Note to File

Study Title:	An Open-Label Tolerability and Efficacy Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome
Protocol Number:	ZYN2-CL-031.05
Compound:	ZYN002
Sponsor Name:	Harmony Biosciences
Legal Registered Address:	630 W. Germantown Pike, Suite 215 Plymouth Meeting, PA 19462 USA
Statistical Analysis Plan Date:	25 May 2022
Description:	Dosing was adjusted based on weight. Therefore, the decision was made to collect data as a single arm ("ZYN002") instead of by dose or by period because the dosing is not relevant to the interpretation of the study results and based on pharmacokinetic modeling, exposure is consistent across doses. The Protocol and Statistical Analysis Plan will not be updated. Instead, this Note to File has been written to state how data were collected.
Effective Date:	16 February 2026

Sponsor Signatory:

PPD

16 Feb 2026

PPD

Date

Executive Director, Regulatory Medical Writing
Harmony Biosciences
630 W. Germantown Pike, Suite 215
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STATISTICAL ANALYSIS PLAN

ZYN002 Cannabidiol (CBD)

Protocol Number: ZYN2-CL-031.05

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

Sponsor:

Zynerba Pharmaceuticals Pty., Ltd.
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Southbank, VIC 3006 Australia

Zynerba Pharmaceuticals Pty., Ltd.
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IND Number:	130876
Date of Plan:	25 May 2022
Based on:	Protocol Version Amendment 05 Dated: 17 August2022
Based on:	CRF Version Date: 01 November 2021

SIGNATURE PAGE

This document has been reviewed and accepted by:

PPD Development Project Manager Zynerba Pharmaceuticals	Signature	Date
PPD, Project Statistician The Griesser Group (TGG)	Signature	Date
PPD, MD Medical Monitor	Signature	Date

PROTOCOL 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
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 additional 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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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-\infty)}$	AUC from time zero (pre-dose) extrapolated to infinite time
$AUC_{(0-\tau)}$	AUC from time zero (pre-dose) to time of last observed quantifiable concentration within a subject across all treatments
BMI	Body mass index
C_{max}	Maximum observed concentration
CRF	Case Report Form
dy	Days
ECG	Electrocardiogram
g	Grams
ITT	Intent-to-Treat Population
Kg	Kilogram
mg	Milligrams
N	Total Sample Size
PK	Pharmacokinetic
s.d.	Standard Deviation
SAE	Serious Adverse Event
SAS	Statistical Analysis System
TGG	The Griesser Group
ULN	Upper Limit of Normal
WHO	World Health Organization

2. INTRODUCTION

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.

CBD is the primary non-psychoactive cannabinoid found in the Cannabis plant. 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 mono-ethyl ether (brand name: Transcutol® HP) is used as a permeation enhancer.

22q11.2 deletion syndrome, (also referred to as 22qDS or 22q) 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 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).

There is a clear need for well-tolerated, pharmacological treatments that provide significant clinical benefits in terms of ameliorating anxiety and associated socio-behavioral deficits, while demonstrating minimal clinically relevant negative side effects.

3. STUDY OBJECTIVE(S) AND ENDPOINT(S)

3.1. Primary Study Objective

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

3.2. Secondary and Exploratory Study Objectives

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.

4. STUDY DESIGN

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 22q. Male and female patients with 22q will be treated in Period 1 for 14 weeks.

Patients with less than a 25% improvement from baseline in the ABC-C Irritability subscale may have their total dose increased by the investigator 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. Only patients taking AED medications for treatment of seizures or epilepsy will have an additional one or two-week Taper Period.

Approximately 20 male and female patients, ages 4 to < 18 years, will receive ZYN002.

4.1. Definition of Study Drugs

This study has a 14-week treatment Period 1 and up to a 24-week extension (Period 2) 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.

4.2. Sample Size Considerations

4.2.1. Sample Size Justifications

This study is exploratory in nature and as such, no formal sample size was determined. This is the first study of ZYN002 being used for the indication of 22q. The sample size of 20 patients was deemed large enough to provide a reliable answer for the study objectives.

4.3. Randomization

N/A open label.

4.4. Clinical Scales and Questionnaires

The study questionnaires and scales administered are outlined in Table 2.

