GW Research Ltd.

Trial Code: GWEP1521

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF CANNABIDIOL (GWP42003-P, CBD) AS ADD-ON THERAPY IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX WHO EXPERIENCE INADEQUATELY-CONTROLLED SEIZURES

Statistical Analysis Plan

24 April 2019

NOTE: Both the RCT and OLE Phases of this Trial are Included in this Statistical Analysis Plan

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CONTENTS

ABBREVIATION

7-COOH-CBD		7-carboxy-CBD
7-OH-CBD	-	7-hydroxy-CBD
ABCL	-	Adult Behavior Checklist
AEDs	-	Antiepileptic Drugs
AEs	-	Adverse Events
ANCOVA	-	Analysis of Covariance
ALQ	-	Above Limit of Quantification
ATC	-	Anatomical Therapeutic Chemical
BDRM	-	Blinded Data Review Meeting
BLQ	-	Below Limit of Quantification
CBCL	-	Child Behavior Checklist
CBD	-	Cannabidiol
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
ECG	-	Electrocardiogram
IGF-1	-	Insulin-like Growth Factor-1
IMP	-	Investigational Medicinal Product
ITT	-	Intention to Treat
IVRS	-	Interactive Voice Response System
LGS	-	Lennox-Gastaut Syndrome
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

PGIC	-	Physician Global Impression of Change
PK	-	Pharmacokinetics
PP	-	Per Protocol
QOLCE	-	Quality of Life in Childhood Epilepsy
QOLIE-31-P	-	Quality of Life in Epilepsy, version 2
RM	-	Rescue Medication
SAP	-	Statistical Analysis Plan
SGIC	-	Subject Global Impression of Change
SGICSD	-	Subject Global Impression of Change in Seizure Duration
SOC	-	System Organ Class
SCQ	-	Social Communication Questionnaire
TAND	-	TSC-associated Neuropsychiatric Disorders
TEAE	-	Treatment Emergent Adverse Event
TSC	-	Tuberous Sclerosis Complex
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 trial GWEP1521.

This SAP has been prepared based on the following protocol:

- Protocol GWEP1521 (Version 8, dated 23rd April 2019).

1.1 Rationale

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the formation of nonmalignant tumors (tubers) in multiple organ systems. The clinical signs of TSC arise as a result of inactivating mutations in either of two tumor suppressor genes: *TSC1* (located on chromosome 9q34.13) or *TSC2* (located on chromosome 16p13.3). Thus, inactivating mutations in *TSC1* and *TSC2* lead to inadequate suppression of mTOR signaling, resulting in abnormal cellular growth and tumorigenesis.

Mutations in *TSC1* account for approximately 15% of all cases of TSC whilst approximately 70% of all cases are due to mutations in *TSC2*; ~15% of TSC patients have no identifiable mutation in the coding regions of either gene. Generally, *TSC2* mutations result in a more severe disease phenotype compared with *TSC1* mutations. The birth incidence of TSC is estimated to be 1 in 6,000 with approximately 50,000 individuals in the United States and 1 million individuals worldwide affected.

Tumors in TSC patients can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin and lungs.

Epileptic seizures are the most common clinical manifestation of TSC, affecting more than 70% of patients. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80% of TSC patients. The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms.

Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex focal seizures (with or without secondary generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences. Although infantile spasms resolve with time, the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy, including Lennox–Gastaut syndrome.

Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences.

The pharmacological therapies currently available for TSC-associated epilepsy often produce serious adverse effects, and a significant proportion of patients (37–63%) become resistant to treatment. Consequently, there is a clear need for new, efficacious pharmaceutical treatments for refractory epilepsy. Given the limitations of current synthetic antiepileptic drugs (AEDs), it has been suggested that CBD should be tested for anticonvulsive efficacy in randomized controlled clinical trials, especially in infantile epileptic syndromes. Although there are no published reports to date investigating the efficacy of CBD for seizures in TSC patients, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures whilst taking CBD-enriched cannabis, with over half of those reporting >80% reduction in seizure frequency.

The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

2. TRIAL OBJECTIVES

The protocol defined the trial objectives as:

2.1 Primary Objective

Blinded Phase:

To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with TSC.

Open-label Extension:

To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled seizures.

2.2 Secondary Objectives

Blinded Phase:

- To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.
- To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.
- To evaluate the effects of GWP42003-P on quality of life compared with placebo.
- To evaluate the safety and tolerability of GWP42003-P compared with placebo.

