GW Research Ltd.

Study Code: GWEP1424

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF CANNABIDIOL (GWP42003-P) IN CHILDREN AND YOUNG ADULTS WITH DRAVET SYNDROME

Statistical Analysis Plan

05 October 2018

CONTENTS

ABBREVIATION

ADHD	-	Attention Deficit Hyperactivity Disorder
AEDs	-	Antiepileptic Drugs
AEs	-	Adverse Events
ALQ	-	Above Limit of Quantification
ALT	-	Alanine Aminotransferase
ANCOVA	-	Analysis of Covariance
AST	-	Aspartate Aminotransferase
ATC	-	Anatomical Therapeutic Chemical
BASC-2	-	Behavior Assessment System for Children – Second Edition
BDRM	-	Blinded Data Review Meeting
BLQ	-	Below Limit of Quantification
BSA	-	Body Surface Area
CGIC	-	Caregiver Global Impression of Change
CGICSD	-	Caregiver Global Impression of Change in Seizure Duration
CI	-	Confidence Interval
CMH	-	Cochran–Mantel–Haenszel
CRF	-	Case Report Form
C-SSRS	-	Columbia-Suicide Severity Rating Scale
CWS	-	Cannabis Withdrawal Scale
D-KEFS	-	Delis–Kaplan Executive Function System
DS	-	Dravet Syndrome
ECG	-	Electrocardiogram
EDSS	-	Epworth Daytime Sleepiness Scale
EEG	-	Electroencephalography
eGFR	-	Estimated Glomerular Filtration Rate
IGF-1	-	Insulin-like Growth Factor-1
IMP	-	Investigational Medicinal Product
INR	-	Prothrombin International Normalized Ratio
ITT	-	Intention to Treat
IVRS	-	Interactive Voice Response System
LOCF	-	Last Observation Carried Forward
MAR	-	Missing at Random
MedDRA	-	Medical Dictionary for Regulatory Activities
MI	-	Multiple Imputation

MNAR	-	Missing Not at Random
NOCB	-	Next Observation Carried Backward
NRS	-	Numerical Rating Scale
OLE	-	Open Label Extension
PCWS	-	Pediatric Cannabinoid Withdrawal Scale
PK	-	Pharmacokinetics
PP	-	Per Protocol
QOLCE	-	Quality of Life in Childhood Epilepsy
SAP	-	Statistical Analysis Plan
SOC	-	System Organ Class
TEAE	-	Treatment Emergent Adverse Event
ULN	-	Upper Limit of Normal
Vineland-II	-	Vineland Adaptive Behavior Scales, Second Edition
WAIS-4	-	Wechsler Adult Intelligence Scale - Fourth Edition
WASI-2	-	Wechsler Abbreviated Scale of Intelligence – Second Edition
WISC-4	-	Wechsler Intelligence Scale for Children – Fourth Edition
WPPSI-4	-	Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition

1. INTRODUCTION

This statistical analysis plan (SAP) documents the statistical reporting to be performed for Study GWEP1424. Details of the analysis and reporting of pharmacokinetics (PK) of CBD and its major metabolites are not included as part of this SAP.

This SAP has been prepared based on the following study documents:

- Protocol GWEP1424 (Version 8, dated 06 September 2018).
- Case Report Form (CRF) GWEP1424, Version 1 (dated 08 April 2015).

1.1 Rationale

Dravet syndrome (DS), also known as severe myoclonic epilepsy in infancy, is a rare form of severe epilepsy with onset in early childhood.

DS is characterized by a variety of treatment-resistant seizures (febrile and afebrile, generalized and unilateral, clonic or tonic–clonic) that occur in the first year of life and has a poor cognitive prognosis.

DS is one of the most pharmacoresistant forms of epilepsy, with all seizure types extremely refractory to conventional antiepileptic drugs (AEDs), especially during the first several years.

In this study the active Investigational Medicinal Product (IMP) is GWP42003-P oral solution.

2. STUDY OBJECTIVES

The protocol defined the study objectives as:

2.1 Primary

To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the change during the treatment period of the study compared to baseline in convulsive seizure frequency. The dose response effect between 2 GWP42003-P Dose Levels (10 mg/kg/day and 20 mg/kg/day) and placebo will also be explored. Convulsive seizures are defined as tonic–clonic, tonic, clonic or atonic and non-convulsive seizures as myoclonic, partial or absence.

2.2 Secondary

- To assess changes from baseline in non-convulsive seizure frequency, duration, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, quality of life, growth and development, and conduct behavioral and cognitive assessments in patients taking GWP42003-P as an adjunctive treatment, when compared with placebo.
- To determine the PK of CBD and its major metabolites following single and multiple doses of GWP42003-P and to assess the presence of Δ^9-tetrahydrocannabinol (THC) and its major metabolites in plasma and the presence of THC, CBD and their major metabolites in urine after multiple doses of GWP42003-P.
- To determine effects of GWP42003-P on plasma concentrations of concomitant AEDs, where available.

- To assess the safety of both GWP42003-P doses when compared with placebo.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This study is a randomized, double-blind, 14-week comparison of 2 Dose Levels of GWP42003-P (10 mg/kg/day and 20 mg/kg/day) versus placebo. The treatment period will consist of a 2-week titration period followed by a 12-week maintenance period. The treatment period will be followed by a 10-day taper period and a 4-week follow-up period. The study will aim to determine the efficacy, safety and tolerability of 2 Dose Levels of GWP42003-P compared with placebo.

Following study completion, all patients will be invited to continue to receive GWP42003-P in an open label extension (OLE) study (under a separate protocol).

3.2 Definition of Sample Size

A total of 186 patients will be randomized to one of 4 treatment groups (GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The randomization will be stratified by age group (2–5 years, 6–12 years and 13–18 years). The placebo groups will be pooled for the analyses of efficacy.

For a Wilcoxon–Mann–Whitney test comparing 2 distributions with a 2-sided significance level of 0.05, a sample size of 62 per group is required to obtain a power of at least 80%. This is based on a gamma distribution for the GWP42003-P groups with scale parameter of 65.614 and shape parameter of 1.0886, and a gamma distribution for the placebo group with scale parameter of 40.887 and shape parameter of 2.3059.

Maximum likelihood estimates using the Newton–Raphson approximation were computed for the scale and shape parameters using data from study GWEP1332 Part B.

3.3 Efficacy and Safety Endpoints

3.3.1 Primary Efficacy Endpoint

The primary endpoint is the change in total convulsive seizure frequency during the treatment period (Day 1 to the end of the evaluable period) compared to baseline in patients taking GWP42003-P compared with placebo.

3.3.2 Secondary Efficacy Endpoints

The secondary endpoints will be tested hierarchically, based on the order given in Section 5.5.1, Table 3. No multiplicity adjustments will be made for all other secondary endpoints.

3.3.2.1 Key Secondary Efficacy Endpoints

1. Change in total seizure frequency.
2. Number of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline.
3. Caregiver Global Impression of Change (CGIC) score.

3.3.2.2 Other Secondary Efficacy Endpoints

The following endpoints will be compared between treatment groups over the 14-week, double-blind treatment period:

- Number of patients experiencing a >25% increase, ≥0 to ≤25% increase, >0 to <25% reduction, ≥25 to <50% reduction, ≥50 to <75% reduction or ≥75% reduction in convulsive seizures from baseline.
- Number of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in convulsive seizures from baseline (overall and 4-weekly).
- Number of patients who are convulsive seizure free.
- Change in non-convulsive seizure frequency.
- Change in subtypes of seizures.
- Changes from baseline in number of episodes of status epilepticus.
- Changes from baseline in duration of seizure subtypes as assessed by the Caregiver Global Impression of Change in Seizure Duration (CGICSD).
- Changes from baseline in usage of rescue medication.
- Changes from baseline in number of inpatient hospitalizations due to epilepsy.
- Changes from baseline in Sleep Disruption 0–10 Numerical Rating Scale (0-10 NRS) score.
- Changes from baseline in Epworth Sleepiness Scale (ESS) score.
- Changes from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score.
- Change from baseline in cognitive function as measured with a cognitive assessment battery.

- Changes from baseline in the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) score.
- Change from baseline in growth and development by measurement of height, weight, insulin-like growth factor-1 (IGF-1) levels and Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

PK:

- The plasma concentrations of CBD and its major metabolites will be determined following single and multiple doses of GWP42003-P. The following PK parameters will be calculated from sparse sampling:
  - The concentration at each time interval (C_t) of CBD and its metabolites.
  - Area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable concentration.
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.
- The plasma concentrations of THC and its major metabolites will be determined at a single time point (Visit 8, 2–3 hours post-dose) following multiple doses of GWP42003-P.
- The concentrations of THC, CBD, and their major metabolites will be determined in urine after multiple doses of GWP42003-P.

3.3.3 Safety Variables

The safety profile of GWP42003-P compared with placebo will also be assessed at each Dose Level by measuring:

- Adverse events (AEs).
- Vital signs.
- Physical examination parameters.
- 12-lead electrocardiogram (ECG).
- Clinical laboratory parameters.
- Columbia-Suicide Severity Rating Scale (C-SSRS) score.
- Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale (PCWS) score, as appropriate.
- Abuse liability.
- Effects on menstruation cycles (in females).

4. BLINDED DATA REVIEW MEETING

Prior to breaking the blind, it is anticipated that a Blinded Data Review Meeting (BDRM) will take place. The objectives of the meeting will include:

- Assessment of any study entry violations and protocol deviations.
- Assessment of the use of concomitant medications (including rescue medication) to identify changes which could affect the primary assessment of efficacy.

- Review of any protocol deviations and any potential effect on the study results. Assess the need for additional analyses using a per protocol (PP) population.
- Review of missing data and any potential effect on the study results.
- Safety reporting approach for any patients who potentially received the incorrect IMP during the double-blind phase.
- Assessment of any changes in concomitant AEDs for medical reasons.

The meeting will have access to the following blinded summary tables and listings:

- All pre-randomization patient data.
- All patient efficacy data.
- All concomitant medication data.
- All patient safety data.
- Patient protocol deviation logs.

This SAP documents the currently planned analyses for this study that will be approved prior to breaking the blind for the study. Changes to the analyses planned within any previously approved versions of the SAP will be summarized in Section 5.8 and integrated into the text of the SAP. The minutes of the BDRM will be documented separately.

5. STATISTICAL METHODS

5.1 General Considerations

In all tables, listings and figures, the treatment arms will be referred to and labelled as per Table 1.

Table 1 Study Treatments

Endpoint	Actual Treatment	Treatment Label
Efficacy	Pooled Placebo	Placebo
Safety	10 mg/kg/day Placebo	Placebo 10 mg/kg
	20 mg/kg/day Placebo	Placebo 20 mg/kg
All	10 mg/kg/day GWP42003-P	10 mg/kg
All	20 mg/kg/day GWP42003-P	20 mg/kg

For safety tables where placebo is split by dosing volume, an additional Pooled Placebo column will be included.

In all tables, listings and figures, the study visits will be referred to and labelled as per Table 2.

Table 2 Study Visits

Actual Visit	Visit Label
Visit 1: Screening	Screening
Visit 2: Day 1, baseline visit	Day 1
Visit 3: Day 15	Day 15
Visit 4: Day 29	Day 29
Visit 5: Day 43	Day 43
Visit 6: Day 57	Day 57
Visit 7: Day 71	Day 71
Visit 8: Day 99	End of Treatment
Visit 9: Day 109	End of Taper
Visit 10: Day 137	Safety Follow-Up

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (n), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling into each category. For continuous summaries of seizure frequency, the lower and upper quartiles will also be presented.

Minimum and maximum values will be presented to the same decimal precision as the raw data. Mean and median will be presented to 1 more decimal place than the raw data, and standard deviation to 2 more decimal places than the raw data. Percentages will be presented to 1 decimal place.

