Appendix 1.9 Documentation of Statistical Methods

Statistical Analysis Plan Dated 06 November 2020

GW Research Ltd.

Study Code: GWEP1415

AN OPEN LABEL EXTENSION STUDY TO INVESTIGATE THE SAFETY OF CANNABIDIOL (GWP42003-P; CBD) IN CHILDREN AND ADULTS WITH INADEQUATELY CONTROLLED DRAVET OR LENNOX-GASTAUT SYNDROMES

Statistical Analysis Plan

6th November 2020

CONTENTS

LIST OF ABBREVIATIONS

AEDs	-	Antiepileptic Drugs
AEs	-	Adverse Events
ALQ	-	Above Limit of Quantification
ALT	-	Alanine transaminase
AST	-	Aspartate transaminase
ATC	-	Anatomical Therapeutic Chemical
BLQ	-	Below Limit of Quantification
CBD	-	Cannabidiol
CGIC	-	Caregiver Global Impression of Change
CGICSD	-	Caregiver Global Impression of Change in Seizure Duration
CRF	-	Case Report Form
C-SSRS	-	Columbia-Suicide Severity Rating Scale
CWS	-	Cannabis Withdrawal Scale
DS	-	Dravet Syndrome
ECG	-	Electrocardiogram
EEG	-	Electroencephalography
IGF-1	-	Insulin-like Growth Factor-1
IMP	-	Investigational Medicinal Product
IVRS	-	Interactive Voice Response System
LGS	-	Lennox-Gastaut Syndrome
LOCF	-	Last Observation Carried Forward
MedDRA	-	Medical Dictionary for Regulatory Activities
NRS	-	Numerical Rating Scale
OLE	-	Open Label Extension
PCWS	-	Pediatric Cannabinoid Withdrawal Scale
QOLCE	-	Quality of Life in Childhood Epilepsy
QOLIE-31-P	-	Quality of Life in Epilepsy, Version 2
SAP	-	Statistical Analysis Plan
SGIC	-	Subject Global Impression of Change
SGICSD	-	Subject Global Impression of Change in Seizure Duration
SOC	-	System Organ Class
TEAE	-	Treatment Emergent Adverse Event
ULN	-	Upper Limit of Normal
Vineland-II	-	Vineland Adaptive Behavior Scales, Second Edition

1. INTRODUCTION

This statistical analysis plan (SAP) documents the statistical reporting to be performed for the final analysis of all available data from study GWEP1415.

This SAP has been prepared based on the protocol documents and case report form (CRF).

1.1 Rationales

In this open label extension (OLE) study the Investigational Medicinal Product (IMP) is GWP42003-P oral solution.

This OLE study will provide continued treatment with GWP42003-P for patients with Dravet Syndrome (DS) or Lennox-Gastaut Syndrome (LGS) who have previously completed a double-blind, placebo-controlled, clinical study of GWP42003-P (throughout this document referred to as the "core studies"). The core studies from which patients can enroll in this OLE are detailed below in Table 1.

Table 1 Core Study Information

Study Code	Indication	Phase	Treatment Groups	# of Patients: Planned (Enrolled) [Randomized]	Study Design
GWEP1332 Part A*	DS	II	5 mg/kg 10 mg/kg 20 mg/kg Placebo	30 (41) [34]	4:1 randomized, double-blind, placebo controlled with a 21-day treatment period (3-11 days titration and 14 days maintenance) followed by 10-day taper period.
GWEP1332 Part B	DS	III	20 mg/kg Placebo	100 (177) [120]	1:1 randomized, double-blind, placebo controlled with a 14-week treatment period (2-week titration and 12-week maintenance) followed by 10-day taper period.
GWEP1424	DS	III	10 mg/kg 20 mg/kg Placebo	186 (285) [199]	1:1:1 randomized, double-blind, placebo controlled with a 14-week treatment period (2-week titration and 12-week maintenance) followed by a 10-day taper period.
GWEP1423	LGS	III	20 mg/kg Placebo	100 (200) [171]	1:1 randomized, double-blind, placebo controlled with a 14-week treatment period (2-week titration and 12-week treatment) followed by 10-day taper period.
GWEP1414	LGS	III	10 mg/kg 20 mg/kg Placebo	150 (293) [225]	1:1:1 randomized, double-blind, placebo controlled with a 14-week treatment period (2-week titration and 12-week treatment) followed by 10-day taper period.

TBD: To be determined.

* Study data to be excluded from efficacy tables but included elsewhere.

The study will assess the long-term safety and efficacy of GWP42003-P when taken as adjunctive therapy for DS and LGS.

1.2 IMP Indications

1.2.1 Dravet Syndrome

Dravet syndrome, also known as severe myoclonic epilepsy in infancy, is a rare form of a severe genetically mediated 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 starting in the first year of life and has a poor prognosis for both cognition and control of seizures. The condition is known to also have high mortality.

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.

1.2.2 Lennox-Gastaut Syndrome

Lennox-Gastaut Syndrome is a rare form of severe epilepsy with onset in early childhood. LGS is considered an epileptic encephalopathy in which the epileptic activity contributes to mental deterioration/stagnation and behavioral disorders with a high proportion of patients being drug-resistant.

The onset of LGS usually occurs between 3 and 5 years of age and is characterized by the presence of multiple seizure types (predominantly tonic, atonic and atypical absence seizures), slow (≤2.5 Hz) electroencephalogram (EEG) spikewaves with abnormal background activity when awake and fast (10–20 Hz) polyspikes during sleep. Other seizure types can occur in LGS, including generalized tonic-clonic, focal and myoclonic seizures.

Various behavioral and psychiatric comorbidities are often seen in LGS patients, including attention deficit/hyperactivity disorder, anxiety, aggressive behavior, psychosis and depression. Generally, LGS is more prevalent in boys.