Open-label Extension:

- To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.
- To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old).
- To evaluate the long term effects of GWP42003-P on quality of life.
- To evaluate the long term safety and tolerability of GWP42003-P.

2.3 Exploratory Objectives

Blinded Phase:

- To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.
- To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.
- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant AEDs, if applicable.

Open-label Extension:

- To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features compared with placebo.

3. INVESTIGATIONAL PLAN

3.1 Trial Design

This multicenter trial consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.

Blinded Phase:

The blinded phase of the trial is a randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P vs. placebo. Patients will complete a 1-week screening period and a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003 P or placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18–65 years. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded Investigational Medicinal Product (IMP) for 12 weeks.

Dose escalation for each patient is subject to the investigator's assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the trial.

Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE.

Those patients opting not to enter the OLE will complete a 10-day taper period (down-titrating 10% per day for 10 days).

Open-label Extension Transition:

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo arm will titrate up to 25 mg/kg/day GWP42003-P.
- Patients from the 25 mg/kg/day GWP42003-P arm will continue to take 25 mg/kg/day GWP42003-P.
- Patients from the 50 mg/kg/day GWP42003-P arm will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Open-label Extension:

The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The initial OLE period will last for a maximum of 1 year.

Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found.

3.2 Definition of Sample Size

Blinded Phase:

A total of 210 patients will be enrolled. The 210 patients will be randomly allocated to 1 of 4 treatment arms (GWP42003-P 25 mg/kg/day, GWP42003 P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo arms will be pooled for the analyses of efficacy.

If it is assumed that patients in the placebo arm will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per arm will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.

Open-label Extension:

All patients who wish to continue on IMP following the blinded phase.

3.3 Efficacy and Safety Endpoints

3.3.1 Primary Efficacy Endpoint

Blinded Phase:

The primary endpoint is the change in number of TSC associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.

*Primary endpoint TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Open-label Extension:

The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

3.3.2 Secondary Efficacy Endpoints

Blinded Phase:

The following endpoints will be compared between treatment arms over the 16-week, double-blind treatment period (all changes relative to baseline):

Key:

1. Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency (see Section 5.1.3.7).
2. Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
3. Change in total seizures.

Other:

Antiepileptic Efficacy Measures:

- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure frequency.
- Change in number of TSC-associated seizure-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (in patients less than 18 years old):

- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:

- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Physician Global Impression of Change (PGIC) score.

Safety and Tolerability:

- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters.
- Vital signs.
- Columbia-Suicide Severity Rating Scale (C-SSRS: 19+ years) or C-SSRS Children's (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

Open Label Extension:

The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

Key:

- Percentage change in number of TSC-associated seizures (average per 28 days).
- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency.
- Change in CGIC or SGIC score.
- Change in total seizures.

Other:

Antiepileptic Efficacy Measures:

- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure frequency.
- Change in number of TSC-associated seizure-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (patients less than 18 years):

- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:

- Changes in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in PGIC score.

Safety and Tolerability:

- Clinical laboratory parameters.
- ECG.
- Physical examination parameters (including height and weight).
- Vital signs.
- C-SSRS (19+ years) or C-SSRS Children's (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

3.3.3 Exploratory Endpoints (Double-blind and Open-label Extension)

Antiepileptic Efficacy Measures:

- Change in composite focal seizure score (frequency × severity).
- Change in number of seizures by subtype.
- Change in use of rescue medication.
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

TAND:

Cognitive and Behavioral Function:

- Changes in Vineland Adaptive Behavior Scales, Second Edition (Vineland-II).

- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklists (CBCL) and Adult Behavior Checklist (ABCL).

Autistic Features:

Change in Social Communication Questionnaire (SCQ) score.

PK (Double-blind only):

- The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable time-point will be calculated.
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

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 the identification and agreement on major protocol deviations and the need for a per protocol (PP) analysis set.

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

- Pre-randomization patient data
- Patient efficacy data
- Concomitant medication data
- Patient safety data
- Patient protocol deviation logs

This SAP documents the currently planned analyses for this trial that will be approved prior to breaking the blind for the trial. Changes to the analyses planned within any previously approved versions of the SAP will be summarized in Section 7 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 for the double-blind phase, the trial medications will be referred to and labelled as per Table 1.

Table 1 Blinded Phase Trial Treatments

Endpoint	Actual Treatment	Treatment Label
Efficacy	Pooled Placebo	Placebo
Safety	25 mg/kg/day Placebo	Placebo 25 mg/kg
	50 mg/kg/day Placebo	Placebo 50 mg/kg
All	25 mg/kg/day GWP42003-P	25 mg/kg
All	50 mg/kg/day GWP42003-P	50 mg/kg

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

For OLE tables, columns will be included for treatment received during the double-blind phase (GWP42003-P or placebo, i.e. not split by dose) and overall.