All analyses and summaries will be produced using SAS Version 9.3 or higher.

5.1.1 Missing Data

5.1.1.1 Handling of Missing Data for the Primary Efficacy Endpoint

If a patient withdraws during the treatment period, then the primary analysis variable will be calculated from all the available data, during the treatment period, prior to the patient withdrawing.

Section 5.5.2.1 describes sensitivity analyses to account for missing data arising from unreported days in the Interactive Voice Response System (IVRS), and missing data arising from patients withdrawing during the treatment period.

5.1.1.2 Handling of Missing Data for the Secondary Efficacy Endpoints

5.1.1.2.1 Epworth Sleepiness Scale

If the scores of fewer than 4 of the 8 individual questions are missing, the missing items will be imputed as the mean of the remaining non-missing scores, for the calculation of the total score only. If the scores of 4 or more of the individual questions are missing, the missing items will not be imputed and the total score will be missing; hence, the patient will not be included in the summary or analysis for that visit.

5.1.1.2.2 Quality of Life in Childhood Epilepsy

The calculations of subscale and overall scores for the QOLCE will treat responses of ‘Not Applicable’ as missing values.

For each subscale, if less than 50% of the items within the subscale are missing (including ‘Not Applicable’) then the subscale score will be calculated using the mean of the

non-missing items. If 50% or more of the items within the subscale are missing then the subscale score will not be calculated and will be missing.

For the overall quality of life score, if fewer than 8 of the 16 subscale scores are missing then the overall quality of life score will be calculated using the mean of the non-missing subscale scores. If 8 or more of the subscale scores are missing then the overall quality of life score will not be calculated and will be missing.

5.1.1.3 Adverse Events

Missing and/or incomplete dates/times for AEs will be imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking into account that the start date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing.

The imputation method will only be used to determine treatment emergence, and imputed dates/times will not be presented in AE outputs.

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, 'Severe' will be imputed. If causality data is missing, 'Yes' will be imputed for the question 'Plausible relationship to study medication'.

5.1.1.4 Concomitant Medication

Missing concomitant medication dates will be handled in a similar fashion as described for AEs in Section 5.1.1.3.

5.1.2 Day Numbering

The first day of treatment (Day 1) will be the date of the Visit 2. However, if the first dose of IMP was not administered on site (as indicated on the CRF) then the date of first dose will be calculated using the information on the 'IMP Missed Doses Log' CRF page.

Any days prior to Day 1 will be numbered relative to this day and calculated as:

Date − (Date of Day 1)

to give Day −1, −2, −3 etc.

Any days post Day 1 will be calculated as:

1 + Date − (Date of Day 1)

5.1.3 Definitions

5.1.3.1 Baseline

For clinic visit based endpoints, baseline is defined as the last record or measure collected prior to the first dose of IMP.

For IVRS based endpoints, baseline will include all available data prior to Day 1.

5.1.3.2 Last Visit

Last visit for endpoints assessed at clinic visits is defined as the last scheduled visit (not including the end of taper or safety follow-up visits) at which a patient's last evaluation is performed.

5.1.3.3 Treatment Period

The treatment period is defined as Day 1 to the earlier of:

- Day 99.
- The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF page.

5.1.3.4 Maintenance Period

The maintenance period is defined as Day 15 to the earlier of:

- Day 99.
- The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF page.

5.1.3.5 Convulsive Seizures

Convulsive seizures are defined as tonic–clonic, tonic, clonic or atonic seizures.

5.1.3.6 Non-Convulsive Seizures

Non-convulsive seizures are defined as myoclonic, countable partial, other partial or absence seizures.

5.1.3.7 Total Seizures

Total seizures are defined as the combination of convulsive and non-convulsive seizures.

5.2 Analysis Sets and Protocol Deviations

There will be 3 analysis sets.

5.2.1 Safety Analysis Set

All randomized patients who received at least one dose of IMP will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from this safety analysis set.

Upon blinded review of the data, it was identified that 1 patient was randomized in error, but did not receive IMP. This patient will be excluded from the safety analysis set.

Upon blinded review of the data, it was identified that 4 patients randomized to receive the 10 mg/kg/day dose (GWP42003-P or placebo) incorrectly received up to 20 mg/kg/day (up to 50 mg/kg/day for 1 patient) during the treatment period. For safety reporting, these patients will be assigned to the 20 mg/kg/day dose groups (GWP42003-P or placebo).

5.2.2 Intention to Treat Analysis Set

All randomized patients who received at least one dose of IMP and have post-baseline efficacy data will be included and analyzed according to the treatment group to which they were randomized.

The intention to treat (ITT) analysis set is the primary analysis set for all efficacy endpoints.

Upon blinded review of the data, it was identified that 1 patient was randomized in error, but did not receive IMP. This patient will be excluded from the ITT analysis set.

5.2.3 Per Protocol Analysis Set and Protocol Deviations

If there are a sufficient number of significant protocol deviations in the study, a PP analysis set may also be presented.

All patients who complete the study, with no protocol deviations deemed to compromise the assessment of efficacy, will be included and analyzed according to the treatment group they were randomized to. The rules determining the PP analysis set will be fully defined prior to unblinding of the database.

A listing will be produced of protocol deviations for the clinical study report. These protocol deviations will be imported from the protocol deviations log. Protocol deviations will be classed as minor, important or major, where major deviations are classed as important protocol deviations leading to exclusion from the PP analysis set.

Protocol deviations were reviewed during the BDRM on 21st September 2018. In addition to patients in the ITT analysis set who withdrew from the study during the treatment phase, a number of patients were deemed to have protocol deviations that should lead to exclusion from the PP analysis set. These patients, together with their deviations, are detailed in a separate document finalized prior to unblinding.

5.3 Listings

All data will be listed and ordered by site, treatment, patient number and, where appropriate, chronological order of assessment. Listings will be created for each of the subsequent sections of the SAP.

Visit date need not be included on all of the listings, but day numbers will be included, where appropriate.

Other derived variables (e.g. changes from baseline values) that are calculated for analysis purposes or to aid interpretation of the data will be added to the listings as appropriate.

5.4 Demographic Data and Patient Characteristics

5.4.1 Patient Disposition

Patient disposition, by site, by country and overall, will be summarized using standard summary statistics. The number screened, number of screen failures and number randomized will be included.

A screen failure disposition table will be presented, including number of patients screened, number failing screening, number randomized and the reasons for failing screening.

Patient disposition, including patients treated, patients completed the treatment phase and the taper phase, patients discontinued (including reason for discontinuation) from the treatment and taper phases will be summarized by absolute counts (n) and percentages (%). A further table split by site, and by country will be produced, showing number of patients randomized, withdrawn and completed the treatment phase at each site or in each country.

5.4.2 Analysis Sets

Patients included in the safety, ITT and PP analysis sets, and patients excluded together with reasons for exclusion, will be summarized by absolute counts (n) and percentages (%).

5.4.3 Demographic Data and Baseline Characteristics

The following demographic data will be summarized by treatment group and overall for the safety, ITT and PP analysis sets:

- Age (years);
- Age group (2-5 years, 6-12 years and 13-18 years);
- Sex;
- Race;
- Country;
- Region (United States, Rest of the World);
- Weight at baseline (kg);
- Height at baseline (cm);
- Body mass index at baseline (kg/m^2).

Age will be calculated as:

(Date of screening – date of birth) ÷ 365.25.

The following baseline characteristics will be summarized by treatment group and overall for the safety, ITT and PP analysis sets:

- Average number of convulsive seizures per 28 days.
- Average number of non-convulsive seizures per 28 days.
- Average number of total seizures per 28 days.
- Number of patients with seizures during the baseline period, by seizure type.
- Number of antiepileptic medications a patient has used, prior to the study.
- Number of antiepileptic medications a patient is currently taking.
- Total number of prior and current antiepileptic medications.
- Number of patients taking clobazam (Yes, No, and if no, Prior).
- Number of patients taking valproic acid (Yes, No, and if no, Prior).
- Number of patients taking stiripentol (Yes, No, and if no, Prior).
- Number of patients taking levetiracetam (Yes, No, and if no, Prior).
- Number of patients taking topiramate (Yes, No, and if no, Prior).

The number of prior antiepileptic medications a patient has used will be taken from the 'History of antiepileptic medications and therapies' CRF page. The number of antiepileptic medications a patient is currently taking is based on the 'Concomitant antiepileptic medications' CRF page. If a patient has a medication listed on both the 'History of antiepileptic medications and therapies' and 'Concomitant antiepileptic medications' CRF pages, then the medication is considered concomitant (see Section 5.7.1); this will not be included in the number of prior antiepileptic medications for that patient. Antiepileptic medications starting after the last dose of IMP during the treatment period will not be counted.

Patients taking the same antiepileptic medication type, but where the medications were coded to different generic terms will be counted only once within the medication type. For example, valproate sodium, valproic acid, valproate semisodium and ergenyl chrono will all be counted as valproic acid and counted once under that term.

The number of patients taking clobazam is defined as the number of patients taking clobazam at any point during baseline period or treatment period. The same definition will apply for the number of patients taking valproic acid, stiripentol, levetiracetam and topiramate.

Previous cannabis use will be included within the baseline characteristics listing.

5.4.4 Epilepsy and Dravet Syndrome History

5.4.4.1 Dravet Syndrome History

The following DS history data will be summarized by treatment group and overall for the safety analysis set:

- Was development ever normal? (Yes, No, Unknown).
- If developmental delay is present, age concerns first arose (years).
- Is there intellectual disability, mental retardation or learning disability? (Yes, No).
    - If yes, how severe is the intellectual disability, mental retardation or learning disability? (Mild, Moderate, Severe, Profound, Other, Unknown).
- Was there developmental regression? (Yes, No).
    - If yes, at what age (years).
- Is the patient verbal or nonverbal? (Verbal, Non-Verbal).
    - If Verbal, extent of vocabulary (Single words, 2–3 word phrases, Long sentences, Other).
- Age patient started walking (years).
- Has any medication increased seizure frequency? (Yes, No).
- Has any medication reduced seizure frequency? (Yes, No).
- Has there been a prolonged seizure free period greater than 6 months? (Yes, No).
    - If yes, age at last occurrence (years).

5.4.4.2 History of Seizures No Longer Occurring and History of Current Seizures

Data will be summarized by treatment group and overall for the safety analysis set, separately, for history of seizures no longer occurring and history of current seizures.

The following will be summarized by each seizure type:

- Number of patients with the seizure type.
- Age at onset (years).
- Age of last occurrence (years). For history of seizures no longer occurring only.
- Seizure duration (<2 minutes, 2–10 minutes, >10 minutes, Unknown). For history of current seizures only.

Seizure frequency and trigger data will be listed only.

For patients with more than 1 record for a particular seizure type, the earliest onset, most recent age of last occurrence and longest duration will be used for the summary table.

5.4.4.3 Electroencephalography History

The following electroencephalography (EEG) history data will be summarized by treatment group and overall for the safety analysis set:

- Has the patient ever had a normal EEG? (Yes, No).
    - If yes, how old was the patient when they last had a normal EEG? (Years).
- Has the patient ever had an abnormal EEG? (Yes, No, Unknown).
- If yes:
    - EEG findings (Focal spikes, Generalized spike wave discharges, Hypsarrhythmia, Electrographic seizures).
    - Seizure type (Partial (focal) seizures, Generalized seizures, Other).
        - Generalized seizures type (Generalized spike & wave, Generalized paroxysmal fast activity, Generalized electrodecrement at onset).
    - Seizure features (Background slowing and/or disorganization, Focal slowing, Other).

5.4.4.4 Neuroimaging History

Neuroimaging history data will be listed only.

5.4.5 Medical and Surgical History and Current Medical Conditions

All conditions and diagnoses on the 'non-epilepsy medical history' CRF page will be coded using Version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA v17.1).