Table 2: ZYN2-CL-031 Scales and Questionnaires Administered

Scale	Screening	Visit 2, Day 1	Visit 3, Week 6	Visit 4, Week 14	Visit 5, Week 22	Visit 6, Week 30	Visit 7, Week 38	ET
Aberrant Behavior Checklist (ABC-C)	X	X	X	X	X	X	X	X
Autism Diagnostic Observation Schedule®-2 (ADOS®-2)	X							
Anxiety, Depression and Mood Scale (ADAMS)	X		X	X	X	X	X	X
Clinical Global Impression-Severity (CGI-S)	X	X	X	X	X	X	X	X
Clinical Global Impression-Improvement (CGI-I)			X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale – Children's version (C-SSRS)	X	X	X	X	X	X	X	X
Pediatric Anxiety Rating Scale – Revised (PARS-R)	X	X	X	X	X	X	X	X
Qualitative Caregiver Reported Behavioral Problems Survey	X		X	X	X	X	X	X
Children's Sleep Habit Questionnaire (CSHQ)	X			X			X	X

Assessments completed at Screening are found in Table 3, assessments completed for Period 1 are found in Table 4, and assessments completed for Period 2 are found in Table 5.

Table 3: 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

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

Table 4: 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 4: 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 - Period 1:

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 5: 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 - Period 2:

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.

5. PLANNED ANALYSES

5.1. Planned Interim Analyses

An interim analysis is planned at the conclusion of Period 1 (treatment week 14/Visit 4):

- Estimated Last patient enrolled 21 Feb 2022
- Estimated Last patient completing Period 1 31 May 2022
- Database Lock Period 1 06 June 2022
- Estimated Release of study Tables and Listings 10 June 2022

Data to be evaluated for interim analysis include the following.

- Disposition
- Demographics
- Baseline Characteristics
- Adverse Events
- Medical History
- Concomitant Medications
- Laboratory Data
- C-SSRS Data
- Efficacy scale data for Period 1 for the following scales and questionnaires:
  - ABC-C
  - ADAMS
  - CGI
  - PARS-R

The specific displays to be generated in Period 1 are identified with an "X" in Section 11. Any additional data required for the interim analysis will be produced by an Adhoc Summary Table.

5.2. Data included in Period 1 Analyses

The records to be included in the Period 1 analyses will include all records with a nominal visit of ≤ 4 (Week 14/ET). All summaries will include one column only identified as ZYN002.

In an attempt to include all Period 1 Concomitant Medications and Adverse Events in the Period 1 analyses TGG will need to calculate a Week 14 Date for both subjects who completed Period 1 and who discontinued in Period 1 before Week 14. This will be accomplished by the following steps using the last non-missing value as the actual or imputed Week 14 date:

a) If a subject completes Period 1 then use their actual Week 14 Date.

b) If a subject discontinues before Week 14 date and their last nominal visit is identified as Week 14/ET then add 'X' days to that date to get to Day 98 (7 times 14).

c) If Week 6, TGG will impute the Week 14 cutoff date to be the Week 6 date plus (7 times 8) to get the Week 14 imputed Date

d) If Day 1, TGG will impute the Week 14 date to be Day 1 plus (7 times 14)

Treatment emergent adverse events and concomitant medication summaries will include start dates that occur any time before treatment begins and treatment ends. Refer to Section 6.2.3.

5.3. Timeline Week 38 Final Analysis

- Estimated Last patient completing 6-month extension Period 2 — 14 November 2022
- Estimated Database Lock — 14 December 2022
- Estimated Release of study Tables and Listings — 31 January 2023

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages.

6.1. Day 1

Day 1 is the date of first dose of treatment with study drug.

6.1.1. Study Day

Study days will be numbered relative to the first day of study drug administration.

- Study days will be numbered relative to study start (i.e., ..., –2, –1, 1, 2, ...; with Day 1 being the start of study drug and Day –1 being the day before the start of study drug).
- The elapsed time since Day 1 for an event (e.g. onset of an adverse event) will be calculated as [date of event – date of Day 1 + 1].
- For the purpose of converting days to years or months, one year = 365.25 days, and one month = 30.44 days.