LGS is one of the most pharmacoresistant forms of epilepsy, with all seizure types extremely refractory to conventional AEDs. Sodium valproate is often used to prevent the initial recurrent convulsive seizures and benzodiazepines (e.g. diazepam, midazolam, clonazepam or clobazam) are frequently co-administered to limit the duration of long-lasting seizures and frequency of drop attacks. In most cases however, the relief provided by these agents is insufficient.

2. STUDY OBJECTIVES

The objectives for this SAP are detailed in the following sections.

2.1 Primary

To evaluate the long-term safety and tolerability of GWP42003-P, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS.

2.2 Secondary

All Patients:

To evaluate the effect of GWP42003-P, as adjunctive treatment, on:

- Quality of life.

- Adaptive behavior.
- Need for hospitalizations due to epilepsy.
- Usage of rescue medication.
- Maintenance of seizure frequency reduction and freedom from seizures during the OLE study.
- Frequency of total and subtypes of seizures.
- Change in duration of subtypes of seizures.
- Number of episodes of status epilepticus.
- Cognitive function.
- Growth and development.
- Menstruation cycles (in females).
- Signals indicating drug abuse liability of GWP42003-P.

DS Patients Only:

To evaluate the effect of GWP42003-P, as adjunctive treatment, on:

- Total convulsive seizure frequency.
- Total non-convulsive seizure frequency.
- Number of patients convulsive seizure-free.
- Responder rate (defined in terms of percentage reduction in total convulsive seizure frequency).

LGS Patients Only:

To evaluate the effect of GWP42003-P, as adjunctive treatment, on:

- Drop seizure frequency.
- Non-drop seizure frequency.
- Number of patients drop seizure-free.

Responder rate (defined in terms of percentage reduction in drop seizure frequency).

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a multi-center, OLE study for patients with DS or LGS who have previously participated in double-blind, placebo-controlled, clinical studies of GWP42003-P (the core studies, as detailed in Table 1). This study consists of a 2-week titration period and a maintenance period followed by a 10-day taper period.

3.1.1 Titration Period

When patients have completed the core study from which they enter this study, they may either be receiving Placebo (of varying dose), 5 mg/kg/day GWP42003-P, 10 mg/kg/day GWP42003-P or 20 mg/kg/day GWP42003-P as per their original allocation in their respective core study. Upon entering this study, patients will titrate to 20 mg/kg/day

GWP42003-P using a recommended titration schedule during the 2-week titration period to achieve a stable dose prior to entering the maintenance period.

3.1.2 Maintenance Period

Patients will continue dosing at 20 mg/kg/day GWP42003-P during the maintenance period. However, Investigators may decrease the dose if the patient experiences intolerance, or increase the dose if required for better seizure control, until the optimal dose is found. The Investigator may schedule additional clinic visits to facilitate dose adjustments, e.g. when increasing doses above 20 mg/kg/day GWP42003-P. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. The maximum dose allowed during this study is 30 mg/kg/day GWP42003-P. If seizure freedom is achieved with use of GWP42003-P during the study, the Investigator should consider reducing the dose of concomitant AEDs after six months of seizure freedom.

3.1.3 Study Completion and Taper Period

If market authorization is granted for GWP42003-P (in DS or LGS) or after a maximum period of time receiving treatment, depending on the country in which the patient enrolls, (whichever occurs first), the patient will complete the study. Patients who do not immediately continue to use GWP42003-P will then commence a taper period (down-titrating 10% per day for 10 days) and complete an 'End of Taper Period' visit followed by a Follow-up visit (can be by telephone) four weeks later. If a patient opts not to continue with GWP42003-P treatment, they will commence the 10-day taper period and complete the 'End of Taper Period' visit and the Follow-up visit. If supported by the safety data, the Sponsor will look to extend the duration of this study.

3.2 Definition of Sample Size

As this is an open label safety study, there is no formal sample size calculation. All patients who wished to continue on IMP from the populations included in the double-blind Phase II and Phase III core studies in DS and LGS were eligible for inclusion.

3.3 Safety and Efficacy Endpoints

The safety and efficacy endpoints for this SAP are detailed in the following sections.

3.3.1 Primary Endpoint

The safety of GWP42003-P will be assessed by the AE profile and by evaluating changes in the following, relative to the pre-randomization baseline of the Core Study:

- Vital signs.
- Physical examination (including height and body weight).
- 12-lead electrocardiogram (ECG).
- Columbia-Suicide Severity Rating Scale (C-SSRS) score.
- Cannabis Withdrawal Scale (CWS) score or Pediatric Cannabinoid Withdrawal Scale (PCWS) score, as appropriate.
- Clinical laboratory parameters.

The CWS will be administered to patients aged 18 and older while the PCWS will be administered to patients aged 4–17 (inclusive).

The Children's C-SSRS will be used for patients aged 6–18 (inclusive) and the C-SSRS will be used for patients aged 19 and older.

