – 24-Week Extension Treatment

Study Procedures	24-Week Treatment Period 2 Visit Schedule			Taper Period, If Applicable		Study Visit Week 40 or Week 41 for AED Patients Tapering Study Drug[a]	Un-scheduled Visit(s)
	Visit 5 Week 22 (± 3 days)	Visit 6 Week 30 (± 3 days)	Visit 7 Week 38 EOS/ET[a] (± 3 days)	Week 39 (± 3 days)	Week 40 (± 3 days)		
	Study Drug Dosing			Tapered 50% each week. No Study Visit			
Concomitant Medications	X	X	X			X	X
Physical/Neurological Exam[b]			X			X	
Vital Signs[c]	X	X	X			X	X
12-lead ECG			X				
Laboratory Tests and Urinalysis			X				
Pregnancy Test[d]			X			X	
CBD/THC PK Blood Sample			X				
Blood Sample for Valproic Acid[e, g]			X				
ABC-C	X	X	X				
CGI-S	X	X	X				
CGI-I	X	X	X				
ADAMS	X	X	X				

Table 6: Period 2 Schedule of Assessments – 24-Week Extension Treatment Period, cont'd

Study Procedures	24-Week Treatment Period – Visit Schedule			Taper Period, If Applicable		Study Visit Week 40 or Week 41 for AED Patients Tapering Study Drug[a] Visit[a]	Un-scheduled Visit(s)
	Visit 5 Week 22 (± 3 days)	Visit 6 Week 30 (± 3 days)	Visit 7 Week 38 EOS/ET[a] (± 3 days)	Week 39 (± 3 days)	Week 40 (± 3 days)		
	Study Drug Dosing			Tapered 50% each week. No Study Visit			
C-SSRS	X	X	X			X	X
Qualitative Caregiver Behavioral Problems/Improvements Survey	X	X	X				
Children's Sleep Habit Questionnaire			X				
Pediatric Anxiety Rating Scale-Revised	X	X	X				
Daily Study Drug Application	X	X	X	X	X		
Parent/caregiver Completes Daily Skin Irritation Diary[f, h]	X	X	X	X	X	X	X
Review Patient Skin Irritation Diary	X	X	X			X	X
Skin Irritation Exam[i]			X			X	X
Adverse Event Review	X	X	X			X	X

Table 6 Footnotes - <u>Period 2</u>:

a. Patients who withdraw prior to Period 2 Week 38 will complete the EOS/ET at Week 38. AED patients will taper study drug for 1 or 2 weeks after the EOS Visit and return on Week 40 or 41 for final discharge from the study, unless they are transitioning to receive drug through Special Access.
b. Patients will have both weight and height taken at EOS/ET. For patients taking AEDs and returning on Week 40 or 41 to be discharged from the study, a targeted physical examination (heart, lungs, abdomen and extremities) may be performed, if the investigator deems clinically relevant.
c. Vital signs (including blood pressure, heart rate, respiratory rate, and infrared forehead or oral or tympanic temperature) will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be assessed at each study visit pre-dose.
d. A pregnancy test will be completed at Week 38/EOS/ET for all females of childbearing potential. Pregnancy tests can be plasma or urine.
e. Patients will have a blood sample drawn for plasma level of valproic acid (for patients taking valproate or valproic acid) at Week 38/Visit 7. Where possible, effort should be made to get a trough sample for the valproic acid (for patients receiving valproate/valproic acid). If not, the AED morning dose may be administered prior to the clinic visit. The time of the prior dose of study drug and valproic acid (if applicable) in addition to the time of each blood sample collection will be recorded.
f. Scoring of skin irritation will start the evening of Day 1 through discharge from the study by the parent/caregiver. The site will evaluate the parent/caregiver applying the study treatment at each study visit and provide feedback/additional instruction as applicable.
g. At Week 38, parents/caregivers will administer the dose in the clinic after they have their PK and valproic acid (for patients taking valproate or valproic acid) blood drawn. At Week 38 patients who require a tapering period will be provided a 1 or 2-week supply of study treatment.
h. Parents/caregivers will assess the application site daily and record all irritation scores in their daily skin irritation diary, starting with the PM dose on Day 1. When irritation exists, efforts will be made to apply the gel to a non-irritated area of the upper arms/shoulders and/or right and left upper thighs. Temporary application to the upper thighs can only be used after consultation with the investigator. If the skin irritation score is greater than “2”, the patient will contact the Investigator to determine if an Unscheduled Visit is required.
i. The investigator will perform a skin irritation examination pre-dose at study Visit 7 EOS/ET and Unscheduled Visits. Weeks 5 and 6 the patient can receive their morning dose at home.

7.6.2. Informed Consent

Signed informed consent will be obtained at Screening from parent/caregivers and if applicable assent will be obtained from patients where developmentally appropriate. The informed consent form (ICF) will be signed by the parent/caregiver and the assent by the patient (if applicable) before any study procedures are undertaken. Details about how the ICF will be obtained and documented are provided in Section 17.3.

7.6.3. 22q.11.2 Deletion Syndrome Diagnosis

Patients participating in this study will have a diagnosis of 22q.11.2 (also referred to as 22qDS) confirmed by genetic testing, with or without autistic features.