6.1.2. Baseline Value

Baseline is the last observed non-missing data prior to the first dose of study drug. Per the protocol, this should be the assessment on Day 1 before the first study drug dose with the exception of medical history, demographics, physical and neurological examinations, ECGs, and labs, which are assessed at the screening visit.

6.1.3. Enrollment Date

The date the patient was enrolled into the study (the baseline visit date).

6.1.4. End of Treatment Value

End of treatment value is the last non-missing post-baseline value for each patient.

6.2. Variable Definitions

6.2.1. Age

Patient age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1)/365.25

6.2.2. Body Mass Index

Body mass index (BMI) will be calculated as follows:

$$BMI\ (kg/m^2) = [weight\ (kg)] / [height\ (m)]^2$$

6.2.3. Prior and Concomitant Medication

A prior medication is defined as any non-study medication that started before the date of first dose of study drug.

Concomitant medication is defined as any non-study medication that:

- Started before the date of first dose of study drug and is ongoing throughout the study or ends on/after the date of first study medication administration.
- Started on/after the date of first dose of study drug and is ongoing or ends during the course of study medication.

The start/stop dates recorded in the CRF will be used to determine medication prior to or during the study. A medication can be considered both prior and concomitant if it was started prior to the first dose of study drug and continues to be taken after the first dose of study medication. Unresolved missing start dates will be handled as follows for determination of concomitance:

- Partial dates will be imputed in such a way as to consider the non-study medication as prior and/or concomitant if it is possible that the missing information could lead to a prior and/or concomitant outcome.

6.2.4. Treatment Emergent Adverse Events (TEAEs)

Treatment emergent adverse events (denoted as TEAE hereafter) are defined as adverse events with onset dates on or after the start of study drug.

All reports of adverse events should include the severity and relationship to study drug that are determined by the investigators. In the event of missing information, the following rules will be applied for the adverse event summaries:

- AEs with missing onset dates will be included as treatment- emergent (unless end date is prior to the first dose date)
- AEs with missing severity will be counted as severe in severity
- AEs with missing relationship to study drug will be counted as related

6.3. General Summary Table and Individual Subject Data Listing Considerations

All population summaries will be summarized on the safety analysis set unless otherwise noted.

6.3.1. Patient Disposition

The number of patients enrolled, patients in the safety analysis set, patients in the Modified intent-to-treat set, patients in the Pharmacokinetic set, patients who completed the study, and patients who discontinued the study, will be summarized using descriptive statistics. (Table 14.1.1).

Reasons for study discontinuation will also be summarized for patients who discontinued the study. The number of patients who entered the 6-month extension period will also be summarized. This summary will include the set of enrolled patients.

6.3.2. Demographics

The continuous variables of patient age, weight (kg), height (cm), and BMI (kg/m^2) will be summarized using descriptive statistics. The categorical variables of patient sex, ethnicity, and race will be summarized using descriptive statistics for each category (Table 14.1.2). Missing categories will be presented if necessary.

6.3.3. Baseline Characteristics

Diagnosis, etiology, time since diagnosis (informed consent date-date of diagnosis+1/365.25), ADOS, epilepsy diagnosis, female reproductive status, urine pregnancy test results for female patients of childbearing potential will be summarized (Table 14.1.3) using descriptive statistics.

6.3.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or greater. Patients with a medical history assessment, patients with at least one finding, and findings for each category will be summarized using descriptive statistics by system organ class, and preferred term (Table 14.1.4).

6.3.5. Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term (Table 14.1.5). Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken on or before the first dose date of study drug treatment.

6.3.6. Electrocardiogram

Electrocardiogram findings (normal, abnormal not clinically significant, abnormal clinically significant, and missing) at baseline will be summarized (Table 14.1.6) using descriptive statistics.

6.3.7. Physical Examination/Neurological Examination

Physical/Neurological examination findings for each body system will be summarized at baseline (Tables 14.1.7, 14.1.8) using descriptive statistics.

6.4. Analysis Populations

6.4.1. Safety Analysis Set

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.

6.4.2. Modified Intent-to-Treat (mITT)

Safety patients who have at least one post baseline (PBL) efficacy assessment will be included in the modified Intent-to-Treat population. mITT will be used for all efficacy assessments.