The number of patients with relevant or significant non-epilepsy medical or surgical history and medical history by system organ class, and preferred term, will be summarized by absolute counts (n) and percentages (%). Percentages will be calculated based on the number of patients in the specific treatment group. Two tables will be produced, one including any events classified as resolved at screening, and the other including all current conditions.

5.5 Efficacy Analysis

5.5.1 General Approach

The primary analyses will use the ITT analysis set. Further analyses using the PP analysis set will also be performed for the primary endpoint and secondary endpoints where specified in the sections below.

The primary null hypothesis is:

- Following 14 weeks of treatment there is no difference in effect between the 20 mg/kg/day GWP42003-P treatment group and the placebo treatment group in terms of the change in convulsive seizure frequency during the treatment period compared to baseline.

The null hypothesis will be rejected if there is statistical evidence of a difference between the treatment groups at the α-level of 0.05 for the primary endpoint.

Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Each endpoint, including the primary will have 2 comparisons against placebo (20 mg/kg/day GWP42003-P and 10 mg/kg/day GWP42003-P vs. placebo). Also, 3 key secondary endpoints have been defined.

The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure, in the sequence given in Table 3. One must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis is not rejected then testing will stop and all subsequent analyses will be declared not statistically significant.

Table 3 Hierarchy for Analysis

Test	Endpoint	Treatment Comparison
1	Primary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
2	Primary endpoint	10 mg/kg/day GWP42003-P vs. Placebo
3	1st key secondary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
4	1st key secondary endpoint	10 mg/kg/day GWP42003-P vs. Placebo
5	2nd key secondary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
6	2nd key secondary endpoint	10 mg/kg/day GWP42003-P vs. Placebo
7	3rd key secondary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
8	3rd key secondary endpoint	10 mg/kg/day GWP42003-P vs. Placebo

All statistical tests will be 2-sided and use the 5% significance level.

The assumptions of normality and homogeneity of variance, for endpoints analyzed using parametric tests, will be checked where appropriate via examination of residual plots as well as computation of summary statistics for normality using the Shapiro–Wilk statistical test. If assumptions are violated then alternative non-parametric techniques will be used. In this instance the original parametric tests will be presented as a sensitivity analysis.

5.5.2 Primary Efficacy Endpoint

The primary endpoint is the change in convulsive seizure frequency during the treatment period (see Section 5.1.3.3) of the study compared to baseline (see Section 5.1.3.1) in patients taking GWP42003-P compared with placebo.

The primary endpoint will be analyzed using negative binomial regression on the sum of the convulsive seizure counts during the treatment period. However, convulsive seizure frequency (28-day average) and percentage change in seizure frequency will be presented using summary statistics. Percentage change from baseline in convulsive seizure frequency will be calculated as:

[(Frequency during the treatment period – Frequency during baseline) ÷ Frequency during baseline] × 100

The frequency during each period will be based on 28-day averages and calculated as:

(Number of seizures in the period ÷ Number of reported days in IVRS in the period) × 28

For convulsive seizure endpoints only, if patients are randomized with no convulsive seizures during the baseline period then the percentage change from baseline will be calculated as:

(Frequency during the treatment period + 1) × 100

A mixed effect model with repeated measures will be performed modelling the observed number of convulsive seizures in the baseline period and treatment period implemented within the framework of general linear models using the negative binomial response distribution. The model will include stratified age group (2–5 years, 6–12 years and 13–18 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect. The log transformed number of days in which seizures were reported will be included as an offset. The time variable corresponds to an indicator for the baseline period and treatment period.

The GLIMMIX procedure in SAS will be utilized to perform the analysis with the option maxopt=300 applied. If the model fails to converge, then the statement 'nloptions tech=nrridg;' will be added. If convergence is still not achieved then 'method=laplace' will be utilized. However, if convergence is still not possible, then the model will be changed to utilize the log normal response distribution (log rate model). If the log rate model is required and there are patients with a seizure frequency during the baseline or treatment period of 0 then all patients will have their baseline and treatment period seizure frequency adjusted by adding a value of 1.

The estimated ratio of least squares means for treatment period to baseline period and 95% confidence intervals (CIs) will be presented for each treatment arm. In addition, the estimated ratio of each GWP42003-P group to placebo and 95% CIs will be presented along with the p-value testing the null hypothesis that this ratio is 1.

For each ratio and upper and lower bound of the 95% CI, the percentage reduction will also be presented, calculated as:

$$[1 - (X \div Y)] \times 100\%$$

Where X corresponds to the treatment period estimate, or GWP42003-P ratio, and Y corresponds to the baseline period estimate, or placebo arm ratio.

Primary efficacy analysis will be performed using ITT analysis set.

For a period of time, the limit for the number of daily seizures for each seizure type recorded in IVRS was 99. A >99 seizure log was added to the CRF to allow the capture of the exact number of seizures where the count on a particular day was >99. When deriving the seizure frequencies, the count >99 provided on the CRF will replace the recorded 99 seizures in IVRS for the corresponding seizure type. This will only be done when the corresponding IVRS record was exactly 99.

5.5.2.1 Sensitivity Analyses for the Primary Efficacy Endpoint

The following sensitivity analyses will be conducted for the primary endpoint:

- Primary endpoint analysis repeated using the PP analysis set.
- Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P group and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.
- A rank analysis of covariance (ANCOVA) on percentage change from baseline in convulsive seizure frequency during the treatment period.

  The ranks of the percentage change from baseline and the baseline convulsive seizure frequency will be calculated. The rank of the percentage change from baseline will then be analyzed using an ANCOVA model with the rank of the

baseline convulsive seizure frequency and age group (2–5 years, 6–12 years and 13–18 years) as covariates and treatment group as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.

- ANCOVA of log transformed convulsive seizure frequency during the treatment period.

  The convulsive seizure frequency during the treatment period and the baseline convulsive seizure frequency will be log transformed prior to analysis. The log transformed convulsive seizure frequency during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline convulsive seizure frequency and age group as covariates and treatment group as a fixed factor. The back transformed estimated treatment ratios, together with the 95% CIs and p-values will be presented.

  If there are any patients with no seizures during the baseline or treatment periods, then 1 will be added to the convulsive seizure frequency for all patients prior to log transformation.

- ANCOVA on percentage change from baseline in convulsive seizure frequency during the treatment period including baseline and age group as covariates and treatment group as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.

- Primary endpoint analysis repeated using the maintenance period (see Section 5.1.3.4) rather than the treatment period.

  This analysis will include only patients who have at least 7 days of seizure data within the maintenance period.

- Primary endpoint analysis repeated using each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period).

  This analysis will include only patients who have at least 7 days of seizure data within each corresponding 4-week period rather than the treatment period.

- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the daily mean from the non-missing data for each patient (rounded up to the nearest integer) to impute missing data arising from unreported days in IVRS during the treatment period only (not the baseline period).

  Any intermittent missing data for the number of convulsive seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period (rounded up to the nearest integer) based on using non-missing data:

  Number of seizures ÷ Number of reported days in IVRS

- Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption (see Section 5.5.2.1.1).

- Primary endpoint analysis repeated using the safety analysis set.

5.5.2.1.1 Sensitivity Analysis of Missing Data

Missing data in this trial could potentially arise from the mechanism of MNAR. In order to understand the impact on the trial findings from missing data under the MNAR assumption, sensitivity analyses of the primary endpoint will be carried out for the ITT analysis set by multiple imputations on convulsive seizure frequency, based on time-points corresponding to each 14 days of the treatment period. The final period will consist of 15 days to include Day 99, if applicable.

For each 14 calendar days of the treatment period (15 days for the final period), the convulsive seizure frequency will be calculated as:

[Number of convulsive seizures in the period ÷ Total number of reported days in IVRS for all combined periods (maximum of 99 days)] × 28

For patients with any periods with no reported days in IVRS, the total number of reported days in IVRS will include an additional 14 days for each missing period. For example, if a patient withdraws with 80 reported days in IVRS from 6 of the 7 14-calendar-day periods, then the total number of reported days in IVRS for the above calculation will be the sum of 80 and 14, i.e. 94 days.

Intermittent missing values for intermediate nominal visits before the last nominal visit will be imputed using the MCMC method in PROC MI with an IMPUTE=MONOTONE statement for 100 times for each treatment group separately. The resulting 100 partially imputed datasets will have a monotone missing pattern and will be further imputed under an MNAR assumption that the imputed value for the missing efficacy data of GWP42003-P patients (discontinued for certain reasons) are similar to, worse than, or better than those of placebo patients for the following 2 scenarios:

(1) MNAR assumed for missing values resulting from discontinuation due to AEs in the GWP42003-P groups and Missing at Random (MAR) for others, including other patients discontinued in the GWP42003-P groups and patients in placebo group;

(2) MNAR assumed for missing values resulting from discontinuation due to any reason or any other monotone missing data in the GWP42003-P groups and MAR for others, including patients in placebo group.

For each of the 2 scenarios above, imputation will be carried out once on each of the 100 imputed datasets using the SAS MI procedure (with the 100 imputed datasets included in the 'BY' statement of the MI procedure) as follows:

- Step 1: Monotone missing data under the MAR assumption at treatment period time-point t will be imputed by means and covariance from the observed convulsive seizure frequency at baseline and at each treatment period time-point up to time-point t (in chronological order) in their corresponding treatment groups (i.e., patients in the GWP42003-P groups whose missing data are assumed to be MAR and all patients in the placebo group). The imputation will be realized using the MI procedure with the 'MONOTONE REG' option, for each treatment group separately. The imputation model will include baseline convulsive seizure frequency and each treatment period time-point up to time-point t (in chronological order).
- Step 2: With the data imputed from Step 1, monotone missing data of patients in the GWP42003-P groups under the MNAR assumption will be imputed. At each treatment period time-point t, the input dataset for the MI procedure will include all placebo patients and those patients from each GWP42003-P group that have values missing under MNAR at that time-point. The imputation model will include convulsive seizure frequency at baseline and each treatment period time-point up to

time-point t (in chronological order). After the sequential imputation is completed for all time-points, the imputed values at time-point t plus, a sensitivity parameter, k × standard error of the observed convulsive seizure frequency in the placebo group at the corresponding time-point (calculated using the denominator of the total number of reported days in IVRS for all combined periods, as given above) will then form the final imputed values. The sensitivity parameter k (where, for example, k = 0, ± 0.5, ± 1.0, ± 1.5, etc.) will be used to explore the robustness of the estimated treatment difference to the degree of decrease or increase (positive values of k represent decrease and negative values represent increase) in MNAR efficacy from the placebo patients.

After missing values at all the time-points are imputed, the overall percentage change from baseline in convulsive seizure frequency will be calculated as:

[(The sum of the frequencies of each 14 days of the treatment period – Frequency during baseline) ÷ Frequency during baseline] × 100

If the sum of the frequencies of each 14 days of the treatment period becomes less than zero, as a result of imputation, then the percentage change from baseline in convulsive seizure frequency will be set to −100%.

The data will then be analyzed using a Wilcoxon rank-sum test.

The results of the Wilcoxon rank-sum test on the 100 imputed datasets will be combined to derive an overall p-value. The test statistic will be based on the method provided by Rubin[1] and a modified macro from Mogg[2].

For each analysis, the increment in the positive value of k will stop once the overall p-value is greater than 0.05. The decrease in the negative values of k will continue until the overall p-value becomes smaller than the p-value from the primary efficacy analysis, for the corresponding Dose Level.

5.5.3 Secondary Efficacy Endpoints

5.5.3.1 Key Secondary Efficacy Endpoints

5.5.3.1.1 1st Key Secondary Endpoint: Total Seizures

Summaries and analyses of total seizures (see Section 5.1.3.7) will be performed as per the primary endpoint (Section 5.5.2).

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, and during each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period).

Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each corresponding period.