7.6.4. Demographics

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

7.6.5. Vital Signs

Vital sign determinations include sitting blood pressure, heart rate, respiratory rate, and infrared forehead, or 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 pre-dose at all study visits.

7.6.6. Medical History

A complete medical history for the previous 5 years will be obtained from each patient during the Screening Visit.

7.6.7. 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 each study visit, Unscheduled Visits, the Week 10 Telephone Follow-up call, and at the End of Study Visit.

7.6.8. Review Adverse Events

A review of AEs will be performed at Screening, and each study visit, the Week 10 Telephone Follow-up call, and any Unscheduled Visits. Detailed information regarding AEs can be found in Section 11.2.

7.6.9. Complete Physical/Neurological Examinations

A complete physical and neurological examination, including height and weight will be performed at Screening and Visit 4/Week14 and Visit 7/Week 38 EOS/ET. Only patient weight will be collected at Visit 4 and Visit 7 EOS/ET. Patient weight will be collected with minimal clothing (e.g., no coats, shoes, jumpers or jackets).

A complete physical and neurological examination will be performed at Day 1, Week 6 and Week 38/EOS/ET.

7.6.10. Targeted Physical Examination

For patients taking AEDs and returning on Week 40 or 41 to be discharged from the study, a targeted physical examination (heart, lungs, abdomen and extremities) may be performed, if the investigator deems clinically relevant.

7.6.11. Electrocardiogram

A 12-lead resting ECG will be obtained during the Screening Visit, and at study Visits 2, 3, 4, and 7/EOS/ET Visits. As applicable, ECGs will be conducted pre-dose, within 60 minutes of study drug application. All ECGs will be reviewed by a central reader (Cardiologist). The cardiologist will interpret, sign, and date the ECGs. Clinical interpretations will be recorded in the CRF (normal or abnormal with specific abnormality noted).

Note: one ECG to be collected prior to starting treatment (Screening or Visit 2), provided that ECG is normal or has a finding that is not clinically significant.

7.6.12. Investigator Skin Assessment Examination

At the Screening Visit and Day 1 (prior to dosing), the upper arms/shoulders will be examined to determine there is no 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 where study drug will be applied.

7.6.13. Investigator Skin Irritation Examination

The investigator will conduct a skin irritation examination pre-dose of the application site(s) at Week 6, Week 14, and Week 38 EOS/ET, and Unscheduled Visits. In addition, parents/caregivers will be asked about skin irritation at the Week 10 Telephone Follow-up call. When excessive skin redness is noted, efforts will be made to temporarily apply the gel to a non-red area of the upper arms/shoulders and/or right/left thighs at the approval of the investigator. The investigator will use discretion in suspending dosing for patients with a skin redness score of '4' (intense erythema) but will in all score of '4' cases immediately (within 24 hours) complete an adverse event report and contact their study CRA and the Sponsor Medical Monitor.

Application of ZYN002 to the right or left thigh should be viewed as a temporary alternate application site only until the redness on the upper arms/shoulders is reduced.

Patients having a skin irritation score > '0'at Week 38 will continue to be followed through Unscheduled Visits until the skin irritation score is recorded as '0' (no erythema). At this time, the patient will be discharged from the study.

Refer to Table 7 for the Skin Irritation Scale to be used for skin redness examinations.

Table 7: 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

A de-identified picture of an application site may be taken at the discretion of the Principal Investigator.

Should the patient experience dry skin at the application sites, moisturizing lotion (Cetaphil) which will be supplied by the Sponsor, may be applied two hours post gel application.

7.6.14. Patient Skin Irritation Diary

Parents/caregivers will be instructed on completion of the daily skin irritation diary at Day 1 (Section 20.2). Parent/caregiver scoring of skin irritation will start the evening of Day 1 (PM application) and will continue daily through discharge of the study. Before each evening dose, parents/caregivers will record the skin score in their daily skin irritation diary. When skin redness is noted, patients should apply the gel to a non-red area of the upper arms/shoulders and/or right and left thighs. If the skin irritation score is higher than '2' (moderate erythema) the parent/caregiver will contact the study site to determine if an Unscheduled Visit is required.

Application of ZYN002 to the right or left thigh should be viewed as a temporary alternate application site only until the redness on the upper arms/shoulders is reduced.

The investigator will use discretion in suspending dosing for patients with skin check score of '4' but will in all cases of a score of '4' immediately (within 24 hours) complete an adverse event report and contact their study CRA and the Sponsor Medical Monitor.

The patient's skin check diary will be reviewed by the investigator at Week 6, Week 14, and Week 38 EOS/ET Visit, and Unscheduled Visits.

7.6.15. Clinical Laboratory Testing

All blood samples will be collected and handled in accordance with the instructions from the local laboratory. For collection of laboratory samples, patients should fast for approximately four to eight hours prior to having blood drawn for blood laboratory analysis. Instructions regarding the collection, processing, and shipping of these samples will be provided by the laboratory chosen for this study.

All abnormal laboratory test results will be followed to a satisfactory resolution.

Samples will be collected based on Table 4, Table 5 and Table 6 Schedule of Assessments. Routine laboratory tests (clinical chemistry, hematology, and urinalysis) will be collected at the Screening Visit, Week 6, Week 14, and Week 38 EOS/ET Visits.