6.5. Pharmacokinetic Population

The PK population will consist of all patients who received at least one application of study drug and had a plasma concentration obtained from at least one post baseline assessment.

6.6. Efficacy Analysis

All efficacy analyses will be on the mITT Analysis Set.

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.

6.7. Exploratory Efficacy Analysis

This study is the first study of ZYN002 in 22q patients. As such, a primary efficacy endpoint was not selected. The primary *objective* is to analyze for safety and tolerability along with determining the most clinically meaningful efficacy data resulting from this study.

The first step will be to analyze change from baseline to the end of the 14-week treatment period (Period 1). The results of the change from baseline will guide the additional types of exploratory analysis to be completed.

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

The ABC-C instrument is a scale for rating inappropriate and maladaptive behavior of people with developmental disabilities, including intellectual disability and autism spectrum disorder (ASD), (Aman & Singh, 2017). Change and percent change from Baseline to Weeks 6, 14, 22, 30 and 38/ET in the ABC-C subscales of Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity Noncompliance, and Inappropriate Speech will be calculated. In addition, a t-test will be used to test if within treatment changes from baseline are different from 0. Responder analyses (25% and 35% improvement) from baseline to each visit in each subscale will be calculated.

The Aberrant Behavior Checklist - Community, 2nd Edition, is completed 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. ABC consists of five subscales as follows:

Table 6: ABC-C Subscale Scoring

Subscale Number	Subscale Name	Total Score for Response to Questions	Range
I	Irritability	2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50. 52, 57	0 to 45
II	Social Withdrawal	3, 5, 12, 16, 20, 23, 26, 30, 32, 37, 40, 42, 43, 53, 55, 58	0 to 48
III	Stereotypic Behavior	6, 11, 17, 27, 35, 45, 49	0 to 21
IV	Hyperactivity Noncompliance	1, 7, 13, 15, 18, 21, 24, 28, 31, 38, 39, 44, 48, 51, 54, 56	0 to 48
V	Inappropriate Speech	9, 22, 33, 46	0 to 12

Additionally, the ABC-C irritability subscale was used as criteria in order for patients to be eligible to participate in Period 2. Patients had to have a >35% irritability improvement in change from baseline to end of Period 1, in order to participate in the 6-month extension (Period 2).

6.7.1. 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 22q or other pervasive developmental disorders from 12 months through adulthood (Lord et al. 2000). The ADOS®-2 will be completed at Screening. The comparison score will be used to determine the level of 22q related symptoms as follows:

Low = 1 to 4 - no worse than mild autism symptoms
Moderate = 5 to 7 - moderate autism symptoms
High = 8 to 10 - high level of autism symptoms

6.7.2. Clinical Global Impression – Improvement, Severity Scales

The Clinical Global Impression Scales, Severity and Improvement, 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 (Table 7). 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 22q. Change and percent change from Baseline to Weeks 6, 14, 22, 30 and 38/ET in the CGI-S score will be calculated. In addition, a t-test will be used to test if within treatment changes from baseline are different from '0'.

Table 7: Clinician Global Impression-Severity (CGI-S) Scale

Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?

Score	Description
1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill

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, Visit 4, Visit 5, Visit 6 and Visit 7/EOS/ET. A summary of counts and percentages for each category will be tabulated at each post baseline visit. In addition, a shift table from baseline to each post baseline visit will be produced Table 8:

Table 8: Clinician Global Impression - Improvement (CGI-I) Scale

Rate total improvement whether or not, in your judgement, it is due entirely to study drug.

Compared to his condition at admission to the project, how much has he changed?

Score	Description	Category
1	Very much improved	Improved
2	Much improved	Improved
3	Minimally improved	Not improved
4	No change	Not improved
5	Minimally worse	Not Improved
6	Much worse	Not improved
7	Very much worse	Not Improved

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

The C-SSRS (Children's version) is to be completed at Screening and 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. Patient counts and percentages will be summarized for the C-SSRS.

6.7.4. 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. A listing will be prepared for the open text responses for the final analysis.