5.5.3.1.2 2nd Key Secondary Endpoint: Convulsive Seizure Treatment Responders (≥50% Reduction in Convulsive Seizure Frequency)

The proportion of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizure frequency from baseline, during the treatment period, will be summarized by treatment group and analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group.

The proportion of patients who are considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratios (GWP42003-P groups vs. placebo), 95% CI for the odds ratios, and the p-values from the CMH test will be presented. If no patients in a particular treatment group are considered responders then the odds ratio and 95% CI for the odds ratio will not be calculated.

The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, and during each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period).

Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each period.

5.5.3.1.3 3rd Key Secondary Endpoint: Caregiver Global Impression of Change

The CGIC will be assessed at Visits 3, 4, 6 and 8 (end of treatment). The CGIC comprises the following question to be rated on a 7-point scale:

- Since your child started treatment, please assess the status of your child's overall condition (comparing their condition now to their condition before treatment) using the scale below.

The possible responses are: Very Much Improved; Much Improved; Slightly Improved; No Change; Slightly Worse; Much Worse; Very Much Worse.

The responses above are based on comparison with a brief description of the patient's overall condition used as a memory aid from Visit 2.

Each response will be coded with a score from 1 to 7, where 1 = Very Much Improved, and 7 = Very Much Worse.

The CGIC response/score, recorded at each visit, will be summarized, on both a categorical and continuous scale, by treatment group.

The score at the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment group as a factor. The estimated odds ratios (GWP42003-P arms vs. placebo), 95% CI for the odds ratios, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented. Analysis performed at the last visit will be considered the main analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.

Should the proportional odds assumption not hold, i.e. if the p-value for the score test for proportional odds assumption is <0.05, then, as a sensitivity analysis, the scores will also be analyzed using a Cochran-Armitage trend test. This will be presented together with the results of the ordinal logistic regression.

5.5.3.2 Other Secondary Efficacy Endpoints

5.5.3.2.1 Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom

The number of patients experiencing >25% increase, ≥0 to ≤25% increase, >0 to <25% reduction, ≥25 to <50% reduction, ≥50 to <75% reduction or ≥75% reduction in convulsive seizure frequency from baseline during the treatment period will be summarized by treatment group.

In addition to the key secondary endpoint, the proportion of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in convulsive seizure frequency from baseline and the proportion of patients who are convulsive seizure free, defined as those with a 100% reduction in convulsive seizure frequency from baseline, during the treatment period, will be summarized by treatment group and analyzed using a CMH test stratified by age as described in Section 5.5.3.1.2.

Additionally, the proportion of patients responding will be presented graphically, by treatment arm, by plotting the percent reduction against the cumulative proportion of patients achieving that level of reduction. The x-axis will be the percent reduction from baseline and the y-axis will be the proportion of patients with at least that amount of reduction, i.e. $y = Pr(X \geq x)$.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, and during each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period).

Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each corresponding period.

5.5.3.2.2 Status Epilepticus

The number of convulsive seizures greater than 30 minutes in duration and the number of non-convulsive seizures greater than 30 minutes in duration will be collected daily via IVRS.

The number of patients with convulsive and non-convulsive seizures greater than 30 minutes in duration, will be presented for the baseline and treatment periods.

In addition, the number of patients with any episodes post-baseline and no episodes during the baseline period, will be summarized by treatment group.

5.5.3.2.3 Non-Convulsive Seizures

Non-convulsive seizures will be summarized and analyzed as per the primary endpoint (Section 5.5.2). Patients with no non-convulsive seizures during the baseline period will be excluded from the analysis.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, and during each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period).

Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each corresponding period.

Non-convulsive seizure responders and freedom will also be summarized and analyzed using the methods described in Section 5.5.3.2.1. Patients with no non-convulsive seizures during the baseline period will be excluded from the analysis.

5.5.3.2.4 Individual Seizure Types

For each individual seizure type (tonic–clonic, tonic, clonic, atonic, myoclonic, countable partial, other partial and absence seizures) summaries and analyses will be performed as per the primary endpoint (Section 5.5.2). Patients with no seizures during the baseline period, for a particular seizure type, will be excluded from the analysis of that seizure type.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis for tonic, tonic–clonic, atonic and clonic seizures only, using data for only the maintenance period, and during each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period).

Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only patients who have at least 7 days of seizure data within each corresponding period.

Individual seizure type responders and freedom will also be summarized and analyzed using the methods described in Section 5.5.3.2.1. However, the summaries and analyses during the maintenance period and during each 4 weeks of the maintenance period will be produced for tonic, tonic–clonic, atonic and clonic seizures only. Patients with no corresponding seizures, for a particular seizure type, during the baseline period will be excluded from the analysis for that seizure type.

In addition, the number of patients with an occurrence of an individual seizure type not experienced in the baseline period will be summarized by treatment group.

An occurrence of an individual seizure type not experienced in the baseline period is calculated as seizure types with no seizures experienced during the baseline period and at least one seizure experienced at any time post first dose of IMP.

5.5.3.2.5 Caregiver Global Impression of Change in Seizure Duration

The CGICSD comprises the following question to be rated on a 3-point scale for each seizure type:

- Since the patient started treatment, please assess the average duration of the patient's seizures (comparing their condition now to their condition before treatment) using the scale below.

The 3 possible responses are:

- Decrease in average duration.
- No change in average duration.
- Increase in average duration.

The caregiver will be asked to assess the average duration of the patient's seizures at Visit 2 (prior to commencement of IMP) as a memory aid for assessment at the end of treatment visit.

Each response will be coded with a score from 1 to 3, where 1 = Decrease in average duration, and 3 = Increase in average duration.

For each seizure type, the CGICSD will be summarized by treatment group and analyzed using ordinal logistic regression.

Proportional odds modelling will be carried out by including treatment group and age group as factors. The estimated odds ratios (GWP42003-P groups vs. placebo), 95% CI for the odds ratios, and the p-values testing the null hypothesis that the odds ratio is equal to 1, will be presented.

5.5.3.2.6 Inpatient Hospitalizations due to Epilepsy

The number of inpatient epilepsy-related hospitalizations since the previous visit are recorded at every visit starting from Visit 2 (Day 1).

The number of patients with inpatient epilepsy-related hospitalizations will be presented for the baseline and treatment periods.

5.5.3.2.7 Sleep Disruption 0-10 Numerical Rating Scale

The sleep disruption 0-10 NRS will be performed at Visits 2 (Day 1), 3, 4, 6 and 8 (end of treatment). The patient's caregiver will be asked:

- "On a scale of '0 to 10', please indicate the number that best describes your child's sleep disruption in the last week."

The markers range from 0 = slept extremely well, to 10 = unable to sleep at all.

The sleep disruption 0-10 NRS score, recorded at each visit, will be summarized, on a continuous scale, by treatment group. The change from baseline (Visit 2) will also be included.

The change from baseline to the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ANCOVA. The model will include baseline and age group as covariates and treatment group as fixed factor. Analysis performed at the last visit will be considered the main analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

5.5.3.2.8 Epworth Sleepiness Scale

The ESS is a questionnaire that provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The ESS contains 8 questions that are rated on a 4-point numerical scale (0–3). The total ESS score is the sum of the 8 item-scores and can range between 0 and 24. Higher total scores represent greater levels of daytime sleepiness.

The ESS questionnaire will be completed at Visits 2 (Day 1), 3, 4, 6 and 8 (end of treatment) by the patient's caregiver.

The total score, recorded at each visit, will be summarized, on a continuous scale, by treatment group. The change from baseline (Visit 2) will also be included.

The change from baseline in the total score to the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.7. Analysis performed at the last visit will be considered the main analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.

Missing data arising from missing individual questions will be handled according to Section 5.1.1.2.1.

5.5.3.2.9 Quality of Life in Childhood Epilepsy

The QOLCE is a parent-reported questionnaire that evaluates health related quality of life in children aged 4–18 years old. It contains 76 items with 16 subscales covering 7 domains of life function: physical activities, social activities, cognition, emotional well-being, behavior, general health, and general quality of life. The QOLCE will be completed by the parent or caregiver at Visits 2 (Day 1) and 8 (end of treatment).

All items in the questionnaire are rated on a 5-point or 6-point categorical scale. Based on the responses to the items in each domain, scores for 16 subscales are derived. The subscales are presented in Table 4.

Table 4 QOLCE Subscales

Subscale	Item Domains	Items Used
Physical Restrictions	Physical Activities	3.1 (a to j)
Energy/Fatigue	Physical Activities	3.2 (a,b)
Attention/Concentration	Cognition	5.1 (a,d,e,f,g)
Memory	Cognition	5.1 (j,k,l,m,n,o)
Language	Cognition	5.1 (p,q,r,s,t,u,v,w)
Other Cognitive	Cognition	5.1 (b,c,h)
Depression	Emotional Well-Being	4.1 (a,d,e,l)
Anxiety	Emotional Well-Being	4.1 (b,g,j,n,o,p)
Control/Helplessness	Emotional Well-Being	4.1 (c,f,h,i)
Self-esteem	Emotional Well-Being	4.1 (k,m,q,r,s)
Social Interactions	Social Activities	6.1 (c,f,h)
Social Activities	Social Activities	6.1 (a,e) and 6.2
Stigma Item	Social Activities	6.1 (i)
Behavior	Behavior	7.1 (a,c,f,g,h,l,j,k,l,m,o,q,r,s,t)
General Health Item	General Health	8.1
Quality of Life Item	Quality of Life	9.1

Items within each subscale will be coded and linearly transformed, according to the methods of Sabaz et al.[3], to a score of 0 to 100, where 0 represents the lowest or poorest category and 100 represents the highest level of functioning.

A subscale score is calculated for each subscale by computing the mean of the items within the subscale. An 'Overall Quality of Life Score' can be calculated by taking the mean of the subscale scores.

Individual items will be listed only. The subscale scores and the overall quality of life score, recorded at each visit, will be summarized, on a continuous scale, by treatment group. The change from baseline (Visit 2) will also be included.

The change from baseline to the end of treatment visit, for the overall quality of life score, and the attention/concentration, memory, language, other cognitive, social interactions and behavior subscale scores only, will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.7. Exploratory analyses may also be performed on other subscale scores.

Missing data will be handled according to Section 5.1.1.2.2.

5.5.3.2.10 Vineland Adaptive Behavior Scales, Second Edition

The Vineland-II is an individually administered instrument for assessing adaptive behaviors. The Vineland-II assessments will be made at Visits 2 (Day 1), 3, 4, 6 and 8 (end of treatment).

The Vineland-II consists of 44 adaptive behavior domains and a maladaptive behavior domain. The details of each domain are presented in Table 5.