3.3.2 Secondary Endpoints

All Patients:

- Change in quality of life as measured with Quality of Life in Childhood Epilepsy (QOLCE) if 18 years of age or younger, or Quality of Life in Epilepsy (QOLIE) if 19 years of age or older, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in Subject/Caregiver Global Impression of Change (S/CGIC), relative to the pre-randomization baseline of the Core Study.
- Change in adaptive behavior as measured with the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II), relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in the number of inpatient epilepsy-related hospitalizations (number of hospitalizations due to epilepsy in each 28-day period), relative to the pre-randomization baseline of the Core Study.
- Change in the use of rescue medication (number of days used in each 28-day period), relative to the pre-randomization baseline of the Core Study.
- Maintenance of seizure frequency reduction and freedom from seizures during the OLE study.
- Percentage change in the frequency of total seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in total seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in total seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the frequencies of subtypes of seizures, relative to the pre-randomization baseline of the Core Study.
- Changes in duration of seizure subtypes as assessed by the Subject/Caregiver Global Impression of Change in Seizure Duration (S/CGICSD), relative to the pre-randomization baseline of the Core Study.
- Change in the number of episodes of status epilepticus, relative to the pre-randomization baseline of the Core Study.
- Change in cognitive function as measured with a cognitive assessment battery, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in growth and development for patients less than 18 years of age 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), relative to the pre-randomization baseline of the Core Study.
- Effects on menstruation cycles (in females).
- Drug abuse liability, as measured by AEs of abuse potential, drug accountability and Study Medication Use and Behavior Survey in patients aged 12 and older.

DS Patients Only:

- Percentage change in total convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.
- Percentage change in total non-convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in convulsive seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in convulsive seizures, relative to the pre-randomization baseline of the Core Study.

LGS Patients Only:

- Percentage change in the number of drop seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in drop seizures, relative to the pre-randomization baseline of the Core Study.

4. STATISTICAL METHODS

4.1 General Considerations

All tables will be presented by indication (where appropriate), including an overall count, as follows:

Dravet Syndrome (N=XX)	Lennox-Gastaut Syndrome (N=XX)	Overall (N=XX)

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: Day 1	Day 1
Visit 2: Day 15	Day 15
Visit 3: Day 29	Day 29
Visit 4: Day 85	Day 85
Visit 5: Month 6 or Week 24	Week 24
Visit 6: Month 9 or Week 38	Week 38
Visit 7: Week 48 or End of Treatment (only patients who completed at 1 year)*	Week 48
Visit 8: Week 76	Week 76
End of Treatment (only patients who completed on or after Day 400)*	End of Treatment

End of Treatment (withdrawn patients only)	End of Treatment
End of Taper	End of Taper
Post-Taper Safety Call	Post-Taper Safety Call
Safety Follow-Up	Safety Follow-Up

* For some patients, the end of treatment visit occurs after one year in the OLE, whereas for other patients the end of treatment visit occurs after two or more years in the OLE.

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 in 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 one more decimal place than the raw data, and standard deviation to 2 more decimal places than the raw data. Percentages will be presented to one decimal place.

For patients who enter the OLE on the same day as the core study end of treatment or end of taper visit, the CRF for this study did not require some data to be entered for a second time. Hence, for visit based endpoints, if a patient does not have data entered in this study at Visit 1, then data from the end of treatment or end of taper visit in the core study will be used, provided that the date of collection is on Day 1 of the OLE.

Unless otherwise stated, all summaries will be presented by indication.

All analyses and summaries will be produced using SAS Version 9.4.

4.1.1.1 Choice of Baseline

For all visit-based endpoints, change from baseline will be calculated with reference to the core study baseline only.

For seizure-related endpoints, percentage change from baseline will be calculated from the core study baseline period.

4.1.2 Handling of Missing Data

4.1.2.1 Seizure Data

If a patient withdraws during the time after which they have taken their first dose in the OLE, then seizure frequencies will be calculated from all the available data prior to the patient withdrawing.

Last observation carried forward (LOCF) methodologies that will be carried out on seizure data are discussed in Section 4.5.9.

4.1.2.2 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, time to first onset of AE and time to AE resolution, 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'.

4.1.2.3 Concomitant Medication

Missing concomitant medication dates will be handled in a similar fashion as described for AEs in Section 4.1.2.2.

4.1.3 Day Numbering

The first day of open label treatment (Day 1) will be the date of Visit 1. Any days prior to Day 1, including visits that occur in the core studies that are referenced in this study, 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)

4.1.4 Definitions

4.1.4.1 Core Study Baseline

For interactive voice response system (IVRS) based endpoints, the core study baseline will include all available data prior to Day 1 of the core study as per the derivation in the core study.

For visit based endpoints, the core study baseline will be the visit that was assigned as baseline in the core study. No re-derivation will be carried out.

4.1.4.2 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 patient's last evaluation is performed.

4.1.4.3 Last 12 Weeks

The last 12 weeks (84 days) for IVRS based endpoints is defined as all available data from 12 weeks prior to the earliest of the date of the patient completing/withdrawing from the study, the last call to IVRS, or the last dose date as recorded on the "End of Treatment Study Outcome" page of the CRF.

4.1.4.4 Total Seizures

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

4.1.4.5 Drop Seizures (LGS Patients Only)

Drop seizures are defined as the subset of tonic-clonic, tonic or atonic seizures that are reported as drop seizures in IVRS.

4.1.4.6 Convulsive Seizures

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

4.2 Analysis Sets

There will be one analysis set.

4.2.1 Safety Analysis Set

The safety analysis set will be defined as all patients who receive at least one dose of IMP in the study. Only patients for whom it has been confirmed that they did not take any IMP will be excluded.

4.3 Listings

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

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

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

4.4 Demographic Data and Patient Characteristics

4.4.1 General Approach

All endpoints will be summarized on the safety analysis set, unless specified otherwise. Endpoints will be summarized by indication including an appropriate overall summary, unless specified otherwise. Each individual endpoint section also describes any further categorization of the data along with what is described in this section. Data from all core studies will be used in demographic and patient characteristics outputs.

4.4.2 Patient Disposition

Patient disposition will be summarized using standard summary statistics.

The following patient disposition items will be summarized by absolute counts (n) and percentages (%):

- Completed treatment period
- Discontinued from treatment period (including reason for discontinuation)
- Completed taper period
- Discontinued from taper period (including reason for discontinuation)

A further table split by site will be produced, showing number of patients enrolled, withdrawn and completed the treatment period at each site.