6.7.5. Children's Sleep Habit Questionnaire (CSHQ)

CSHQ will be evaluated for the change from Baseline to Week 38 (EOS/ET). The Children's Sleep Habit Questionnaire will be completed by the parent/caregiver at Screening 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)". A listing by patient of the questionnaire responses will be prepared along with a summary of change from baseline to EOS/ET.
Pharmacokinetic (PK) Analysis Set.

6.7.6. 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).

6.7.7. 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. PHARMACOKINETIC ANALYSES

7.1.1. 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 each 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.

7.1.2. PK Sample Determination of AED Medications

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 AED dose and the time of plasma sample collection.

Descriptive statistics (arithmetic mean, median, SD, minimum, maximum, coefficient of variation, geometric mean [plasma concentration]) for the AED plasma trough concentrations and elapse time will be presented at each nominal PK sampling time.

8. SAFETY ANALYSES

The safety analysis set will be used for all safety analyses. Study drug administration, AEs and concomitant medications will be summarized by treatment period (Period 1, 2, and overall).

8.1. Study Drug Administration

Number of Sachets Dispensed and returned will be summarized overall and for each Period. In addition, the duration of treatment will be summarized overall and for each period.

8.1.1. Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or greater. Treatment emergent adverse events (TEAEs) are defined as adverse events with onset dates on or after the first dose of study drug.

All AE summaries will include total number of TEAEs and total number of patients with AEs.

An overall summary of adverse events will include number (%) of patients reporting ≥ 1 TEAE (and number of TEAEs), TEAE by Severity (and number of TEAEs), treatment-related TEAEs (and number of TEAEs), SAEs (and number of TEAEs), TEAE by outcome (and number of TEAEs), TEAEs that resulted in treatment discontinuation (and number of TEAEs). In addition, the total number of TEAEs by subject will be summarized.

Additionally, summaries will be presented for all TEAEs by system organ class and preferred term (overall and by severity). TEAEs determined by the investigator to be treatment-related (overall and by severity). Serious AEs will also be summarized. Adverse events causing permanent discontinuation from treatment will be summarized, fatal adverse events will be summarized, and TEAEs by preferred term in descending order will be summarized.

The incidence of adverse events will be summarized using descriptive statistics by system organ class and preferred term. Patients are counted only once in each system organ class category, and only once in each preferred term category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by severity, patients and TEAEs are counted at the greatest severity.

AEs will be summarized separately for each treatment Period (1, 2) and overall (the whole study).

Listings for fatal AEs, serious AEs, and AEs leading to discontinuation, will also be presented.

8.1.2. Vital Signs

Vitals signs at each visit and changes from baseline to each visit will be summarized using descriptive statistics.

8.1.3. Electrocardiogram

ECG parameters at each visit and changes from baseline to each visit will be summarized using descriptive statistics. In addition, shifts in ECG's (normal, abnormal not clinically significant, abnormal clinically significant) from baseline to each visit will be summarized descriptively.

8.1.4. Physical Examination

Shifts (normal, abnormal, NCS, and abnormal CS) from baseline to each visit will be summarized using patient counts for each category.

8.1.5. Neurological Examination/Targeted Neurological Examination

Shifts (normal, abnormal NCS, and abnormal, CS) from baseline to each visit collected will be summarized using patient counts for each category in the neurological examination.

8.1.6. Clinical Laboratory Tests

Clinical labs (Chemistry, Hematology, Urinalysis, and Testosterone) results at each visit and change from baseline to each visit will be summarized using descriptive statistics. In addition, clinically significant chemistry and hematology labs will be summarized. In addition, shift tables for chemistry and hematology will be prepared.

8.1.7. Concomitant Medications

All concomitant medications will be coded using WHO Drug. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Concomitant medications will include all medications taken on or after Day 1.

Concomitant medications will be summarized separately for each treatment Period (1, 2) and overall (the whole study).

8.1.8. Patient Skin Irritation Score

The total number of patient skin irritation scores (0=No Skin redness to 4=Intense Redness with Blisters or Broken Skin) collected from the diary will be displayed within each treatment period overall and within 2-week intervals. The number of subjects with an assessment overall and within each 2-week period will be summarized. In addition, the total number of unique subjects for each category will be displayed.

8.1.9. Investigator Skin Irritation Score

The investigators skin irritation score (0=No Erythema to 4=Intense Erythema with Edema and Blistering/Erosion) for the left shoulder and upper arm and right shoulder and upper arm will be summarized using descriptive statistics.