Table 5 Content Description of the Vineland-II

Domains and Subdomains	Number of Items	Age Range (Years)	Content
Adaptive Behavior Domains			
Communication Domain	**99**	≥0	
Receptive	20	≥0	How the individual listens and pays attention, and what he or she understands
Expressive	54	≥0	What the individual says, how he or she uses words and sentences to gather and provide information
Written	25	≥3	What the individual understands about how letters make words, and what he or she reads and writes
Daily Living Skills Domain	**109**	≥0	
Personal	41	≥0	How the individual eats, dresses and practices personal hygiene
Domestic	24	≥1	What household tasks the individual performs
Community	44	≥1	How the individual uses time, money, the telephone, the computer and job skills
Socialization Domain	**99**	≥0	
Interpersonal Relationships	38	≥0	How the individual interacts with others
Play and Leisure Time	31	≥0	How the individual plays and uses leisure time
Coping Skills	30	≥1	How the individual demonstrates responsibility and sensitivity to others
Motor Skills Domain	76	≥0 to <7	
Gross	40	≥0 to <7	How the individual uses arms and legs for movement and coordination
Fine	36	≥0 to <7	How the individual uses hands and fingers to manipulate objects
Maladaptive Behavior Domain			
Maladaptive Behavior Index	**36**	≥3	A composite of Internalizing, Externalizing, and Other types of undesirable behavior that may interfere with the individual's adaptive functioning
Internalizing (Section A)	11	≥3	
Externalizing (Section B)	10	≥3	
Other (Section C)	15	≥3	
Maladaptive Behavior Critical Items	**14**	≥3	More severe maladaptive behaviors that may provide clinically important information

For each subdomain, a raw score is calculated based on the responses to the individual items within the subdomain. For the maladaptive behavior index, the raw score is the sum

of the 3 subdomain raw scores. Using the raw score and the patients' age the following are obtained:

- v-Scale Score: a type of standard score scale (standardized by age) to describe an individual's relative level of functioning. Ranging from a score of 1 to 24.
- 90% CI for the v-Scale Score: a range of scores that has a certain likelihood of including the individual's true score.
- Adaptive Level: a means to describe an individual's performance using terms that are nearly universal (Low, Moderately Low, Adequate, Moderately High, High).
    - For the maladaptive behavior index and maladaptive behavior subdomains the adaptive levels are: Average, Elevated or Clinically Significant.
- Age Equivalent: the age at which the raw score is average. Not applicable for the maladaptive behavior index and maladaptive behavior subdomains.

For each adaptive behavior domain, the sum of the v-scale scores of the subdomains is used along with the patients' age to obtain the following:

- Standard Score (standardized by age). Ranging from a score of 20 to 160.
- 90% CI for the domain standard score.
- Percentile Rank: the percentage of people whom the individual outperformed in his or her age group.
- Adaptive Level (Low, Moderately Low, Adequate, Moderately High, High).
- Stanine: whole number score ranging from 1 to 9 and representing a specific range of percentile ranks.

An adaptive behavior composite can then be obtained using the sum of the adaptive behavior domain standard scores (excluding the motor skills domain for patients ≥7 years of age). The same derived information as the adaptive behavior domain is obtained for the adaptive behavior composite.

For the maladaptive behavior index, all items within each section must be answered for a raw score to be calculated. If any of the items are missing then the maladaptive behavior index score will be missing.

For the adaptive behavior subdomains, the derivation of the raw score allows for up to 2 missing values or answers of "Don't Know" within the items used for scoring. If there are more than 2 missing values or answers of "Don't Know" then the raw score will not be calculated and the subdomain score, domain score and adaptive behavior composite score will be missing.

The adaptive levels corresponding to the v-scale scores and standard scores are presented in Table 6.

Table 6 Adaptive Levels by v-Scale Scores and Standard Scores

Adaptive Level	v-Scale Score for Subdomains and Maladaptive Behavior Index	Standard Score for Domains and Adaptive Behavior Composite
Adaptive Behavior Domains		
Low	1 to 9	20 to 70
Moderately Low	10 to 12	71 to 85
Adequate	13 to 17	86 to 114
Moderately High	18 to 20	115 to 129

High	21 to 24	130 to 160
Maladaptive Behavior Domain		
Clinically Significant	21 to 24	
Elevated	18 to 20	
Average	1 to 17	

The v-scale score from the 11 adaptive behavior subdomains, 3 maladaptive behavior subdomains and the maladaptive behavior index, and the standard score from the 4 adaptive behavior domains and the adaptive behavior composite, recorded at each visit, will be summarized, on a continuous scale, by treatment group. The change from baseline (Visit 2) will also be included.

The change from baseline to the end of treatment visit and last visit (if different to the end of treatment), for the 4 adaptive behavior domains, the adaptive behavior composite and the maladaptive behavior index only, will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.7. Analysis performed at the last visit will be considered the main analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.

The adaptive level from the 11 adaptive behavior subdomains, 4 adaptive behavior domains, the adaptive behavior composite, the 3 maladaptive behavior subdomains and the maladaptive behavior index, recorded at each visit, will be summarized, on a categorical scale, by treatment group.

The adaptive level from the 4 adaptive behavior domains, the adaptive behavior composite and the maladaptive behavior index only will be analyzed using ordinal logistic regression. Factors for treatment and age group will be included along with the baseline adaptive level as a covariate. The estimated odds ratios (GWP42003-P groups vs. placebo), 95% CI for the odds ratios, and the p-values testing the null hypothesis that the odds ratio is equal to 1, will be presented.

Each adaptive level for adaptive behavior will be coded with a score from 1 to 5, where 1 = Low, and 5 = High. Each adaptive level for the maladaptive behavior index will be coded with a score from 1 to 3, where 1 = Clinically Significant, and 3 = Average.

The individual responses within each domain will not be listed, only the derived information for each subdomain and domain will be listed.

5.5.3.2.11 Cognitive Assessment Battery

The cognitive assessment battery will be administered at Visit 2 (baseline) and Visit 8 (end of treatment). The items are age specific and the age of the patient at entry is the age used when choosing the items to be given. Children and adults are to complete the battery as able. It is expected that a number of patients will only be able to complete part of the battery and some may not be able to complete it at all. Parents and/or caregivers are to complete certain items.

The battery items will only be administered to a sub-group of sites that have the expertise to conduct the test. Assessments are conducted by an experienced psychometrician.

A summary of the patient and parent measures are given in Table 7.

Table 7 Neuropsychological Protocol for Epilepsy Patients Treated with Cannabidiol – Patient and Parent Measures

Category	Function	Measures	Age Range
Patient	Intelligence **IQ**	Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-4) Vocabulary, Matrix Reasoning	2;6 - 5;11 years
		Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2) Vocabulary, Matrix Reasoning (Including Wechsler: 'Digit Span' subtest from Wechsler Intelligence Scale for Children – Fourth Edition (WISC-4) and Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-4); 'Coding' subtest from WISC-4 & WAIS-4; 'Bug Search' from WPPSI-4)	6 - adult
	Attention/Executive **Trail Making**	Trail Making Test Delis–Kaplan Executive Function System (D-KEFS)	9 - adult
	Language **Naming** **Fluency**	Expressive One-Word Picture Vocabulary Test-4th Edition	2 - adult
		NEPSY-2 Word Generation	2 - 5 years
		F-A-S and Animals	6 - adult
	Visual-Spatial **VMI**	Developmental Test of Visual Motor Integration-6	2 - adult
	Fine Motor Speed **Pegs**	Purdue Pegboard	4 - adult
Parent	Executive	Behavior Rating Inventory of Executive Function (Parent and Teacher)	3 - 21 years
	Attention	Attention deficit hyperactivity disorder (ADHD) Checklist (Parent and Teacher)	All ages
	Mood/Anxiety	Behavior Assessment System for Children – Second Edition (BASC-2) (Parent and Teacher)	3 - 21 years
	Free-form report	Behavior Report Form (Parent and Teacher)	All ages

The following patient measures will be summarized, on a continuous scale, by treatment group at each visit and including the change from baseline using the score recorded on the CRF:

- Intelligence:
  - WPPSI-4 T score:
    - Receptive Vocabulary.
    - Matrix Reasoning.
    - Bug Search.
  - WASI-2 T score:
    - Vocabulary.
    - Matrix Reasoning.
  - WISC-4 and WAIS-4:
    - Coding scaled score.

        - Digit Span (Forward, Backward, Longest forward, Longest Backward).

- Attention/Executive:
    - D-KEFS scaled scores.
- Language:
    - Expressive One-Word Picture Vocabulary Test-4th Edition scaled score.
    - NEPSY-2 Word Generation scaled score.
- Visual-Spatial:
    - Developmental Test of Visual Motor Integration-6 standard score.
- Fine Motor Speed:
    - Dominant hand, non-dominant hand and both hands Z scores.

The following parent measures will be summarized, on a continuous scale, by treatment group at each visit and including the change from baseline using the scored recorded on the CRF:

- Executive:
    - Behavior Rating Inventory of Executive Function T scores for indexes and composite.
- Mood/Anxiety:
    - BASC-2 T scores for composite scores.

The behavior report form will be summarized, on a categorical scale, by treatment at each visit.

The ADHD checklist consists of 18 questions, questions 1 to 9 relate to inattention and questions 10 to 18 relate to hyperactivity. A derived Inattention and Hyperactivity score can be calculated by taking the sum of the corresponding question responses, where 0 = 'Not at all' and 3 = 'Very much' and dividing by 9. A combined score can also be calculated by taking the sum of the responses from questions 1 to 18 and dividing by 18. The Inattention, Hyperactivity and combined scores will be summarized, on a continuous scale, at each visit and by treatment group. The change from baseline (Visit 2) will also be included.

5.5.4 Exploratory Efficacy Endpoints

5.5.4.1 Time to Baseline Convulsive Seizure Frequency

Time to baseline convulsive seizure frequency is defined as the number of reported days in IVRS, from Day 1, that it takes for the cumulative number of convulsive seizures experienced to be greater than or equal to the number of seizures (per 28 days) experienced during the baseline period and will be calculated as:

Date criterion was achieved – Date of Day 1 – Number of unreported days in IVRS between Day 1 and date criterion was achieved + 1

Patients who complete the study without experiencing greater than or equal to the number of seizures (per 28 days) experienced during the baseline period, or who withdraw from the study, will be censored at the earlier of:

- Day 99.
- The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF page.

The exact day used for censoring will be the day obtained from above minus the number of unreported days in IVRS between Day 1 and the day obtained from above.

Time to baseline convulsive seizure frequency will be summarized on a continuous scale, by treatment group, for patients in the ITT analysis set. The lower and upper quartiles will also be presented. The Kaplan–Meier estimates for the median time to baseline convulsive seizure frequency will be presented along with 95% CIs for the median and p-values from log-rank tests comparing each GWP42003-P group with placebo. A Kaplan–Meier plot will also be produced.

The above will be repeated using Day 15 instead of Day 1 as the start day for counting the cumulative number of convulsive seizures.

5.5.4.2 Number of Convulsive Seizure Free Days

The number of convulsive seizure free days during each period will be based on 28-day averages and calculated as:

(Number of seizure free days in the period ÷ Number of reported days in IVRS in the period) × 28

The change from baseline in convulsive seizure free days per 28 days will be analyzed for the treatment period using an ANCOVA approach. The model will include baseline and age group as covariates and treatment group as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

The analysis will be repeated for the maintenance period. Analysis on the maintenance period will include only patients who have at least 7 days of seizure data within the maintenance period.

5.5.5 Subgroup Analyses

To assess the degree of effect heterogeneity, effect modifier analyses are proposed, on the ITT analysis set, for the primary efficacy endpoint and the key secondary efficacy endpoint of ≥50% reduction in convulsive seizure frequency.

For the primary efficacy endpoint, the effect modifier analysis will be performed using the negative binomial regression analysis as described in Section 5.5.2. The model will be updated to include covariates for each level of the effect being tested (excluding a reference level), individually and with interactions with time, interactions with treatment arm and interactions with time and treatment. A separate model will be used for testing each effect. The treatment ratios (GWP42003-P vs. placebo), percent reduction and 95% confidence intervals will be presented for each level of the effect. In addition, the effect by time by treatment arm interaction p-value, testing the hypothesis that the effect level treatment ratios are homogeneous, will be presented.

For the key secondary efficacy endpoint of ≥50% reduction in convulsive seizure frequency, patients with a ≥50% reduction in seizure frequency will be modelled using logistic regression, including stratified age group and treatment arm as covariates. The model will also include covariates for each level of the effect being tested (excluding a reference level), individually and with interactions with treatment arm. A separate model will be used for

testing each effect. The number and percent of responders, and odds ratios and 95% confidence intervals will be presented for each level of the effect. In addition, the effect by treatment arm interaction p-value, testing the hypothesis that the effect level odds ratios are homogeneous, will be presented.