The number of patients who withdrew at any time and by each 12 week period (described in Section 4.5.9) will also be summarized by indication and core study.

4.4.3 Analysis Sets

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

The number of patients included in the safety analysis set from each core study will also be presented.

4.4.4 Demographic Data and Baseline Characteristics

The following demographic data will be summarized:

- Age (years);
- Age group (2-5 years, 6-11 years,12-17 years and 18-55 years);
- Sex;
- Race;
- Country;
- Region (US, Rest of the World);
- Weight at Visit 1 (kg);
- Height at Visit 1 (cm);
- Body mass index at Visit 1 (kg/m^2).

Age will be calculated as:

(Date of Visit 1 – date of birth) ÷ 365.25

The following baseline characteristics will be summarized by indication and overall:

- Number of AEDs a patient is currently taking.
- Number of patients taking clobazam (Yes, No).
- Number of patients taking valproic acid (Yes, No).
- Number of patients taking lamotrigine (Yes, No).
- Number of patients taking levetiracetam (Yes, No).
- Number of patients taking rufinamide (Yes, No).
- Number of patients taking topiramate (Yes, No).
- Number of patients taking felbamate (Yes, No).

The number of AEDs a patient is currently taking is based on the 'Concomitant antiepileptic medications' CRF page. Patients taking the same AED type, but where the AED were coded to different generic terms will be counted only once within the AED 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.

4.4.5 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).

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 indication.

4.5 Safety and Efficacy Analysis

The safety of GWP42003-P is the primary endpoint and the aim of this study is to evaluate long term safety and tolerability and as such, there will be no formal hypothesis testing. Endpoints will be summarized as detailed in the following sections.

4.5.1 General Approach

All endpoints will be summarized on the safety analysis set, unless specified otherwise. Endpoints will be summarized by indication including an appropriate overall summary, unless specified otherwise. Each individual endpoint section also describes any further categorization of the data above that described in this section.

Throughout this section, whenever change from baseline is referenced and the endpoint is non-seizure related the baseline that is used will be the core study baseline. Please refer to Section 4.5.9 for specific rules for the choice of baseline for seizure-related endpoints.

4.5.2 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 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 within this OLE study. 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 study medication 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 study medication is recorded on the CRF as ‘yes’. If the data on plausibility relationship to study medication is missing then the AE will be considered treatment-related.

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

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

The following summaries will be generated:

- 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 treatment-related TEAEs.
- Summary of TEAEs by maximal severity.
- Summary of TEAEs by sex.
- Summary of serious TEAEs.
- Summary of treatment-related serious TEAEs.
- Summary of TEAEs leading to permanent discontinuation of study medication.

- Summary of treatment-related TEAEs leading to permanent discontinuation of study medication.
- Summary of fatal TEAEs.
- Summary of TEAEs by time of first onset of AE.
- Summary of TEAEs by time to AE resolution.
- List of patients experiencing TEAEs by SOC and preferred term.

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

- Weeks 1 to 2 (Day 1 to 14).
- Weeks 3 to 6 (Day 15 to 42).
- Weeks 7 to 10 (Day 43 to 70).
- Weeks 11 to 14 (Day 71 to 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 OLE 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 to 14 days).
- 3 weeks (15 to 21 days).
- 4 weeks (22 to 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.

For time of first onset of AE and time to AE resolution, partial or missing dates will be handled according to Section 4.1.2.2. 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 start date will be imputed as the date of first dose of IMP in the OLE (Day 1). 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 4.1.3. 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).

4.5.3 Clinical Laboratory Evaluation

4.5.3.1 Hematology and Biochemistry

Summaries for hematology and biochemistry will be presented 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.

For post-baseline visits where laboratory samples are repeated, the values from the first non-missing repeat sample taken for the visit, provided it is taken no more than 7 days after the initial sample, will be used. If no values from repeat samples taken within 7 days are available, then the results from the visit sample should be used.

Shift tables for hematology and biochemistry parameters will be constructed, based upon normal ranges and GW toxicity limits (See Section 6), to determine the categorical shifts from core study 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.

An additional table will be produced, summarizing the number of patients with at least one incidence post-Visit 1 of potential Hy's Law case. Potential Hy's Law case is determined by any increase of alanine transaminase (ALT) or aspartate transaminase (AST) to ≥3 times the upper limit of normal (ULN) for patients with normal values at core study baseline (or ≥3 times core study baseline value for patients with elevated values at core study baseline) and to >2 times the ULN for patients with normal values at core study baseline (or >2 times baseline value for patients with elevated values at core study baseline) in total bilirubin.

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

4.5.3.2 Urinalysis

Urinalysis is assessed, using dipsticks, at the same visits as biochemistry and hematology. Urinalysis results will be listed only.

4.5.4 Quality of Life in Childhood Epilepsy (2–18 Years)

The QOLCE is a parent-reported questionnaire that evaluates health related quality of life in children aged 2–18 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.

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 3.

Table 3 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 [1].**Error! Reference source not found.**, 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 indication. The change from baseline will also be included.

The individual responses will not be listed, only the derived information for each derived score will be listed.

4.5.5 Quality of Life in Epilepsy, Version 2 (19 Years and Above)

The QOLIE-31-P is a survey of health-related quality of life for adults with epilepsy. It comprises 38 questions about health and daily activities and also includes questions designed to evaluate how much distress the patient feels about problems and worries related to epilepsy. The QOLIE-31-P will be administered to patients aged 19 years or older. Should the patient be unable to complete the QOLIE-31-P independently, it is permissible for their caregiver to assist.