8.1.10. Columbia Suicide Severity Rating Scale – Children's' (Baseline and Since Last Visit)

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

8.1.11. AED Medications

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

- Plasma concentration occurring at Day 1
- Elapse time between last AED dose and the time of plasma sample collection.

Descriptive statistics (arithmetic mean, median, SD, minimum, maximum, coefficient of variation, geometric mean [plasma concentration]) for the AED plasma trough concentrations and elapse time will be presented at each nominal PK sampling time: screening, pre-dose on study Visit 3/Week 6, Visit 4/Week 14, and Visit 7/Week 38 EOS/ET Visits.

8.1.12. CBD and THC Plasma Levels

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

- Steady-state plasma concentration occurring just prior to the next dose of ZYN002.
- Elapsed time between the last ZYN002 dose and time of plasma sample collection.

Descriptive statistics (arithmetic mean, median, SD, minimum, maximum, coefficient of variation, geometric mean [plasma concentration]) for the plasma trough concentrations and elapsed time will be presented for all patients combined at each nominal blood sampling time (pre-dose Weeks 6, 14, 38, and ET).

Exploratory analyses on the effect of CBD on plasma levels of AEDs, or vice versa, may be explored. Analyses for CBD metabolites are exploratory and may be conducted. CBD and THC plasma levels will be summarized at each visit using descriptive statistics.

9. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® Version 9 or higher. All data collected on the electronic case report form (eCRF) will be listed.

10. CHANGES FROM THE PROTOCOL

None identified.

11. LIST OF SUMMARIES AND LISTINGS

Summary Number	Title	Population	Period 1 Display
14.1.1	Summary of Patient Disposition	Enrolled	X
14.1.2	Summary of Demographics	Safety Analysis Set	X
14.1.3	Summary of Baseline Characteristics	Safety Analysis Set	X
14.1.4	Summary of Medical History	Safety Analysis Set	X
14.1.5	Summary of Prior Medications by Therapeutic Class and Preferred Term	Safety Analysis Set	X
14.1.6	Summary of Electrocardiogram Findings at Baseline	Safety Analysis Set	X
14.1.7	Summary of Physical Examination Findings at Baseline	Safety Analysis Set	X
14.1.8	Summary of Neurological Examination Findings at Baseline	Safety Analysis Set	X
14.2.1	Summary of Change from Baseline to Weeks 6, 14, 22, 30, and 38 in the ABC-C Checklist	mITT Analysis Set	X
14.2.2	Summary of 25% and 50% responders at Weeks 6, 14, 22, 30, and 38 in the ABC-C Checklist	mITT Analysis Set	X
14.2.3	Summary of Change from Baseline to Weeks 6, 14, 22, 30, and 38 in the ADAMS Checklist	mITT Analysis Set	X
14.2.4	Summary of Change from Baseline to Weeks 6, 14, 22, 30, and 38 in the CGI-S Scale	mITT Analysis Set	X
14.2.5.1	Summary of CGI-I at Baseline, Weeks 6, 14, 22, 30, and 38	mITT Analysis Set	X
14.2.5.2	Shifts from Baseline to Weeks 6, 14, 22, 30 , and 38 in CGI-I	mITT Analysis Set	X
14.2.6.1	Summary of Change from Baseline to Weeks 6, 14, 22, 30, and 38 in the PARs-R Scale	mITT Analysis Set	X
14.2.6.2	Summary of Shifts from Baseline to Weeks 6, 14, 22, 30, and 38 in CGI –I Categories (≤52 and > 52)	mITT Analysis Set	X
14.3.1.1.1	Summary of Sachet Information (Period 1)	Safety Analysis Set	X
14.3.1.1.2	Summary of Study Drug Duration (Period 1)	Safety Analysis Set	X
14.3.1.2.1	Summary of Sachet Information (Period 2)	Safety Analysis Set	
14.3.1.2.2	Summary of Study Drug Duration (Period 2)	Safety Analysis Set	
14.3.1.3.1	Summary of Sachet Information (Overall)	Safety Analysis Set	
14.3.1.3.2	Summary of Study Drug Duration (Overall)	Safety Analysis Set	
14.3.2.1.1	Overall Summary of Treatment Emergent Adverse Events (Period 1)	Safety Analysis Set	X
14.3.2.1.2	Overall Summary of Treatment Emergent Adverse Events (Period 2)	Safety Analysis Set	
14.3.2.1.3	Overall Summary of Treatment Emergent Adverse Events (Overall)	Safety Analysis Set	
14.3.2.2.1	Summary of Treatment Emergent Adverse Events by System Organ Class, and Preferred Term (Period 1)	Safety Analysis Set	X
14.3.2.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class, and Preferred Term (Period 2)	Safety Analysis Set	
14.3.2.2.3	Summary of Treatment Emergent Adverse Events by System Organ Class, and Preferred Term (Overall)	Safety Analysis Set	
14.3.2.3.1.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Period 1)	Safety Analysis Set	X
14.3.2.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity Including All Events by Treatment Group (Period 1)	Safety Analysis Set	X