7.6.15.1. Screening (Days -28 to -8) Laboratory Tests

- Routine blood chemistry tests will include: glucose, total bilirubin, serum glutamic oxaloacetic transaminase/aspartate transaminase (SGOT/AST), serum glutamic pyruvic transaminase/alanine transaminase (SGPT/ALT), alkaline phosphatase, blood urea nitrogen, creatinine, amylase, total protein, uric acid, sodium, chloride, bicarbonate, potassium, calcium, phosphorous, albumin, triglycerides, cholesterol: low density lipoprotein (LDL) and high density lipoprotein (HDL).
- 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 for sympathomimetic amines (amphetamines; benzodiazepines; buprenorphine; cannabinoids; methadone; cocaine (metabolites); opiates (except barbiturates for AED medication).
- Blood test for the presence of 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.
- Pregnancy test, females only (plasma or urine).
- Optional: DNA sample for genomic screening.

7.6.15.2. Week 6, Week 14, and Week 38 (±3 days) Laboratory Tests

- 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.
- 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.
- Pregnancy test, females only (plasma or urine).

7.6.15.3. End of Study Visit or Early Termination

- Each patient will have an End of Study Visit/ET completed at Week 38. 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.
- 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.
- Pregnancy test, females only (plasma or urine).

7.6.16. Unscheduled Visits

If the skin irritation score is >'0' at Week 38, and weeks 40 or 41 for patients taking AED medications, the patient will have Unscheduled Visit(s) until the skin irritation score is rated as '0' (no erythema). The following assessments will be completed at the Unscheduled Visit:

- Concomitant medication review
- Vital signs
- C-SSRS
- Site review of patient Skin Irritation Diary
- Skin irritation examination
- Adverse event review

7.6.17. Hepatitis/HIV Screen

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

7.6.18. Pregnancy Test

Pregnancy tests will be collected at Screening, Week 6, and Week 14/EOS/ET Visits for female patients of child bearing potential. Any patient that is pregnant will be excluded or discontinued from the study, as applicable. Pregnancy test can be plasma or urine.

7.6.19. Toxicology Screen

Urine drug screen for sympathomimetic amines (amphetamines; benzodiazepines; buprenorphine; cannabinoids; methadone; cocaine (metabolites); and opiates (except barbiturates for AED medication) will be done at Screening. In addition, a blood test for the presence of ethanol will be done at Screening. A positive toxicology screen will result in excluding the patient from the study.

7.6.20. Blood Samples for Valproic Acid

At Screening, Week 6, Week 14, and Week 38 EOS/ET Visits, patients will have blood drawn for plasma level of their valproic acid (for patients receiving valproate or valproic acid).

All effort should be made to obtain a trough sample for the valproate/valproic acid. AED name, time taken, and amount and date of the last dose will be captured before the blood samples are collected. At each monthly visit, the Investigator will review the valproic acid (for patients receiving valproate or valproic acid) level and the dose of concomitant AEDs in the event they require adjusting if the patient experiences AEs that warrant a dose change.

7.6.21. Blood Sample for CBD/THC PK

At the Screening Visit, Week 6/Visit 3 and Week 14/Visit 4, and Week 38/Visit 7 EOS/ET, blood will be drawn for a trough plasma level for the determination of CBD/THC. All PK blood samples will be collected pre-dose.

7.6.22. Telephone Follow-up at Week 10

There will be a Telephone Follow-up call at Week 10 only for patients who had their dose adjusted at Week 6. The purpose of the call is to confirm the patient is tolerating the increased dose. Concomitant medications and adverse events will be reviewed at the Telephone Follow-up call, along with enquiring about patient skin irritation.

7.7. Study Questionnaires and Scales

7.7.1. Assessments of 22qDS Symptomatology

The same site rater should be used for all clinician-reported assessments across all visits. The same parent/caregiver should be used for all parent/caregiver-reported assessments across all visits.

7.7.2. Aberrant Behavior Checklist-Community (ABC-C)

The Aberrant Behavior Checklist- Community, 2nd Edition, will be completed by the parent/caregiver, with support from the site staff, at Screening, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 EOS/ET. The ABC-C asks responders to rate behaviors from "0 - not at all a problem" to "3 - the problem is severe in degree" across 58 questions. Use of the checklist has been validated in a variety of clinical populations.

7.7.3. Autism Diagnostic Observation Schedule® (ADOS®-2)

The ADOS (Western Psychological Services) is a semi-structured assessment of communication, social interaction and play or imaginative use of materials for individuals suspected of having 22qDS or other pervasive developmental disorders from 12 months through adulthood (Lord et al. 2000). The ADOS®-2 consists of various activities to allow the observation of social and communication behaviors related to the diagnosis of pervasive developmental disorders. The ADOS®-2 includes five modules for use with different age groups and language level. In this version, a Toddler Module has been included. For this patient population, the appropriate module will be utilized based on age and language level. Each subject will be administered one module. The assessment is administered by a certified rater and requires 35 to 40 minutes to complete. The ADOS®-2 is a diagnostic tool and this information will be used to document the presence of autism or other pervasive developmental disorders. This assessment will only be administered at sites with qualified individuals based on the publisher's criteria. The ADOS®-2 will be completed at Screening.

7.7.4. Clinical Global Impressions Scale-Severity and Improvement

The Clinical Global Impression Scales, Severity (CGI-S) and Improvement (CGI-I), are commonly used in clinical trials (Leigh et al. 2013) as they allow the clinician to utilize the history from the caregiver and incorporate the score into a clinical rating for the severity of symptoms.

CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1 - normal, not at all ill; 2 - borderline mentally ill; 3 - mildly ill; 4 - moderately ill; 5 - markedly ill; 6 - severely ill; or 7 - extremely ill. CGI-S will be assessed at Screening, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 EOS/ET to judge the severity of the symptoms of 22qDS at the onset of and throughout the study.

CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a Baseline state at the beginning of the intervention and rated as: 1 - very much improved; 2 - much improved; 3 - minimally improved; 4 - no change; 5 - minimally worse; 6 - much worse; or 7 - very much worse. Information from both the clinician and the parent/caregiver history are incorporated into a clinical rating. CGI-I will be assessed at Visit 3 and Visit 4/EOS/ET.

7.7.5. Columbia Suicide Severity Rating Scale (Children's Version)

The C-SSRS (Children's version) is to be completed at Screening, all study visits including Unscheduled Visits. The C-SSRS assessment will be conducted only if the patients are of an appropriate age (6 years or older) and capable of understanding and answering the questions in the Investigator's opinion. For patients under the age of 6 or who are not capable of understanding and answering the questions in the Investigator's opinion, the Investigator will consider the trend in ABC-C Irritability when assessing the risk of self-harm for an individual patient.

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 an SAE.

7.7.6. Anxiety, Depression, and Mood Scale (ADAMS)

The Anxiety, Depression, and Mood Scale will be completed by the parent/caregiver, with support from the site staff, at Screening, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 EOS/ET. The ADAMS will be used as a comprehensive assessment of anxiety, depression, and mood among the FXS patients. The ADAMS is comprised of 28 items, which are rated on a scale of "0 - not a problem" to "3 - severe problem." The ADAMS yields a total score as well as five subscale scores: "Manic/Hyperactive Behavior," "Depressed Mood," "Social Avoidance," "General Anxiety," and "Compulsive Behavior." The ADAMS has been validated and has demonstrated good internal consistency and test-retest reliability. Interrater reliability has been shown to be satisfactory (Esbensen et al. 2003).

7.7.7. Qualitative Caregiver Behavioral Problems Survey

At the Screening Visit, the parent/caregiver will be asked the following question "What are the three behavioral, emotional, or social problems that most impacted your son/daughter and his/her family in approximately the past year?" At Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 EOS/ET the parent/caregiver will be reminded of their responses at the Screening Visit in order to rate the three questions for improvement or worsening.

7.7.8. Children's Sleep Habit Questionnaire (CSHQ)

The Children's Sleep Habit Questionnaire will be completed by the parent/caregiver at Screening Visit 4, and Visit 7 EOS/ET. The parent/caregiver will complete a questionnaire comprised of 33 questions about their child's sleep habits and possible difficulties with sleep. They will be asked to think about the past week in your child's life when answering the questions. If last week was unusual for a specific reason (such as their child had an ear infection and did not sleep well or the TV set was broken), they will choose the most recent typical week. They will:

- Answer USUALLY if something occurs 5 or more times in a week.
- Answer SOMETIMES if it occurs 2-4 times in a week.
- Answer RARELY if something occurs never or 1 time during a week.

Parent/caregiver will also indicate whether or not the sleep habit is a problem by circling "Yes", "No," or "not applicable (N/A)".

7.7.9. Pediatric Anxiety Rating Scale – Revised (PARS-R)

The PARS-R will be completed at Screening, Weeks 14, 22, 30, and Week 38. The patient must have a severity score of 10 or higher at Screening and Visit 2 in order to be eligible for participation.

The PARS-R is a clinician-rated caregiver interview that covers 61 behaviors related to anxiety (Riddle, Ginsburg, Palapattu, &Walkup 2004, Riddle et al. 2002). The PARS-R provides broad coverage of separation anxiety, social phobia, and generalized anxiety. Symptoms are further categorized into Social Interactions or Performance Situations, Separation, Generalized, Specific Phobia, Panic Symptoms/Physical Signs, Obsessive-Compulsive, Health/Illness Concerns, and Other. The interviewer assesses the severity by quantifying the frequency and degree of interference and avoidance in family, school and community settings. Each of seven severity items is scored on a scale of 1 to 5, with 5 being the most severe and frequent. The final score is the sum of five of the seven severity items. The five item scale is recommended for use during treatment studies (Riddle et al. 2004, Riddle et al. 2002). Studies show excellent inter-rater reliability (even across sites kappa .87-.90) and test retest reliability after 3 to 8 weeks in 49 individuals with FXS ages 5 to 35 years of age (Russo- Ponsaran et al. 2014 AJIDD). The PARS-R correlates well with other anxiety measures (Russo-Ponsaran et al. 2014) and has been used in clinical trials in individuals with Autism Spectrum Disorder ASD (Storch et al. 2014) and is currently being utilized in several trials in FXS.