The questionnaire consists of the following 7 subscales: energy, mood, daily activities, cognition, medication effects, seizure worry, and overall quality of life. Each subscale consists of a number of questions in addition to a 'distress' item. The raw score for each question and the 'distress' item are converted to a 0-100 score according to the scoring manual [2] **Error! Reference source not found.** (higher scores reflecting greater well-being). The converted scores for each question within the subscale are then used to calculate a final subscale weighted score (higher scores reflect better quality of life; lower ones, worse quality of life) as follows:

(Sum of converted scores for each question in the subscale ÷ Number of questions in the subscale) × 'distress' item converted score

The total score (ranging from 0 to 100) is then calculated as:

(Sum of all subscale weighted scores ÷ Sum of all subscale 'distress' item converted scores) × 100

Individual items will be listed only. The weighted subscale scores and the total score, recorded at each visit, will be summarized, on a continuous scale, by indication. The change from baseline will also be included.

The individual responses will not be listed, only the derived information for each derived score will be listed.

4.5.6 Vineland Adaptive Behavior Scales, Second Edition

The Vineland-II is an individually administered instrument for assessing adaptive behaviors and consists of 4 adaptive behavior domains and a maladaptive behavior domain. The details of each domain are presented in Table 4.

Table 4 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 5.

Table 5 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 indication. The change from baseline will also be included.

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.

4.5.7 Cognitive Assessment Battery

The cognitive assessment battery will be administered at Day 1, Week 48 (Day 336), Week 76 (Day 532) and at 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 6.

Table 6 Neuropsychological Protocol for Epilepsy Patients Treated with Cannabidiol – Patient and Parent Measures

Category	Function	Measures	Age Range
Patient	Intelligence **IQ**	WPPSI-4 Vocabulary, Matrix Reasoning	2;6 - 5;11 years
		WASI-2 Vocabulary, Matrix Reasoning (Including Wechsler: 'Digit Span' subtest from WISC-4 and WAIS-4; 'Coding' subtest from WISC-4 & WAIS-4; 'Bug Search' from WPPSI-4)	6 - adult
	Attention/Executive **Trail Making**	Trail Making Test D-KEFS	9 - adult
	Language **Naming Fluency**	Expressive One-Word Picture Vocabulary Test-4th Ed	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	ADHD Checklist (Parent and Teacher)	All ages
	Mood/Anxiety	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 indication at each visit and including the change from baseline using the scored 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:
  - DKEFS scaled scores.
- Language:

- Expressive One-Word Picture Vocabulary Test-4th Ed 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 indication 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 indication 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 indication. The change from baseline (Section 4.1.1.1) will also be included.

4.5.8 Vital Signs, Other Physical Findings and Other Safety Data

4.5.8.1 Vital Signs

All vital signs measurements are taken in a sitting position after five minutes of rest.

Summaries for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature and respiratory rate) will be presented for each vital sign parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

Based on the criteria presented in Section 6, clinically significant changes from core study baseline in vital signs measurements and other defined flagged values will be identified at each visit. The number of patients with a clinically significant change from core study baseline will be summarized by parameter and visit. The number of patients with at least one post-baseline flagged vital sign parameter value will be summarized by parameter and flagged criteria.

4.5.8.2 Electrocardiogram

Summaries for ECGs will be presented for ventricular rate, PR interval, QRS duration, mean QT duration (overall, and for males and females separately) and QTcB (overall, and for males and females separately), at each visit. Change from baseline to each post-baseline visit will also be presented.

Based on the criteria presented in Section 6, 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 and flagged criteria.

4.5.8.3 Physical Examination

Any relevant physical examination findings at Visit 1 are included as part of the patient's medical history. Any changes seen after Visit 1 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.

4.5.8.4 Columbia-Suicide Severity Rating Scale

The C-SSRS is completed 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 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. Suicidality is defined as at least one occurrence of suicidal behavior or suicidal ideation.

4.5.8.5 Cannabis Withdrawal Scale (18 Years and Above)

The CWS is a 19-item scale with each item (withdrawal symptom) measured on a 0–10 numerical rating scale (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 carried out for any patient completing the study or withdrawing early.

The 2 derived scores, recorded at each visit, will be summarized on a continuous scale. The change from core study baseline 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 CWS was to be completed for patients aged 18 years and above only. However, summaries will be based on all patients who have a completed questionnaire, regardless of age.

4.5.8.6 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 carried out at the end of taper visit and at the safety phone call and follow-up visit for any patient completing the study or withdrawing early.

The derived score recorded at each visit will be summarized on a continuous scale by visit. The change from baseline will also be included.

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

The PCWS was to be completed for patients aged 4 to 17 years only. However, summaries will be based on all patients who have a completed questionnaire, regardless of age.

4.5.8.7 Subject/Caregiver Global Impression of Change

The SGIC and CGIC comprise the following questions to be rated on a 7-point scale:

CGIC:

- 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.

SGIC:

- Since you started treatment, please assess the status of your overall condition (comparing your condition now to your 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.

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

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

A combined score will also be summarized and will be defined as follows:

- If both a CGIC and SGIC are completed then the CGIC will be used.
- If only a CGIC is completed then the CGIC will be used.
- If only a SGIC is completed then the SGIC will be used.

4.5.8.8 Subject/Caregiver Global Impression of Change in Seizure Duration

The SGICSD and CGICSD comprise the following questions to be rated on a 3-point scale for each seizure type:

CGICSD:

- 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.

SGICSD:

- Since you started treatment, please assess the average duration of your seizures (comparing your condition now to your 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 patient/caregiver will be asked to assess the average duration of seizures at Visit 1 (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 SGICSD and CGICSD will be summarized separately for each visit.