Summary Number	Title	Population	Period 1 Display
14.3.2.3.2.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Period 2)	Safety Analysis Set	
14.3.2.3.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity Including All Events by Treatment Group (Period 2)	Safety Analysis Set	
14.3.2.3.3.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Overall)	Safety Analysis Set	
14.3.2.3.3.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity Including All Events by Treatment Group (Overall)	Safety Analysis Set	
14.3.2.4.1	Summary of Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term (Period 1)	Safety Analysis Set	X
14.3.2.4.2	Summary of Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term (Period 2)	Safety Analysis Set	
14.3.2.4.3	Summary of Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term (Overall)	Safety Analysis Set	
14.3.2.5.1	Summary of Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Period 1)	Safety Analysis Set	X
14.3.2.5.2	Summary of Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Period 2)	Safety Analysis Set	
14.3.2.5.3	Summary of Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Overall)	Safety Analysis Set	
14.3.2.6.1	Summary of Serious Adverse Events by System Organ Class, Preferred Term (Period 1)	Safety Analysis Set	X
14.3.2.6.2	Summary of Serious Adverse Events by System Organ Class, Preferred Term (Period 2)	Safety Analysis Set	
14.3.2.6.3	Summary of Serious Adverse Events by System Organ Class, Preferred Term (Overall)	Safety Analysis Set	
14.3.2.7.1	Summary of Adverse Events Leading to Treatment Discontinuation by System Organ Class, Preferred Term (Period 1)	Safety Analysis Set	X
14.3.2.7.2	Summary of Adverse Events Leading to Treatment Discontinuation by System Organ Class, Preferred Term (Period 2)	Safety Analysis Set	
14.3.2.7.3	Summary of Adverse Events Leading to Treatment Discontinuation by System Organ Class, Preferred Term (Overall)	Safety Analysis Set	
14.3.2.8.1	Summary of Fatal Adverse Events by System Organ Class, Preferred Term (Period 1)	Safety Analysis Set	X
14.3.2.8.2	Summary of Fatal Adverse Events by System Organ Class, Preferred Term (Period 2)	Safety Analysis Set	
14.3.2.8.3	Summary of Fatal Adverse Events by System Organ Class, Preferred Term (Overall)	Safety Analysis Set	
14.3.2.9.1	Summary of Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency (Period 1)	Safety Analysis Set	X
14.3.2.9.2	Summary of Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency (Period 2)	Safety Analysis Set	
14.3.2.9.3	Summary of Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency (Overall)	Safety Analysis Set	
14.3.3	Summary of Vital Signs by Visit	Safety Analysis Set	X
14.3.4.1	Summary of Electrocardiogram by Visit	Safety Analysis Set	X
14.3.4.2	Summary of Shifts from Baseline to Each Visit in Electrocardiogram Findings	Safety Analysis Set	X
14.3.5.1	Summary of Shifts from Baseline to each Visit in Physical Exam Findings	Safety Analysis Set	X