7.8. End of Study / Early Termination Visit

All patients will complete the EOS/ET Visit assessments at Week 38. Patients not taking AEDs will only have a morning dose of study drug at the Week 38 Visit before discharge from the study. The following will be completed at the EOS/ET Visit:

- Laboratory and urinalysis tests as defined in Section 7.6.15.3.
- Concomitant medication review
- Physical/neurological examination
- Vital signs
- 12-lead ECG
- Pregnancy test (females only)
- Collection and site review of patient Daily Skin Irritation Diary (diary for AED patients will also be collected Week 16 or 17)
- CBD/THC plasma sample drawn
- Valproic acid plasma sample drawn (for patients taking valproate or valproic acid)
- Skin irritation examination
- Adverse event review
- Completion of patient questionnaires and scales – refer to Table 5 and Table 6 in Section 7.7
- Study drug will be applied (last dose for patients not taking AED medication, not applicable to ET patients)

Patients not on AEDs who are prematurely discontinued will complete the early termination procedures at Visit 7 EOS/ET.

Patients taking valproate or valproic acid for treatment of seizures or epilepsy including patients who prematurely discontinue, will taper their current study dose in the following manner beginning at Visit 7 EOS/ET. Should patients taking AEDs at the EOS continue to receive drug through Special Access (if available) they will not taper their dose.

- Participants who weigh 35 kg or less and were receiving 250 mg daily dose of ZYN002, will be reduced to 125 mg daily dose over one week. Only one sachet will be applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 40.
    - If the participant's dose was increased at Week 6 to 500 mg daily dose of ZYN002, the dose will be reduced to 250 mg daily dose over one week with 2 sachets applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 40.
- Participants who weigh 35 kg or more and were receiving 500 mg daily dose of ZYN002, will be reduced over two weeks. During the first week the dose will be reduced to 125 mg two times a day (applied 12 hours apart) which will make the total daily dose 250 mg. This is one sachet in the morning and one sachet in the evening. During the second week, the dose will decrease to 125 mg daily dose, which means one sachet each day for a week applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 41.

    - If the participant's dose was increased at Week 6 to 750 mg daily dose of ZYN002, the dose will be reduced to 375 mg daily dose during the first week with one sachet applied in the morning and 2 sachets applied every evening. During the second week, the dose will decrease to 250 mg daily dose, which means 2 sachets each day for a week applied each day around the same time in the evening. After the taper, the participants will discontinue from the study at Week 41.

- Patients tapering their dose will have all Visit 7 EOS/ET assessments completed.
- At Week 38, patients will have their original dose in the morning and will have their evening dose as their new tapered dose.
- Patients will return at Week 40 or 41 and have the following assessments completed:
    - Concomitant medication review
    - Vital signs
    - Targeted physical exam if investigator deems clinically relevant
    - Pregnancy test (females only)
    - C-SSRS administered
    - Collection and review of Skin Irritation Diary
    - Skin irritation examination
    - Adverse event review

Patients having a skin irritation score > '0' at Week38 will continue to be followed through Unscheduled Visits until the skin irritation score is recorded as '0' (no erythema).

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

Patients must qualify based on meeting all of the inclusion and none of the exclusion criteria to be eligible to enroll.

1. Male or female children and adolescents aged 4 to < 18 years, at the time of Screening.
2. Judged by the Investigator to be in generally good health at Screening based upon the results of a medical history, physical examination, and clinical laboratory test results. Laboratory results outside of the reference range must be documented as not clinically significant by the Investigator.
3. Patients must have a diagnosis of 22qDS confirmed by genetic testing, with or without autistic features.
4. Patients have a CGI-S score of 4 or higher at Screening and Visit 2.
5. Patients must have a severity score on the PARS-R of 10 or higher at Screening and Visit 2.
6. Patients with a history of seizure disorders must currently be receiving treatment with a stable regimen of one or two AEDs, or must be seizure-free for one year if not currently receiving AEDs.
7. If patients are receiving non-pharmacological behavioral and/or dietary interventions, they must be stable for three months prior to Screening.
8. Patients have a body mass index between 12–35 kg / m^2 (inclusive).
9. Patient has demonstrated stable calcium levels for one year prior to Screening.
10. Females of childbearing potential must have a negative pregnancy test at the Screening Visit and a negative pregnancy test at all designated study visits.
11. Patients and parents/caregivers agree to abide by all study restrictions and comply with all study procedures.
12. Patients and parents/caregivers must be adequately informed of the nature and risks of the study and give written informed consent (and assent if applicable) prior to Screening.
13. Parents/caregiver(s) must provide written consent to assist in study drug administration.
14. In the Investigator's opinion, patients and parents/caregivers are reliable and willing and able to comply with all protocol requirements and procedures.

8.2. Patient Exclusion Criteria

Any of the following is considered criterion for exclusion:

1. Females who are pregnant, nursing, or planning a pregnancy; females of childbearing potential and male patients with a partner of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined below for the duration of therapy and for three months after the last dose of study medication.
    a. Standard acceptable methods of contraception include abstinence or the use of a highly effective method of contraception, including hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom, vasectomy, or intrauterine device.
2. History of significant allergic condition, significant drug-related hypersensitivity, or allergic reaction to any compound or chemical class related to ZYN002 or its excipients.
3. Exposure to any investigational drug or device ≤ 30 days prior to Screening or at any time during the study.
4. Patient has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 2 times the upper limit of normal (ULN) or has alkaline phosphatase levels ≥ 3 times the ULN as determined from Screening safety laboratories.
5. Use of cannabis or any THC or CBD-containing product within three months of Screening Visit or during the study.
6. Patient has a positive drug screen for sympathomimetic amines (amphetamines (unless prescribed); benzodiazepines; buprenorphine; cannabinoids; methadone; cocaine (metabolites); and opiates; (excludes barbiturates used as AED medication), including ethanol.
7. Patient is using the following AEDs: clobazam, phenobarbital, ethosuximide, felbamate, carbamazepine, phenytoin, or vigabatrin.
8. Patient is using any strong inhibitor/inducer of CYP3A4 or sensitive substrate for CYP3A4 including but not limited to 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, pimozide, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinioin, vincristine, vinorelbine, St. John's Wort, and grapefruit juice/products.
9. Patient with diagnosis of known genetic disorder, other than 22qDS (i.e. Prader-Willi Syndrome, Angelman Syndrome, Fragile X Syndrome, Rett Syndrome etc.).
10. Patient has diagnosis of DiGeorge or Velocardiofacial syndrome without the presence of 22qDS.
11. Patient has a primary psychiatric diagnosis other than 22qDS or anxiety, including bipolar disorder, psychosis, schizophrenia, post-traumatic stress disorder (PTSD) or major depressive disorder.
12. Patient is on stable treatment of > 6 months of not more than two psychoactive medications at screening or throughout the study (with the exception of one psychoactive medication prescribed for sleep).
13. Patient has an advanced, severe, or unstable disease that may interfere with the study outcome evaluations.
14. Patient is expected to initiate or change pharmacologic or non-pharmacologic

interventions during the course of the study.

15. Patient has an acute or progressive neurological disease, or any psychiatric disorder or severe mental abnormalities that are likely to require changes in drug therapy or interfere with the objectives of the study or ability to adhere to protocol requirements.
16. Patient has a positive result for the presence of HBsAg, HCV, or HIV antibodies.
17. Patients at risk of needing cardiovascular surgical repair within the upcoming12 months.
18. Patient has unstable cardiovascular disease, such as advanced arteriosclerosis, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, cardiac conduction problems, exercise-related cardiac events including syncope and pre-syncope, risk factors for Torsades de pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT Syndrome), other serious or other clinically unstable cardiac problems as indicated by history, physical examination or ECG.
19. 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 medication.
20. 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 absorption of the study drug.
21. History of treatment for, or evidence of, drug abuse within the past year.
22. Patient responds “yes” to Question ‘4’ or ‘5’ on the C-SSRS (Children) during Screening or at any time on study.

8.3. Randomization Criteria

Not applicable as this is a single-arm study.

8.4. 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 after receiving study drug, the reason(s) must be stated on the CRF, and a final evaluation of the patient should be performed.

The Investigator and/or Sponsor may discontinue any patient’s participation for any reason including (not all inclusive): any adverse event, clinically significant worsening in seizure frequency, adverse change in any laboratory test, or failure to comply with the protocol. Laboratory 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 will not be replaced. All effort must be made to ensure that the End of Study/Early Termination Visit procedures are completed at the time of discontinuation.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

ZYN002 is pharmaceutically manufactured CBD in a clear permeation-enhanced gel formulation. The drug product will be supplied as a 4.2% w/w gel contained in a foil-lined sachet. Each sachet is nominally filled to dispense 2.98 g of gel. The gel will be applied to clean, dry, intact skin of the upper arms/shoulders and can temporarily be applied to the right and left thighs. The study drug treatment dosing volumes are as follows:

- Patients ≤ 35 kg will receive 125 or 250 mg CBD applied Q12H (± 2 hours); total daily dose of 250 or 500 mg CBD. Each application will consist of **one sachet or two sachets** of ZYN002 CBD 4.2% concentration, containing 2.98 g of gel. Dosing is up to 38 weeks.
- Patients >35 kg will receive 250 or 375 mg CBD applied Q12H (±2 hours); total daily dose of 500 or 750 mg CBD. Each application will consist of **two or three sachets** of ZYN002 CBD 4.2% concentration, each sachet containing 2.98 g of gel. Dosing is up to 38 weeks.

The last date of study drug treatment will be collected and recorded in the CRF.

9.2. Concomitant Medications

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

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

Refer to the following site for examples of strong inhibitors/inducers of CYP 3A4 and CYP 3A4 substrates with narrow therapeutic indexes:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

9.2.1. Concomitant Medications Allowed

Patients may take hormonal contraception and AEDs (not in the exclusion criteria) during study participation.

Patients on a stable treatment of >6 months are allowed two psychoactive medications at screening or throughout the study.

For the purposes of the protocol, the following sedative medications, when used as a single, bedtime dose – need not be considered one of the two allowed psychotropic medications:

- Clonidine
- Guanfacine
- Melatonin
- Diphenhydramine or other sedating antihistamine medications

9.2.2. Concomitant Medications Not Allowed

Other prescription or OTC medications may be taken as approved in advance by the investigator and recorded in the CRF.

The following medications are not allowed: any strong inhibitor/inducer of CYP3A4 or sensitive substrate for CYP3A4 including but not limited to 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, pimozide, quinidine, ranolazine, sirolimus, tacrolimus, temsirolimus, toremifene, tretinioin, vincristine, vinorelbine, St. John's Wort, and grapefruit juice/products.

In addition, the following AED medications are not allowed: clobazam, phenobarbital, ethosuximide, felbamate, carbamazepine, phenytoin, or vigabatrin.