A combined score will also be summarized. The combined score will be defined as follows:

- If both a CGICSD and SGICSD are completed then the CGICSD will be used.
- If only a CGICSD is completed then the CGICSD will be used.
- If only a SGICSD is completed then the SGICSD will be used.

4.5.8.9 Inpatient Hospitalizations due to Epilepsy

The number of patients with any inpatient epilepsy-related hospitalizations since the previous visit will be presented for each relevant visit, including the baseline visit as established in the core studies.

4.5.8.10 Concomitant Medication and Rescue 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.
- Other concomitant medications.

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

The start day and stop day will be included in the listing according to Section 4.1.3. 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.

4.5.8.11 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.

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 (males only), and breasts (females only).

Patients will be examined at Visit 1 (Day 1) and the end of treatment visit. 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.

4.5.8.12 Menstruation

Caregivers will be asked if the female patient is menstruating and details will be recorded as part of their medical history (Visit 1); any changes in normal cycles will be captured at the end of treatment visit.

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

4.5.8.13 Exposure to Study Medication

Patients are required to take IMP twice daily (morning and evening). The first OLE dose will be taken in the clinic on Visit 1 (Day 1). The date of final dose in the study 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 study 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.

The total number of dosing days in the study will be summarized for all patients, and patients who completed the treatment phase. The modal dose will be calculated for each patient over the same periods associated with IVRS calls for seizure reporting and will subsequently be summarized. Furthermore, a categorical summary of patients whose largest dose was 20 mg/kg/day or less, patients whose largest dose was over 20 mg/kg/day and less than 30 mg/kg/day, and patients whose largest dose was 30 mg/kg/day or more during the OLE study will be presented.

The above summaries will be repeated for the following subgroups:

- Excluding data for patients from study GWEP1332 Part A
- Patients taking clobazam
- Patients not taking clobazam
- Core study actual treatment: GWP42003-P
- Core study actual treatment: Placebo
- Patients taking clobazam; core study actual treatment: GWP42003-P
- Patients not taking clobazam; core study actual treatment: GWP42003-P
- Patients taking clobazam; core study actual treatment: Placebo
- Patients not taking clobazam; core study actual treatment: Placebo

The modal dose for each patient will be calculated across their entire period of exposure, and the number of patients and patient-years exposure will be summarized in the following groups:

- ≤ 20mg/kg/day
- 20 - < 25mg/kg/day
- ≥ 25mg/kg/day

For each group, the total number of patient-years of exposure will be calculated as the sum of the total number of dosing days for each patient divided by 365.25. For the calculation of modal dose, patients will be assumed to be taking 20 mg/kg/day unless a dose adjustment is recorded.

Any missed doses during treatment should be recorded on the 'IMP Missed Doses Log' CRF page.

4.5.9 Seizure Data

The seizure frequency (per 28 days) and percentage change from baseline for total seizures, drop seizures and convulsive seizures during the study will be evaluated for each of the following 12 week periods:

- Week 1 (Day 1) to Week 12 (Day 84)
- Week 13 (Day 85) to Week 24 (Day 168)
- Week 25 (Day 169) to Week 36 (Day 252)
- Week 37 (Day 253) to Week 48 (Day 336)
- Week 49 (Day 337) to Week 60 (Day 420)
- Week 61 (Day 421) to Week 72 (Day 504)
- Week 73 (Day 505) to Week 84 (Day 588)
- Week 85 (Day 589) to Week 96 (Day 672)
- And so on for each 12-week interval

Please note that drop seizures are recorded for LGS patients only.

The percentage change from the baseline period each of the above periods will be presented, including for the last 12 weeks (Section 4.1.4.3).

Percentage change from the baseline period will be calculated as:

((Frequency during the individual period – frequency during baseline period in core study) ÷ frequency during baseline period in core study) × 100

In this study, seizures are recorded on a weekly basis whereas in all core studies, seizures are recorded on a daily basis. Caregivers/patients are expected to call the IVRS system to record the frequencies of seizure subtypes experienced every 7 days from Visit 1 (Day 1) until the end of their participation. The frequency during each of the periods mentioned above will be based on 28-day averages and will be calculated as:

Average number of seizures per day in the period × 28

All calls that take place during the period in question will contribute to the calculation of the average number of seizures per day in that period.

The average number of seizures per day in the period will be calculated as the average of:

Number of seizures reported ÷ Number of days since last call

The number of days since the last call will be calculated as follows, and is dependent on whether the call took place <7, 7 or >7 days after the previous call (or after the date of Visit 1 (Day 1) in the case of the first call in the first period):

- If the call takes place exactly 7 days after the previous call, then the number of days since the last call will be 7.
- If the call takes place <7 days after the previous call, then the number of days since the last call will be calculated as:

  (Date of current call – date of previous call) + 1
- If the call takes place >7 days after the previous call, then the number of days since the last call will be 7.

For the seizure types and periods listed above, summary statistics will be presented for raw seizure frequencies and percentage change from baseline from core study baseline period. In addition, the number of patients with ≥25%, ≥50%, ≥75% and 100% reduction in seizure frequency will be presented.

Furthermore, the percentage change from the core study baseline period will be presented for convulsive seizures from Dravet patients only and for drop seizures for LGS patients only.

All outputs will be repeated with the inclusion of an LOCF imputation step, which is described in the following steps:

- If a patient has valid data for ≥1 consecutive periods from and inclusive of the first period but only missing periods thereafter, then imputation of the missing period(s) will be carried out using the last 12 weeks of valid data (see Section 4.1.4.3).
- If a patient has intermittent missing periods (i.e. ≥1 missing period that falls after a populated period 1 and before subsequent populated periods), then the missing period(s) will be imputed with the closest earlier non-missing period of data.
- If the patient has ≥1 consecutive periods of missing data from and inclusive of the first period then no imputation will occur and data from the patient will be excluded from any LOCF presentations.