The following effects will be tested:

- Age group (2-5 years, 6-12 years and 13-18 years). Note: stratified age group will be removed as a covariate for this model.
- Sex (Male, Female).
- Region (US, Rest of the World).
- Clobazam use (Yes, No).
- Valproic acid use (Yes, No).
- Stiripentol use (Yes, No).
- Clobazam use and Stiripentol use (Yes/Yes, Yes/No, No/Yes, No/No).
- Levetiracetam use (Yes, No).
- Topiramate use (Yes, No).
- Baseline average convulsive seizure frequency per 28 days (≤ observed Tertile 1, > observed Tertile 1 to ≤ observed Tertile 2,> observed Tertile 2). The observed tertile values will be rounded to the nearest whole number.
- Number of concurrent AEDs (<3, ≥3).
- Number of prior AEDs (<4, ≥4).
- Number of prior and concurrent AEDs (<8, ≥8).

5.6 Safety Evaluation

5.6.1 Exposure to IMP

Patients are required to take IMP twice daily (morning and evening). The first dose will be taken in the clinic on Day 1. The date of final dose in the treatment phase will be recorded on the CRF. The date of final dose, for patients who enter the taper period, will be recorded on the CRF at the end of taper visit.

The total number of dosing days in the treatment phase will be calculated as:

(Date of last dose in the treatment phase – Date of Day 1) + 1

The date of last dose in the treatment phase will be obtained from the CRF at the end of treatment visit.

Any missed doses during treatment should be recorded on the 'IMP Missed Doses Log' CRF page. The number of days with any missed doses and the number of days where IMP was not taken in the AM nor PM will be summarized based on data in the treatment phase (Day 1 to end of treatment visit).

In addition, the number of days in which IMP was taken at least once (AM or PM) will be summarized and calculated as:

Total number of dosing days – the number of days where IMP was not taken in the AM nor PM

The number of days in which IMP was taken both AM and PM will be summarized and calculated as:

Total number of dosing days – the number of days with any missed doses

The above summaries will be presented for all patients and repeated for patients who completed the treatment phase.

In addition, the expected daily volume of IMP to be administered during the treatment phase, once a patient has titrated to target dose, will be summarized by treatment.

The expected daily volume of IMP will be calculated as:

2 × [Weight (kg) at Day 1 ÷ 10 and rounded to the nearest 0.1]

for patients randomized to the 20 mg/kg/day dose level and:

2 × [Weight (kg) at Day 1 ÷ 20 and rounded to the nearest 0.1]

for patients randomized to the 10 mg/kg/day dose level.

Finally, IMP compliance will be summarized by treatment and calculated as:

100 × (Number of days IMP taken at least once + number of days IMP taken both AM and PM) ÷ (2 × day of completion or withdrawal during the treatment period)

5.6.2 Adverse Events

All reported AEs will be classified by system organ class (SOC), preferred term and lower level term using Version 17.1 of MedDRA.

Summaries will be presented by treatment group as well as SOC and preferred term.

A treatment emergent AE (TEAE) is defined as an AE with a start date on or after the first dose of IMP. If an AE has a partial start date and it is unclear from the partial date (or the stop date) whether the AE started prior to or post first dose of IMP then the AE will be considered treatment emergent. If the start date of the AE is the same as the date of first dose of IMP and the plausible relationship to IMP is marked on the CRF as “Prior to study medication” then the AE will not be considered treatment emergent.

An AE will be considered treatment-related if the plausibility relationship to IMP is recorded on the CRF as ‘yes’. If the data on plausibility relationship to IMP is missing then the AE will be considered treatment-related.

An AE will be considered leading to permanent discontinuation of IMP if the action taken with IMP is recorded on the CRF as ‘study medication stopped’ or the outcome is recorded on the CRF as ‘patient died’.

An AE will be considered leading to IMP dose reduction excluding permanent discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’, ‘dose reduced temporarily’ or ‘study medication interrupted’.

An AE will be considered leading to temporary IMP dose reduction if the action taken with IMP is recorded on the CRF as ‘dose reduced temporarily’.

An AE will be considered leading to permanent IMP dose reduction excluding permanent discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’.

An AE will be considered fatal if the outcome is recorded on the CRF as ‘patient died’.

The following summaries will be generated (counts are by patient unless specified otherwise):

- Overall summary of AEs, including number of patients reporting each of; TEAEs, treatment-related TEAEs, TEAEs leading to withdrawal, treatment-related TEAEs leading to withdrawal, serious TEAEs, treatment-related serious TEAEs.
- Summary of TEAEs.
- Summary of TEAEs by event.
- Summary of treatment-related TEAEs.
- Summary of treatment-related TEAEs by event
- Summary of TEAEs by maximal severity.
- Summary of TEAEs by sex.
- Summary of serious TEAEs.
- Summary of serious TEAEs by event.
- Summary of non-serious TEAEs.
- Summary of non-serious TEAEs by event.
- Summary of treatment-related serious TEAEs.
- Summary of treatment-related serious TEAEs by event.
- Summary of TEAEs leading to permanent discontinuation of IMP.
- Summary of treatment-related TEAEs leading to permanent discontinuation of IMP.
- Summary of TEAEs leading to IMP dose reduction excluding permanent discontinuation (by resolution and overall).
- Summary of treatment-related TEAEs leading to IMP dose reduction excluding permanent discontinuation (by resolution and overall).
- Summary of TEAEs leading to temporary IMP dose reduction (by resolution and overall).
- Summary of treatment-related TEAEs leading to temporary IMP dose reduction (by resolution and overall).
- Summary of TEAEs leading to permanent IMP dose reduction excluding permanent discontinuation (by resolution and overall).
- Summary of treatment-related TEAEs leading to permanent IMP dose reduction excluding permanent discontinuation (by resolution and overall).
- Summary of fatal TEAEs.
- Summary of TEAEs by time of first onset of AE.
- Summary of TEAEs by time to AE resolution.
- Summary of TEAEs reported in ≥ 2% of patients (after rounding) in the GWP42003-P treatment groups and where the incidence is greater than the placebo treatment group.
- List of patients experiencing TEAEs by SOC and preferred term.
- Summary of pre-treatment AEs.

For the summary of TEAEs by maximal severity, for each patient, the worst severity recorded by preferred term, SOC and overall will be used for summary purposes. If severity is missing, the worst case (severe) will be assumed.

For summaries by resolution, AEs with an outcome of 'recovered' or 'recovered with sequelae' will be summarized as 'Resolved' and AEs with an outcome of 'continuing', 'patient died' or those with a missing outcome will be summarized as 'Not resolved'.

For the summary of TEAEs by time of first onset of AE, data will be summarized under the following categories:

- Weeks 1–2 (Day 1–14).
- Weeks 3–6 (Day 15–42).
- Weeks 7–10 (Day 43–70).
- Weeks 11–14 (Day 71–98).
- >14 weeks (> Day 98).

The time to first onset of AE will be calculated for TEAEs as:

Start date of AE – Date of first dose of IMP + 1

If patients have multiple occurrences of an AE then the AE will be counted once for the first occurrence only. Percentages will be based on the number of patients in the safety analysis set who have a visit or follow-up call within each time period above.

For the summary of TEAEs by time to AE resolution, data will be summarized under the following categories:

- 1 week (≤7 days).
- 2 weeks (8–14 days).
- 3 weeks (15–21 days).
- 4 weeks (22–28 days).
- >4 weeks (>28 days).
- Ongoing (for AEs not resolved).

The time to AE resolution will be calculated for TEAEs as:

Stop date of AE – Start date of AE + 1

If patients have multiple occurrences of an AE then the AE will be counted once for the occurrence with the longest time to AE resolution. However, if any of the AEs are not resolved then the AE will be counted once within the 'Ongoing' category.

The start and stop day of the AE relative to the first dose of IMP (as recorded on the CRF) will be calculated as per Section 5.1.2. For partial dates, if it is clear from the partial date that the start/stop day was prior to the first dose of IMP, then 'pre' will be listed, similarly if it is clear that the event was post the first dose of IMP then 'post' will be listed as the start/stop day as appropriate.

All AEs will be listed. Listings will include the start and stop day of the AE, a flag for treatment emergence, and limited demographic information about the patient (age, sex, race and weight at screening). A separate listing will be provided for pre-treatment AEs, serious AEs and events of special interest (see Appendix 1).

5.6.3 Clinical Laboratory Evaluation

5.6.3.1 Hematology and Biochemistry

Hematology and biochemistry safety parameters are measured at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6, Visit 8 (end of treatment) and Visit 9 (end of taper).

Summaries will be presented by treatment group for each laboratory parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

If values for any of the parameters are below or above the limit of quantification of the assay (BLQ or ALQ), then they will be included in the summary tables at the BLQ or ALQ thresholds. However, for estimated creatinine clearance, results >60 are reported only as '>60'. Hence, estimated glomerular filtration rate (eGFR) will be calculated as:

For patients who are ≥18 years at screening, the Cockroft-Gualt equation will be used:

$$\text{eGFR (mL/min)} = [(140 - \text{age}) \times \text{weight} \times k] / \text{serum creatinine}$$

where age is measured in years, weight is measured in kg, k = 1.23 if male, k = 1.04 if female and serum creatinine is measured in µmol/L. eGFR will be indexed to body surface area (BSA) using the following formula:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = \text{eGFR (mL/min)} \times 1.73/\text{BSA}$$

where BSA is based on the Du Bois and Du Bois formula:

$$\text{weight}^{0.425} \times \text{height}^{0.725} \times 0.007184$$

where weight is measured in kg and height is measured in cm.

For patients who are <18 years at screening, the revised Schwartz estimate will be used:

$$(36.2 \times \text{height}) / \text{serum creatinine}$$

where height is measured in cm and serum creatinine is measured in µmol/L. When available, enzymatic serum creatinine will be used. Otherwise, the Jaffe serum creatinine will be used. If height or weight is missing at the collection date, then the closest value to the sample date will be used. If there is more than one height or weight value on the same day or 2 height or weight values equally distant from the collection date, then the mean will be used. The eGFR will be summarized separately for each method.

Where laboratory samples are repeated, the baseline value is defined as the final recorded value prior to the first dose of IMP. If the Visit 2 data are missing then, where possible, the Visit 1 measurements will be used as baseline.

Shift tables for hematology and biochemistry parameters will be constructed, based upon normal ranges and GW toxicity limits (See Section 8), to determine the categorical shifts from baseline to each post-baseline visit. Values will be categorized as 'Normal', 'Low' or 'High' based on normal ranges and 'Toxically Low', 'Toxically Normal' or 'Toxically High' based on GW toxicity limits.

For eGFR, results will be assigned to the following grades:

- Normal: >60 ml/min/1.73 m^2
- Grade 1: 60 ml/min/1.73 m^2
- Grade 2: ≥30 and <60 ml/min/1.73 m^2
- Grade 3: ≥15 and <30 ml/min/1.73 m^2

- Grade 4: <15 ml/min/1.73 m2

A separate shift table will be produced for eGFR based upon the above grades to determine the categorical shifts from baseline to each post-baseline visit.

Scatter plots will be produced for each laboratory parameter presenting the maximum post baseline result divided by the upper limit of normal (ULN) on the Y-axis, and the baseline result divided by the ULN on the X-axis. However, for prothrombin international normalized ratio (INR), both axes will present the raw results rather than dividing by ULN.

An additional table will be produced, summarizing the number of patients meeting the following criteria:

- Alanine aminotransferase (ALT) > 1×ULN at baseline
- Aspartate aminotransferase (AST) > 1×ULN at baseline
- AT > 1×ULN at baseline
- Treatment emergent ALT > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AST > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AT > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent AT > 3×ULN and either bilirubin > 2×ULN or INR > 1.5

where AT is AST or ALT, and treatment emergent is defined as criteria not met at baseline, but met at any time post-baseline. The above will be summarized overall and for the following subgroups:Sex (Male, Female).