9.3. Duration of Treatment

All patients will complete an initial Screening Visit, and participate in Period 1, 14-week Treatment Period. Patients that have made a ≥35% improvement on the ABC-C irritability subscale will be allowed to continue to Period 2 for an additional 24 weeks of treatment. Patients taking AEDs will have a Taper Period of an additional one or two weeks, unless they are transitioning to receive drug through Special Access, if available.

Patients will complete an EOS Visit at Week 38. Patients taking AEDs will return on Week 40, or Week 41 when they will be discharged from the study, unless the skin irritation score is > '0', the patient will continue to be followed through an Unscheduled Visit until the skin irritation score is recorded as '0' (no erythema). At this time, the patient will be discharged from the study.

9.4. 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 study site visit to last until their next study visit.

All parents/caregivers will be provided with a sufficient supply of study drug for the patient during their site visit. Up to a 7-Day Replacement kit(s), containing the patient's assigned study drug, will also be supplied at each visit, as needed during the study. The Replacement kit(s) are to be returned at each study visit so that drug accountability can be performed. The Replacement

kits are to be used in situations where a visit is outside the visit window and the patient requires additional study drug prior to a visit and/or study drug is inadvertently lost/damaged/destroyed. Parents/caregivers will bring the used and unused sachets, in the baggies provided, to each visit. The site will perform drug accountability (if all sachets were completely or partially utilized) at each study visit and record compliance for the previous visit.

At Week 38, patients taking concomitant AED's for treatment of seizures or epilepsy, will be provided a one or two-week supply to complete the Tapering Period (Weeks 39 and/or Week 40), unless they are transitioning to receive drug through Special Access, if available. Patients will bring their used and unused sachets to the site at each study 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 last visit.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

ZYN002 is a transdermal pharmaceutically manufactured cannabidiol gel. It is a clear transdermal gel containing a 4.2% w/w concentration of CBD for topical application.

10.2. Study Drug Packaging and Labeling

ZYN002 drug product will be packaged in sachets.

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

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

10.3. Study Drug Storage

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

10.4. Study Drug Preparation

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

10.5. Administration

The site will instruct parents/caregivers on how to apply the gel and the first dose of study drug will be applied by the parent/caregiver at the Day 1 visit, and at each subsequent study visit. Patients will be instructed to withhold their morning dose of ZYN002 until a blood sample is collected at Week 6. Week 14 and Week 38 EOS/ET.

Patients will be permitted to shower or clean the application site(s) area up to 30 minutes prior to the study dose.

Parents/caregivers will use gloves (supplied by the Sponsor) to apply the study drug. Parents/caregivers will apply all study drug to clean, dry, intact skin, thoroughly massaging it into the right and/or left upper arms and shoulders until the area is dry. The study drug will be rubbed in completely and must be dry prior to dressing.

Patients should keep the application site dry for six hours but may apply an approved moisturizing lotion (Cetaphil), provided by the Sponsor, two hours after dosing. The application site should be covered to minimize sun exposure when going outside during the day. Sunscreen at the application site may be used two hours after dosing. If redness occurs at the application site, the parent (after consultation with the Investigator) may switch the application site temporarily to the upper thighs.

10.6. Study Drug Accountability

Patients will bring the unused and used sachets to the site at each study 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 with study drug application since the previous visit.

10.7. Study Drug Handling and Disposal

Used sachets will be placed in baggies (provided by Sponsor). Unused sachets should be returned in the way in which they were dispensed (box and/or baggies). For drug accountability purposes the patient number, initials and Visit number will be written on the outside of the box/baggie.

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

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Patient safety will be monitored at each study visit using standard measures, including physical and neurological exams, examination of skin at application sites for irritation, vital signs (including oral, infrared forehead or tympanic temperature), 12-lead ECGs, the C-SSRS, safety laboratory tests, urinalysis, and AE monitoring.

11.2. 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 parent/patient's response to how they are feeling. Patients having TEAEs will be followed until they return to normal or become stabilized.

All TEAEs that occur during the course of the study must be reported in detail on the appropriate CRFs, patient's source document record, and on any other report form required by National Law. All efforts will be made to follow-up adverse events until resolution.

11.2.1. Definition of Adverse Events

11.2.1.1. 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 CRF

page and on any other report form required by national law. All TEAEs must be followed to a satisfactory resolution.

All AEs will be collected from study Screening until the patient is discharged from the study.

Application site irritation scores 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 study. 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 participant, the necessary information must be collected from the participant, while respecting the confidentiality of the partner.

Although pregnancy occurring in a clinical study 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. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

The date of onset and resolution of the adverse event will be collected.

11.2.1.2. 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.

11.3. Relationship to Study Drug

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

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

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

11.4. Adverse Event Severity

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

Intensity will be assessed according to the following scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.1.2 . An AE of severe intensity may not be considered serious.

11.5. 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 email.

24 Hour SAE Telephone:	+1 919-265-4976
Email:	saereport031@zynerba.com

The definition for a ‘protocol defined expedited event’ for the purposes of this study is a Skin Irritation score of ‘4’, “intense erythema with edema and blistering/erosion” (see Table 7).

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 CRF and/or study file.

All SAEs (related and unrelated) will be followed from the signing of the ICF until the End of Study Visit, 30 days post last dose of study drug or the patient is lost to follow up (whichever comes last). Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator up to 30 days after the study should be reported. All SAEs must be reported to the Sponsor within one business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a PDF copy by email to the Sponsor.