Summaries related to seizures as presented in this section and subsequent sections will include patients from all core studies except GWEP1332 Part A, from which data will be listed only.

The seizure frequency (per 28 days) and percentage change from baseline for total seizures, drop seizures and convulsive seizures during the study will be evaluated for the periods described in Section 4.5.9 and for the following subgroups:

- Patients taking clobazam
- Patients not taking clobazam
- Core study actual treatment: GWP42003-P
- Core study actual treatment: Placebo
- Patients taking clobazam; core study actual treatment: GWP42003-P
- Patients not taking clobazam; core study actual treatment: GWP42003-P
- Patients taking clobazam; core study actual treatment: Placebo
- Patients not taking clobazam; core study actual treatment: Placebo
- Patients with data at Week 37 (Day 253) to Week 48 (Day 336) ^
- Patients with data at Week 37 (Day 253) to Week 48 (Day 336); patients taking clobazam ^
- Patients with data at Week 37 (Day 253) to Week 48 (Day 336); Patients not taking clobazam ^

^ Only for convulsive and drop seizures.

4.5.9.1 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 weekly via IVRS.

The number of patients with convulsive and non-convulsive seizures greater than 30 minutes in duration will be presented for each of the periods mentioned in Section 4.5.9.

4.6 Other Measures

4.6.1 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 (at the end of treatment or end of taper visit, 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. Percentages will be based on the number of patients completing the survey.

4.6.2 Plasma Concentrations of CBD and its Major Metabolites

Plasma concentrations for CBD and major metabolites 7-carboxy cannabidiol and 7-hydroxy cannabidiol will be listed only for patients in the safety analysis set.

4.6.3 Plasma Concentrations of Concomitant AEDs

Blood sampling concentrations for AEDs will be listed only for patients in the safety analysis set.

4.6.4 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.

4.6.5 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.

4.6.6 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. 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.

4.7 Changes in the Conduct of the Study or Planned Analysis

A number of additional summaries have been added, compared to the protocol, and are described in the sections above. These additions are not detailed in this section.

The following endpoints described in the protocol are not included as part of the planned analysis in this SAP due to the nature of the collection of data for the endpoint not being compatible with a continuous summary of change from baseline:

- Change in the number of inpatient epilepsy-related hospitalizations (number of hospitalizations due to epilepsy in each 28-day period), relative to the pre randomization baseline of the Core Study.
- Change in the use of rescue medication (number of days used in each 28 day period), relative to the pre-randomization baseline of the Core Study.
- Change in the number of episodes of status epilepticus, relative to the pre randomization baseline of the Core Study.

The following endpoints described in the protocol are not included as part of the planned analysis in this SAP as they were not deemed necessary for the assessment of the objectives of this trial:

- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in total seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the frequencies of subtypes of seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in total non-convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in convulsive seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in drop seizures, relative to the pre-randomization baseline of the Core Study.

In addition, the protocol included summaries of medical history. However, this was not collected as part of the OLE and is reported as part of the core studies only.

5. AMENDMENTS

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

Date	Section	Description of Change

6. REFERENCES

1 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.

2 QOLIE Development Group. Scoring Manual for the QOLIE-31-P: Patient-Weighted Quality of Life in Epilepsy (v2).

7. 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 4.5.8.1) are presented in Table 7.

Table 7 Ranges for Clinically Significant Changes in Vital Signs

Vital Sign	Range
Sitting Systolic BP	Change: < -20, > 20
Sitting Diastolic BP	Change: < -10, > 10
Pulse Rate	Change: < -15, > 15
Weight	Percent Change: ≤ -7, ≥ 7

Defined flagged values that will be used to identify low or high vital signs parameters (See Section 4.5.8.1) are presented in Table 8.

Table 8 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 4.5.8.2) are presented in Table 9.

Table 9 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 10 and Table 11.

Table 10 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
ASAT (SGOT)		≥2.6xUL
ALAT (SGPT)		≥2.6xUL
Lactate Dehydrogenase (LDH)		≥2.6xUL
Alkaline phosphatase		≥2.6xUL
Gamma GT		≥2.6xUL
Bilirubin		≥1.26xUL
Albumin	≤0.84xLL	
Total protein	≤0.84xLL	≥1.16xUL
Urea		≥2.6xUL
Blood urea nitrogen (BUN)		≥2.6xUL
Creatinine		≥2.6xUL
Uric acid		≥1.16xUL

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

Table 11 Toxicity Criteria for Hematology Parameters

Parameter	Toxicity Decrease	Toxicity Increase
Hemoglobin (g/dL)	≤9.4	
Hematocrit (%)	≤28	
Red cell count	≤0.84xLL	
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 ratio		>1.5xUL
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	

Parameter	Toxicity Decrease	Toxicity Increase
Promyelocytes		≥1.1
Metamyelocytes (x10^9/L)		≥1.1
Myclocytes (x10^9/L)		≥1.1