- Valproic acid use (Yes, No).
- Clobazam use (Yes, No).
- Valproic acid use and Clobazam use (Yes/Yes, Yes/No, No/Yes, No/No).
- Patients taking 3 or more current AEDs.
- Patients taking 4 or more current AEDs.

A separate table will be produced, by treatment group and visit, presenting the incidence of patients with urinalysis or blood results indicative of a medical condition at Visit 1 and indicative of an AE after Visit 1.

All laboratory data will be listed; listings will include limited demographic information about the patient (age, sex, race and weight at baseline). Abnormal laboratory values will be listed separately. A further listing will be created for the laboratory reference ranges and toxicity limits.

5.6.3.2 Urinalysis

Urinalysis is assessed, using dipsticks, at the same visits as biochemistry and hematology.

Urinalysis results will be listed only.

5.6.3.3 Pregnancy Test and Urine THC Screen

Serum pregnancy test results and urine THC screen results will be summarized by treatment group and visit.

5.6.4 Vital Signs, Other Physical Findings and Other Safety Data

5.6.4.1 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature and respiratory rate) are measured at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6, Visit 8 (end of treatment) and Visit 9 (end of taper).

At Visit 1 and Visit 2, systolic and diastolic blood pressure are collected in the sitting, supine and standing positions. At all other visits, systolic and diastolic blood pressure are collected in the sitting position only.

Summaries will be presented by treatment group for each vital sign parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

A separate table will be produced, by treatment group and visit, presenting the incidence of patients with vital signs indicative of a medical condition at Visit 1 and indicative of an AE after Visit 1.

Based on the criteria presented in Section 8, potentially clinically significant changes from baseline in vital signs measurements and other defined flagged values will be identified at each visit. The number of patients with a potentially clinically significant change from baseline will be summarized by parameter, visit and treatment group. The number of patients with at least one post-baseline flagged vital sign parameter value will be summarized by parameter, flagged criteria and treatment group.

5.6.4.2 Electrocardiogram

An ECG will be performed at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6, Visit 8 (end of treatment) and Visit 9 (end of taper).

Summaries will be presented by treatment group for ventricular rate, PR interval, QRS duration, QT interval and QTcB, at each visit. Change from baseline to each post-baseline visit will also be presented.

A separate table will be produced, by treatment group and visit, presenting the incidence of patients with an ECG indicative of a medical condition at Visit 1 and indicative of an AE after Visit 1.

Based on the criteria presented in Section 8, defined flagged values will be identified at each visit. The number of patients with at least one post-baseline flagged ECG parameter value will be summarized by parameter, flagged criteria and treatment group.

5.6.4.3 Physical Examination

A physical examination will be performed at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6, Visit 8 (end of treatment) and Visit 9 (end of taper).

Any relevant findings at screening are included as part of the patient's medical history. Any changes seen after screening that are indicative of an AE are to be recorded as such on the AE form and included as part of the AE summaries.

Additionally, height and weight are recorded as part of the physical examination. Height and weight will be summarized and listed together with the vital signs parameters.

Incidence of patients with a physical examination indicative of a medical condition at Visit 1 and indicative of an AE after Visit 1 will be summarized by treatment group and visit.

5.6.4.4 Columbia-Suicide Severity Rating Scale (Children's)

The C-SSRS is completed at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6, Visit 8 (end of treatment) and Visit 9 (end of taper), for patients who are 6 years and older and capable of understanding and answering the questions, in the investigator's opinion. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. At the screening visit, questions are in relation to lifetime experiences and all subsequent questioning in relation to the last assessment.

The following C-SSRS data will be summarized by treatment group at each visit for patients in the safety analysis set:

- Incidence of the following suicidal ideation:
  - Wish to be dead.
  - Non-specific active suicidal thoughts.
  - Active suicidal ideation with any methods (not plan) without intent to act.
  - Active suicidal ideation with some intent to act, without specific plan.
  - Active suicidal ideation with specific plan and intent.
- Incidence of the following suicidal behavior:
  - Actual attempt.
  - Interrupted attempt.
  - Aborted attempt.
  - Preparatory acts or behavior.
  - Suicidal behavior.
  - Completed suicide.

In addition, the number of patients with any suicidality, any suicidal ideation and any suicidal behavior will be summarized by treatment group at screening, baseline and at any time post-baseline. Suicidality is defined as at least one occurrence of suicidal behavior or suicidal ideation.

The number of patients experiencing the following, at any time post-baseline, will also be summarized:

- Complete suicidality.
- Emergence of suicidal ideation.
- Worsening of suicidal ideation.
- Emergence of suicidal behavior.

Emergence of suicidal ideation is defined as having no suicidal ideation at baseline and having reported any type of suicidal ideation at any time post-baseline. Worsening of suicidal ideation is defined to occur when the most severe suicidal ideation rating at any time post-baseline is more severe than its rating at baseline. Emergence of suicidal behavior is defined as having no suicidal behavior at baseline and reporting any type of suicidal behavior at any time post-baseline. If the C-SSRS was not completed at screening or baseline then the patient will not be included in summaries of emergence or worsening of suicidal ideation or behavior.

5.6.4.5 Growth and Development

IGF-1 levels will be analyzed as part of the clinical laboratory testing. IGF-1 levels will be summarized on a continuous scale, including change from baseline, by treatment group.

Change from baseline to the end of treatment visit for IGF-1 levels will also be plotted against the Tanner Stages, weight, and height recorded at baseline.

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging. The patients will undergo a discreet physical examination and be assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only).

Patients will be examined at Visit 2 (Day 1) and Visit 8 (end of treatment). Once a patient reaches a score of V (i.e., 5) the examination need not be performed again.

Tanner Stages will be summarized on a categorical scale, by treatment group.

5.6.4.6 Menstruation

Caregivers will be asked if the female patient is menstruating and details will be recorded as part of their medical history (Visit 2); any changes in normal cycles will be captured at Visit 8 (end of treatment).

Menstruation details will be summarized as appropriate, including any changes in normal cycles at the end of treatment, by treatment group.

5.6.4.7 Cannabis Withdrawal Scale (18 Years)

The CWS is a 19-item scale with each item (withdrawal symptom) measured on a 0–10 NRS (0 = Not at all; 5 = Moderately; 10 = Extremely). The patient or their caregiver is asked to record the extent to which each withdrawal symptom was experienced in the last 24 hours and also to rate the negative impact on normal daily activities (i.e., 2 separate scores are recorded for each item using the same 0–10 NRS). Scores are calculated as the sum of the 19 items for each measure, i.e., each separate score has a theoretical maximum of 190.

The CWS will be used at Visit 2, to establish a baseline score, and then again at Visit 9, the safety follow-up telephone call on Day 123 and Visit 10 for any patient completing the study or withdrawing early. Patients entering the OLE on the day of Visit 8 will continue taking IMP; in this instance withdrawal will be evaluated at the end of their participation in the OLE.

The 2 derived scores, recorded at each visit, will be summarized, on a continuous scale, by treatment group. The change from baseline (Visit 2) will also be included.

If any of the individual items are missing, for each measure, then the corresponding derived score will not be calculated.

The summary will be presented separately for all patients with a completed scale and patients 18 years of age.

5.6.4.8 Pediatric Cannabinoid Withdrawal Scale (4–17 Years)

The PCWS was developed from the 19-item validated CWS (adults) that assesses mood, behavioral and physical symptoms associated with cannabis, which was based on the Marijuana Withdrawal Checklist. The modified 10-item PCWS was developed from a low

literacy version of the CWS. Symptoms specific to adult cannabis withdrawal have been removed and the wording has been amended to be comprehensible to children of the specified age range.

Ratings are based on a 4-point scale where 0 = none, 1 = a little bit, 2 = quite a bit, and 3 = a lot. This rating scale has been compacted from the original 11-point Likert scale used for the CWS in order to simplify the range of options to consider for potential intellectually disabled children. The PCWS was designed with epileptic children in mind as a tool to assess the safety of cannabinoid medications with respect to the stimulation of cannabinoid withdrawal syndrome when medications are withdrawn. As there may be a wide range of intellectual or developmental difficulties in severely epileptic children, from no intellectual or developmental impairment to extreme, the PCWS has been designed to be administered by a treating clinician, either directly to the child, or to the parent or caregiver of the child, reflecting on the child's symptoms within the chosen timeframe.

A derived score is calculated as the sum of the 10 items and has a theoretical maximum score of 30.

The PCWS will be used at Visit 2, to establish a baseline score, and then again at Visit 9, the safety follow-up telephone call on Day 123 and Visit 10 for any patient completing the study or withdrawing early. Patients entering the OLE on the day of Visit 8 will continue taking IMP; in this instance withdrawal will be evaluated at the end of their participation in the OLE.

The derived score, recorded at each visit, will be summarized, on a continuous scale, by treatment group. The change from baseline (Visit 2) will also be included.

If any of the individual items are missing, then the derived score will not be calculated.

The summary will be presented separately for all patients with a completed scale and patients 4–17 years of age.

5.7 Other Measures

5.7.1 Concomitant Medication

Medications will be coded using the World Health Organization Drug Dictionary, Version June 2014.

A medication will be considered concomitant if it has a start date on or after the first dose of IMP or if it was started prior to the first dose of IMP and was ongoing. If a medication has a partial or missing start/stop date and it is unclear from the date whether the medication was taken after the first dose of IMP then it will be considered concomitant.

For summaries and listings of medications the following approach will be used to determine the Anatomical Therapeutic Chemical (ATC) term to be presented:

- If coded to level 4 then the level 4 coded term will be presented.
- If coding is not performed at level 4 but level 3 coding is present then level 3 coded term will be presented.
- If coding is not performed at level 3 but level 2 coding is present then the level 2 coded term will be presented.
- If coding is not performed at level 2 but level 1 coding is present then the level 1 coded term will be presented.

Summaries of each of the following by ATC term and preferred term will be summarized by absolute counts (n) and percentages (%):

- History of antiepileptic medications;
- Concomitant antiepileptic medications;
- Concomitant rescue medications; and
- Other concomitant medications.

The ATC term, preferred term, reported generic name and reported brand name will be listed.

An additional summary table will be produced for concomitant antiepileptic therapies, displaying the number and percentage of patients with a vagus nerve stimulation device or on a ketogenic diet.

The start day and stop day will be included in the listing according to Section 5.1.2. If the date is partial and the exact day is unknown then the text 'pre' or 'post' will replace the start or stop day if it is clear from the partial date that the medication started or stopped prior to or after the first dose of IMP.

5.7.2 Plasma Concentrations of Concomitant Antiepileptic Drugs

Blood sampling for AEDs will be performed at Visit 2 (Day 1), Visit 4, Visit 6 and Visit 8 (end of treatment). For each AED, plasma concentrations will be summarized by treatment group at each visit for patients in the safety analysis set.

5.7.3 Caregiver Impression of Investigational Medicinal Product Palatability

The caregiver's impression of palatability of the IMP will be assessed at Visit 8 (end of treatment). The Caregiver will be asked the following question to be rated on a 5-point scale:

- Overall, how acceptable did your child find the study medication?

The possible responses are: Liked it a lot; Liked it; Neither liked nor disliked it; Didn't like it; Didn't like it at all.

The caregiver's impression of palatability of the IMP will be summarized, on a categorical scale, by treatment group.

5.7.4 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit (Visit 8 or Visit 9, as applicable).

The form will be completed for all patients 12 years of age and older in the study.

Each question will be summarized, on a categorical scale, by treatment group. Percentages will be based on the number of patients completing the survey, in each treatment group. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.5 Supplemental Drug Accountability Form

This form consists of 7 questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified.

The triggering drug accountability discrepancies are as follows:

- Missing bottle(s).
- Compliance issues where one or more bottles are used compared to what was the expected use, according to the IVRS report and paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the IVRS report and paper diary.