Summary Tables, continued

Summary Number	Title	Population	Period 1 Display
14.3.5.2	Summary of Shifts from Baseline to each Visit in Neurological Exam Findings	Safety Analysis Set	X
14.3.5.3	Summary of Shifts from Baseline to each Visit in Chemistry and Hematology	Safety Analysis Set	X
14.3.6.1.1	Summary of Chemistry Laboratory Results and Changes from Baseline to Each Visit	Safety Analysis Set	X
14.3.6.1.2	Summary of Clinically Significant Chemistry Laboratory Values	Safety Analysis Set	X
14.3.6.2.1	Summary of Hematology Laboratory Results and Changes from Baseline to Each Visit	Safety Analysis Set	X
14.3.6.2.2	Summary of Clinically Significant Hematology Laboratory Values	Safety Analysis Set	X
14.3.6.3	Summary of Urinalysis Laboratory Values	Safety Analysis Set	X
14.3.6.4	Summary of Testosterone Laboratory Values	Safety Analysis Set	X
14.3.7	Summary of Concomitant Medications by Therapeutic Class and Preferred Term	Safety Analysis Set	X
14.3.8.1	Summary of Patient Monthly Skin Irritation Scores	Safety Analysis Set	
14.3.8.2	Summary of Investigators Skin Irritation Scores at Each Visit	Safety Analysis Set	
14.3.9	Summary of Columbia Suicide Severity Rating Scale Children's Version Positive Ratings	Safety Analysis Set	
14.3.10	Summary of Trough Plasma Concentrations for Anti-Epileptic Drugs at each Sampling Time (Weeks 6, 14, and 38)	PK Analysis Set	
14.3.11	Summary of CBD and THC Plasma Levels at Each Visit by Dose	Safety Analysis Set	

11.1. Individual Patient Data Listings

Listing Number	Title	Population
16.1	Listing of Patient Disposition	Enrolled
16.2	Listing of Demographics	Enrolled
16.3	Listing of Baseline Characteristics	Enrolled
16.4	Listing of Medical History	Enrolled
16.5.1	Listing of Prior/Concomitant Medications	Enrolled
16.5.2	Listing of Anti-Epileptic Drugs	Enrolled
16.6.1	Listing of Physical Exam Results	Enrolled
16.6.2	Listing of Neurological Exam Results	Enrolled
16.7	Listing of Protocol Deviations	Enrolled
16.8	Listing of Inclusion and Exclusion	Enrolled
16.9.1	Listing of Urine Drug Screen	Enrolled
16.9.2	Listing of Serum/Urine Pregnancy Results (Female Patients Only)	Enrolled
16.10	Listing of Vital Signs	Enrolled
16.11	Listing of 12-Lead ECG	Enrolled
16.12.1	Listing of Skin Assessment Examination	Enrolled
16.12.2	Listing of Skin Irritation Examination	Enrolled
16.13	Listing of Study Drug Application Record	Enrolled
16.14.1	Listing of Chemistry Labs	Enrolled
16.14.2	Listing of Hematology Labs	Enrolled
16.14.3	Listing of Urinalysis Labs	Enrolled
16.15	Listing of Testosterone Labs (Male Patients Only)	Enrolled
16.16	Listing of Columbia Suicide Severity Rating Scale (CSSRS-Children)	Enrolled
16.17	Listing of Pharmacokinetic Blood Sample Collection Record	Enrolled
16.18.1	Listing of Adverse Events	Enrolled
16.18.2	Listing of Deaths	Enrolled
16.18.3	Listing of Serious Adverse Events	Enrolled
16.18.4	Listing of Adverse Events Leading to Discontinuation	Enrolled
16.18.5	Listing of Patient Skin Irritation from Diary	Enrolled
16.20	Listing of Qualitative Caregiver Reported Behavioral Problems Survey	Enrolled
16.21	Listing of Children's Sleep Habit Questionnaire	Enrolled
16.22	Listing of ABC-C Checklist	Enrolled
16.23	Listing of CGI-S Scale	Enrolled
16.24	Listing of CGI-I Scale	Enrolled
16.25	Listing of PARS-R	Enrolled
16.26	Listing of ADAMS Scale	Enrolled
16.27	Listing of C-SSRS	Enrolled
16.28	Listing of AED Blood Sample	Enrolled

12. REFERENCES

Aman, M., & Singh, N. (2017). *ABC-2: Aberrant Behavior Checklist - Community/Residential Manual, 2nd Edition.* E.