The Sponsor representative is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator’s responsibility to notify the HREC 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 study. Each site is responsible for notifying its HREC of these additional SAEs.

12. PHARMACOKINETIC ASSESSMENTS

12.1. Blood Sample Collection

A 2-3 -mL blood sample (trough) for PK analysis of CBD/THC will be collected into sodium heparin tubes at Screening, pre-dose on study Visit 3/Week 6, Visit 4/Week 14, and Visit 7/Week 38 EOS/ET Visits.

In addition, a separate blood sample for valproic acid levels (for patients taking valproate or valproic acid for treatment of seizures or epilepsy) will be collected at Screening, Week 6, 14, and Week 38 EOS/ET Visits. Valproic acid samples will be analyzed by a local laboratory. For patients receiving valproate/valproic acid medication and having a Taper Period their final blood draw for PK and valproic acid levels will be taken at Week 38.

PK blood samples for CBD/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 standard polypropylene cryovial tubes for the plasma aliquots. 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 a lab chosen by the Sponsor.

An inventory of the samples shipped will accompany the package.

12.2. 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/THC concentrations in plasma.

Plasma samples for valproic acid will be analyzed through a local laboratory.

All analysis will be completed to Good Laboratory Practice (GLP) standards. Plasma PK and valproic acid results will be provided in a separate bioanalytical report.

Additional analysis of collected plasma may be conducted to investigate the metabolism of CBD. If conducted, the results from the metabolite investigation will be reported separately in a stand-alone report. Additionally, quantitation of selected metabolites from collected plasma may be conducted.

13. STATISTICS

13.1. Determination of Sample Size

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

13.2. Analysis Populations

13.2.1. Intent-to-Treat Population

All efficacy assessments taken at study Weeks 6, 14, 22, 30, and 38 will be summarized by dose for each patient.

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 received at least one application of study drug and have plasma concentration obtained from at least one of the Treatment Period evaluations (Week 6, Week 14, and Week 38 EOS/ET).

13.3. Efficacy Analysis

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) for continuous data and number (n) and percentage (%) for categorical data will be presented for all efficacy and safety parameters.

Baseline will be defined as the last assessment prior to the first dose of ZYN002.

All efficacy assessments will be summarized by dose for each patient.

13.4. Pharmacokinetic Analyses

13.4.1. PK Sample for Determination of CBD/THC

The following PK parameters for determination of CBD/THC 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 at ach nominal blood sampling time (Screening, pre-dose Week 6, 14, and Week 38 EOS/ET. Analyses for CBD metabolites are exploratory and may be conducted.

13.4.2. PK Sample Determination of Valproic Acid

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

- Plasma concentration occurring at Screening, pre-dose Week 6, 14, and Week 38 EOS/ET.
- Elapsed time between last valproate/valproic acid 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 valproic acid plasma trough concentrations and elapse time will be presented at each nominal PK sampling time.

13.5. Statistical Methods

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) for continuous data and number (n) and percentage (%) for categorical data will be presented for all efficacy and safety parameters.

All efficacy assessments will be summarized at Weeks 6, 14, 22, 30, and 38.

Vital sign assessments (actual and change from screening) taken at study Day 1, Weeks 6, 14, 22, 30, and 38 will be summarized using descriptive statistics and presented by maintenance dose.

ECGs (actual and change from Screening) will be summarized by actual treatment group. ECG results including any clinically significant findings will be summarized at each study visit.

Safety laboratory and urinalysis assessments taken at Week 6, 14, and Week 38 (actual and change from screening) will be summarized by treatment at the time of the assessment.

Application site irritation will be summarized using counts and percentages for each respective site irritation score (0, 1, 2, 3, or 4) by dose at the time of assessment.

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

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

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

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

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

14.2. Audits and Inspections

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

15. 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 CRFs with that recorded in the original patient records. In this study, source document review of specific types of information will be conducted for all patients.

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor or their representative may conduct a quality assurance audit. Please see Section 17 for more details regarding the audit process.

16. ETHICS

16.1. Human Research Ethics Committee (HREC)

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 a HREC. HREC approval of the protocol, ICF and patient information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require HREC approval prior to implementation of any changes made to the study design.

16.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki and GCP guidelines. The investigator is responsible for reporting to the HREC 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, HREC approvals, protocols, and CRFs.

16.3. Patient Information and Informed Consent

The study protocol and ICF must be approved by the investigator's HREC and a copy of the approved ICF must be supplied to the Sponsor.

The parent/caregiver will be asked to read the consent form. If the parent/caregiver decides that the patient should participate in the study, the parent/caregiver will be asked to sign and date the form as evidence of consent. Each parent/caregiver 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 parent/caregiver. The physician will document in the patient's medical chart that the parent/caregiver has signed an ICF to participate in an investigational study, a copy of the ICF will be given to the parent/caregiver, and the original should be retained with the patient's study records.

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

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

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

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

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

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20. APPENDICES

20.1. Application of ZYN02 Gel Instructions

The gel application instructions are attached.

ZYN2-CL-031 Gel Application Instructic

20.2. Skin Irritation Diary

The Skin Irritation Diary is attached.

ZYN2-CL-031 Daily skin check diary_V1_