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 12, Table 13 respectively

Table 12 List of Tables

Table Number	Title	Analysis Set
Table 1.1	Summary of Patient Disposition – Numbers of Patients Enrolled, Withdrawn or Completed by Site	All Enrolled Patients
Table 1.2	Summary of Patient Disposition – Primary Reason for Withdrawals	All Enrolled Patients
Table 1.3	Summary of Withdrawals by Core Study and Visit	Safety Analysis Set
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Table 5.1	Summary of Previous Significant Non-Epilepsy Medical or Surgical History Now Resolved	Safety Analysis Set
Table 5.2	Summary of Significant Non-Epilepsy Medical or Surgical History – Current Conditions	Safety Analysis Set
Table 6.1	Summary of Concomitant Antiepileptic Therapies	Safety Analysis Set
Table 6.2	Summary of Concomitant Antiepileptic Medications	Safety Analysis Set
Table 6.3	Summary of Concomitant Rescue Medications	Safety Analysis Set
Table 6.4	Summary of Other Concomitant Medications	Safety Analysis Set
Table 9.1.1.1	Summary of Total Seizure Frequency	Safety Analysis Set
Table 9.1.1.2	Summary of Total Seizure Frequency (LOCF)	Safety Analysis Set
Table 9.1.2.1	Summary of Drop Seizure Frequency	Safety Analysis Set
Table 9.1.2.2	Summary of Drop Seizure Frequency (LOCF)	Safety Analysis Set
Table 9.1.3.1	Summary of Convulsive Seizure Frequency	Safety Analysis Set
Table 9.1.3.2	Summary of Convulsive Seizure Frequency (LOCF)	Safety Analysis Set
Table 9.2	Summary of Patients with Status Epilepticus	Safety Analysis Set
Table 9.3.1	Summary of the Subject/Caregiver Global Impression of Change	Safety Analysis Set
Table 9.3.2	Summary of Subject/Caregiver Global Impression of Change in Seizure Duration	Safety Analysis Set
Table 9.4.1.1	Summary of Total Seizure Frequency - Patients Taking Clobazam	Safety Analysis Set
Table 9.4.1.2	Summary of Total Seizure Frequency - Patients Not Taking Clobazam	Safety Analysis Set
Table 9.4.2.1	Summary of Drop Seizure Frequency - Patients Taking Clobazam	Safety Analysis Set
Table 9.4.2.2	Summary of Drop Seizure Frequency - Patients Not Taking Clobazam	Safety Analysis Set
Table 9.4.3.1	Summary of Convulsive Seizure Frequency - Patients Taking Clobazam	Safety Analysis Set

Table Number	Title	Analysis Set
Table 9.4.3.2	Summary of Convulsive Seizure Frequency - Patients Not Taking Clobazam	Safety Analysis Set
Table 9.5.1.1	Summary of Total Seizure Frequency - Core Study Actual Treatment of Placebo	Safety Analysis Set
Table 9.5.1.2	Summary of Total Seizure Frequency - Core Study Actual Treatment of Active	Safety Analysis Set
Table 9.5.2.1	Summary of Drop Seizure Frequency - Core Study Actual Treatment of Placebo	Safety Analysis Set
Table 9.5.2.2	Summary of Drop Seizure Frequency - Core Study Actual Treatment of Active	Safety Analysis Set
Table 9.5.3.1	Summary of Convulsive Seizure Frequency - Core Study Actual Treatment of Placebo	Safety Analysis Set
Table 9.5.3.2	Summary of Convulsive Seizure Frequency - Core Study Actual Treatment of Active	Safety Analysis Set
Table 9.5.4.1	Summary of Total Seizure Frequency - Core Study Actual Treatment of Placebo and Taking Clobazam	Safety Analysis Set
Table 9.5.4.2	Summary of Total Seizure Frequency - Core Study Actual Treatment of Placebo and Not Taking Clobazam	Safety Analysis Set
Table 9.5.4.3	Summary of Total Seizure Frequency - Core Study Actual Treatment of Active and Taking Clobazam	Safety Analysis Set
Table 9.5.4.4	Summary of Total Seizure Frequency - Core Study Actual Treatment of Active and Not Taking Clobazam	Safety Analysis Set
Table 9.5.5.1	Summary of Drop Seizure Frequency - Core Study Actual Treatment of Placebo and Taking Clobazam	Safety Analysis Set
Table 9.5.5.2	Summary of Drop Seizure Frequency - Core Study Actual Treatment of Placebo and Not Taking Clobazam	Safety Analysis Set
Table 9.5.5.3	Summary of Drop Seizure Frequency - Core Study Actual Treatment of Active and Taking Clobazam	Safety Analysis Set
Table 9.5.5.4	Summary of Drop Seizure Frequency - Core Study Actual Treatment of Active and Not Taking Clobazam	Safety Analysis Set
Table 9.5.6.1	Summary of Convulsive Seizure Frequency - Core Study Actual Treatment of Placebo and Taking Clobazam	Safety Analysis Set
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Table 9.5.6.3	Summary of Convulsive Seizure Frequency - Core Study Actual Treatment of Active and Taking Clobazam	Safety Analysis Set
Table 9.5.6.4	Summary of Convulsive Seizure Frequency - Core Study Actual Treatment of Active and Not Taking Clobazam	Safety Analysis Set

Table Number	Title	Analysis Set
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Table 9.5.7.2	Summary of Convulsive Seizure Frequency - Patients with Week 37 to 48 Data	Safety Analysis Set
Table 9.5.7.3	Summary of Drop Seizure Frequency - Patients Taking Clobazam - Patients with Week 37 to 48 Data	Safety Analysis Set
Table 9.5.7.4	Summary of Drop Seizure Frequency - Patients Not Taking Clobazam - Patients with Week 37 to 48 Data	Safety Analysis Set
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Table Number	Title	Analysis Set
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Table 10.5.2	Summary of Exposure - Core Study Actual Treatment of Placebo and Not Taking Clobazam	Safety Analysis Set
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Listing 14.11.1	Study Medication Use and Behavior Survey – Part 1	Safety Analysis Set
Listing 14.11.2	Study Medication Use and Behavior Survey – Part 2	Safety Analysis Set
Listing 14.12.1	Supplemental Drug Accountability Form	Safety Analysis Set
Listing 14.12.2	Supplemental Adverse Events Form	Safety Analysis Set
Listing 14.12.3	Site Classification Form	Safety Analysis Set
Listing 15	Investigators' General Comments	Safety Analysis Set