The number of patients completing a form will be summarized by treatment group. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.6 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported.

The categories for triggering AEs of interest are:

- Euphoria or inappropriate elation.
- Inappropriate laughter or exhilaration.
- Mood changes.
- Drunk, high or intoxicated.
- Hallucinations (visual or auditory), dissociations, disorientation, agitation.
- Disturbance in cognition, memory, or attention.
- Drug abuse.
- Drug withdrawal or drug withdrawal syndrome.
- Addiction.
- Overdose.
- Misuse of IMP.
- Thoughts of suicide, attempted suicide or suicide.

The number of patients completing a form will be summarized by treatment group. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.7 Site Classification Form

The investigator reviews the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then completes a Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification.

The number of patients completing a form and the possible relationship and level of the certainty for each category will be summarized, on a categorical scale, by treatment group. If more than one form is completed for a particular patient then they will be summarized under each category for all forms. However, if more than one form is completed with and assigned to the same category, then 'related' would be used over 'not related' and the highest level of certainty will be used for the corresponding chosen relationship. The summary will be presented separately for all patients with a completed form and patients 12 years of age and older.

5.7.8 IVRS Compliance

The number of unreported days in IVRS, during the baseline and treatment periods, will be summarized, on a continuous and categorical scale, by treatment group for patients in the ITT analysis set. For the summary on a continuous scale, the lower and upper quartiles will also be presented.

The percentage IVRS compliance, during the baseline and treatment periods, will also be summarized, on a continuous and categorical scale, and calculated as:

[Number of reported days in IVRS ÷ (Number of reported days in IVRS + Number of unreported days in IVRS)] × 100

5.7.9 Meal Times

Patient meal times will be recorded for the day prior to and the day of Visit 2 (Day 1) and Visit 8 (end of treatment). Meal times will be listed only.

5.8 Changes in the Conduct of the Study or Planned Analysis

The identification of 3 key secondary endpoints and the hierarchical testing procedure were not defined in the protocol, but have been included in the SAP prior to unblinding.

Upon blinded review of IVRS data for the number of convulsive seizures greater than 30 minutes in duration and the number of non-convulsive seizures greater than 30 minutes in duration, it was determined that there were insufficient numbers of patients reporting these seizures to perform analyses planned in the protocol.

Upon blinded review of the number of patients with inpatient epilepsy-related hospitalizations, it was determined that there were insufficient numbers of patients to perform analyses planned in the protocol.

The protocol included changes from baseline in usage of rescue medication as an efficacy endpoint. However, due to inconsistencies in the collection of this data, no analyses are proposed.

The endpoint of number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline has been updated to the following:

- Number of patients experiencing a >25% increase, ≥0 to ≤25% increase, >0 to <25% reduction, ≥25 to <50% reduction, ≥50 to <75% reduction or ≥75% reduction in convulsive seizures from baseline.

6. REFERENCES

1 Rubin DB: Multiple imputation for nonresponse in surveys. John Wiley & Sons, New York 1987.

2 Mogg R, Mehrotra DV (2007). Analysis of antiretroviral immunotherapy trials with potentially non-normal and incomplete longitudinal data. Stat Med. 2007;26(3): 484-497.

3 Sabaz M, Cairns D, Lawson J, Nheu, N, Bleasel A, Bye A. Data instructions for the quality of life in childhood epilepsy questionnaire – parent form.

7. AMENDMENTS

Notable changes to the SAP that were completed prior to unblinding, are given below. Minor changes, clarifications and corrections are not listed.

Date	Section	Description of Change

8. ATTACHMENTS AND APPENDICES

Appendix 1 Adverse Events of Special Interest – Abuse Liability

Withdrawal	Drug withdrawal convulsions Drug withdrawal headache Drug withdrawal maintenance therapy Drug withdrawal syndrome Drug withdrawal syndrome neonatal Drug rehabilitation Rebound effect Steroid withdrawal syndrome Withdrawal arrhythmia Withdrawal syndrome
Drug abuse and dependence	Dopamine dysregulation syndrome Drug abuse Drug abuser Drug dependence Drug dependence, antepartum Drug dependence, postpartum Intentional drug misuse Intentional overdose Maternal use of illicit drugs Neonatal complications of substance abuse Polysubstance dependence Substance abuse Substance abuser Accidental overdose Dependence Disturbance in social behaviour Drug administered at inappropriate site Drug detoxification Drug diversion Drug level above therapeutic Drug level increased Drug screen Drug screen positive Drug tolerance Drug tolerance decreased Drug tolerance increased Medication overuse headache Narcotic bowel syndrome Needle track marks Overdose Prescribed overdose Prescription form tampering Substance use Substance-induced mood disorder Substance-induced psychotic disorder Toxicity to various agents

Appendix 2 Ranges for Clinically Significant Changes and Other Defined Flagged Values in Vital Signs

The range of values that will be used to identify clinically significant changes in vital signs parameters (See Section 5.6.4.1) are presented in Table 8.

Table 8 Ranges for Potentially Clinically Significant Changes in Vital Signs

Vital Sign	Range
Sitting Systolic BP	Change: < -20, > 20
Sitting Diastolic BP	Change: < -10, > 10
Pulse Rate	Change: < -10, > 10
Weight	Percent Change: ≤ -7, ≥ 7

Defined flagged values that will be used to identify low or high vital signs parameters (See Section 5.6.4.1) are presented in Table 9.

Table 9 Other Defined Flagged Values for Vital Signs

Vital Sign	Flag
Sitting Systolic BP	< 90, > 140, > 160
Sitting Diastolic BP	< 50, > 90, > 100
Pulse Rate	< 60, > 100
Temperature	> 38.0, < 36.0
Respiratory Rate	< 12, > 20

Appendix 3 Defined Flagged Values in ECG Parameters

Defined flagged values that will be used to identify low or high ECG parameters (See Section 5.6.4.2) are presented in Table 10.

Table 10 Defined Flagged Values for ECG Parameters

ECG Parameter	Flag
QTc	> 450, > 480, > 500

Appendix 4 Toxicity Criteria for Laboratory Parameters

The toxicity criteria that will be used to identify abnormal laboratory parameters are presented in Table 11 and Table 12.

Table 11 Toxicity Criteria for Biochemistry Parameters

Parameter	Toxicity Decrease	Toxicity Increase
Chloride	≤0.96xLL	≥1.04xUL
Calcium	≤0.89xLL	≥1.16xUL
Sodium	≤0.96xLL	≥1.04xUL
Potassium	≤0.90xLL	≥1.10xUL
Glucose (mmol/L)	≤3.2	≥16
Phosphate	≤0.79xLL	
Cholesterol	≤0.85xLL	≥1.6xUL
AST		≥3xUL
ALT		≥3xUL
Lactate Dehydrogenase		≥2.6xUL
Alkaline phosphatase		≥2xUL
Gamma GT		≥2.6xUL
Bilirubin		>2xUL
Albumin	≤0.84xLL	
Total protein	≤0.84xLL	≥1.16xUL
Urea		≥2.6xUL
Blood urea nitrogen		≥2.6xUL
Creatinine		≥2.6xUL
Uric acid		≥1.16xUL

UL = upper limit of reference range LL = lower limit of reference range

Table 12 Toxicity Criteria for Hematology Parameters

Parameter	Toxicity Decrease	Toxicity Increase
Hemoglobin (g/dL)	≤9.4	
Hematocrit (%)	≤28	
Red cell count	≤0.84xLL	

Parameter	Toxicity Decrease	Toxicity Increase
Mean corpuscular volume	≤0.84xLL	≥1.11xUL
Mean corpuscular hemoglobin	≤0.84xLL	
Mean corpuscular hemoglobin concentration	≤0.84xLL	
Platelets (x10^9/L)	≤74	
Prothrombin time		>1.5xUL
Prothrombin international normalized ratio		>1.5
Total white blood cell count (x10^9/L)	≤2.9	≥21
Total neutrophil count (x10^9/L)	≤1.36	≥14.7
Segmented neutrophil count (x10^9/L)	≤0.75	≥12.3
Eosinophils (x10^9/L)		≥1.5
Basophils (x10^9/L)		≥0.31
Monocytes (x10^9/L)		≥2.1
Lymphocytes (x10^9/L) for patients <18 years (auto hematology)	≤1.0	
Lymphocytes (x10^9/L) for patients <18 years (manual hematology)	≤0.2	
Lymphocytes (x10^9/L) for patients ≥18 years	≤0.2	

UL = upper limit of reference range LL = lower limit of reference range

Appendix 5 List of Tables, Listings and Figures

Lists of the tables, listings and figures to be provided are given below in Table 13, Table 14 and Table 15, respectively.

Table 13 List of Tables

Table Number	Title	Analysis Set
Table 1.1.1	Summary of Patient Disposition – Number of Patients Screened and Randomized by Site	All Screened Patients
Table 1.1.2	Summary of Patient Disposition – Number of Patients Screened and Randomized by Country	All Screened Patients
Table 1.2	Summary of Patient Disposition – Reasons for Screen Failure	All Screened Patients
Table 1.3.1	Summary of Patient Disposition – Numbers of Patients Randomized, Withdrawn or Completed the Treatment Period by Site	All Randomized Patients
Table 1.3.2	Summary of Patient Disposition – Numbers of Patients Randomized, Withdrawn or Completed the Treatment Period by Country	All Randomized Patients
Table 1.4	Summary of Overall Patient Disposition	All Randomized Patients
Table 2.1	Summary of Important Protocol Deviations	All Randomized Patients
Table 2.2	Summary of Analysis Sets	All Randomized Patients
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Table 3.1.3	Summary of Demographic Data	PP Analysis Set
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Table Number	Title	Analysis Set
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Table 8.2.1.1	Summary of Convulsive Seizure Frequency	PP Analysis Set
Table 8.2.1.2	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods	PP Analysis Set
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Table 8.2.4	Analysis of Convulsive Seizure Frequency During the Treatment Period – Log-transformed ANCOVA	ITT Analysis Set
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Table 8.2.7	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods After Imputing Unreported Days in IVRS	ITT Analysis Set
Table 8.2.8	Analysis of Percentage Change from Baseline in Convulsive Seizure Frequency During the Treatment Period After Multiple Imputation to Account for MNAR – Wilcoxon Rank-Sum Test	ITT Analysis Set
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Table 8.2.9.2	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods	Safety Analysis Set
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Table 9.1.1.2	Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Treatment Periods	ITT Analysis Set
Table 9.1.2.1	Summary of Total Seizure Frequency	PP Analysis Set

Table Number	Title	Analysis Set
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Table 9.1.3	Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Maintenance Periods	ITT Analysis Set
Table 9.2.1	Summary and Analysis of Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom During the Treatment Period	ITT Analysis Set
Table 9.2.2	Summary and Analysis of Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom During the Treatment Period	PP Analysis Set
Table 9.2.3	Summary and Analysis of Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom During the Maintenance Period	ITT Analysis Set
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Table 9.6.3	Summary and Analysis of Non-Convulsive Seizure Treatment Responders and Non-Convulsive Seizure Freedom During the Treatment Period	ITT Analysis Set
Table 9.6.4	Summary and Analysis of Non-Convulsive Seizure Treatment Responders and Non-Convulsive Seizure Freedom During the Maintenance Period	ITT Analysis Set
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Table Number	Title	Analysis Set
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Table 9.7.3.3	Summary and Analysis of Atonic Seizure Treatment Responders and Atonic Seizure Freedom During the Treatment Period	ITT Analysis Set
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Table 9.7.4.1.1	Summary of Clonic Seizure Frequency	ITT Analysis Set
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Table 9.7.4.2	Negative Binomial Regression Analysis of Clonic Seizure Count During Baseline and Maintenance Periods	ITT Analysis Set
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Table Number	Title	Analysis Set
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