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

Table 2 Trial Visits

Actual Visit	Visit Label
Visit 1: Screening	Day -35
Visit 2: Day -28, baseline visit	Day -28
Visit 3: Day 1, Randomization	Day 1
Visit 4: Day 15	Day 15
Visit 5: Day 29	Day 29
Visit 6: Day 43	Day 43
Visit 7: Day 57	Day 57
Visit 8: Day 71, Telephone	Day 71
Visit 9: Day 85	Day 85
Visit 10: Day 113	End of Treatment
Visit 11: Day 123	End of Taper
Visit 12: Day 151	Safety Follow-Up
Visit B1: Day 1, Enrollment	OLE Day 1
Visit B2: Day 15	OLE Day 15
Visit B3: Day 36	OLE Day 36
Visit B4: Day 92	OLE Day 92
Visit B5: Day 141, Re-stocking of supplies	OLE Day 141
Visit B6: Day 183	OLE Day 183
Visit B7: Day 232, Re-stocking of supplies	OLE Day 232
Visit B8: Day 274	OLE Day 274
Visit B9: Day 323, Re-stocking of supplies	OLE Day 323
Visit B10: Day 365	OLE End of Treatment
Visit B11: Day 375	OLE End of Taper
Visit B12: Day 389	OLE Post-taper Safety Telephone Call
Day 403	OLE 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 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.

Unless otherwise specified, tables for the blinded phases will be summarized by randomized treatment arm, and for the open-label extension phase will be summarized by double-blind randomized treatment arm and overall.

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, including any data available after the patient withdraws.

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

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

For each subscale, if fewer 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 less 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.

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

For missing questions within subscales, the following rule will be applied:

- For subscales containing 4 or more questions (not including the 'distress' item), apply the following:
  - If less than or equal to 50% of the questions within the subscale are missing then the converted score for the missing questions will be set to the average of the non-missing question converted scores.
  - If more than 50% of the questions within the subscale are missing then the subscale weighted score will be set to missing.
- For subscales containing less than 4 questions (not including the 'distress' item) the subscale weighted score will be set to missing.

For missing 'distress' items, the following rule will be applied:

- If the corresponding subscale weighted score is missing then no imputation is needed and the 'distress' item converted score will be missing.
- If the corresponding subscale weighted score is not missing then set to the average of the non-missing 'distress' item converted scores.

For missing subscale weighted scores or missing 'distress' item converted scores, the following rule will be applied when calculating the total score:

- If 3 or more of the 'distress' item converted scores are missing then the total score will be set to missing.
- If 3 or more of the subscale weighted scores are missing then the total score will be set to missing.

- If less than 3 'distress' item converted scores are missing and less than 3 subscale weighted scores are missing, then the total score will be calculated based on the available non-missing data, following the rules above.

Note: it is possible that a subscale weighted score is missing, but that the corresponding 'distress' item was answered and the converted score is not missing. Following the rules above, the total score would include the non-missing 'distress' item converted score in the calculation even though the corresponding subscale weighted score is missing and hence not included.

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

Blinded Phase:

The first day of treatment (Day 1) will be taken from the Study Medication case report form (CRF) page at Visit 3. However, if this date is missing then the date of Visit 3 will be used.

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)

Open-label Extension:

The first day of treatment in the OLE (OLE Day 1) will be day of entry into the OLE, which is expected to be the same day as the end of treatment visit from the blinded phase. OLE day will be calculated as above but relative to OLE 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 from the day of Visit 2 to Day 1 of the blinded phase.

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 patient's last evaluation is performed.

5.1.3.3 Last 12 Weeks (OLE Only)

The last 12 weeks (84 days) of the OLE for IVRS based endpoints is defined as all available data from 12 weeks prior to the earliest of the date of the patient completing the OLE, or the last call to IVRS.

5.1.3.4 Treatment Period

The treatment period of the double-blind phase is defined as Day 1 to Day 113.

5.1.3.5 Titration Period

The titration period of the double-blind phase is defined as Day 1 to Day 28.

5.1.3.6 Maintenance Period

The maintenance period of the double-blind phase is defined as Day 29 to Day 113.

5.1.3.7 TSC-associated Seizures

TSC-associated seizures are defined as focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, and generalized seizures (tonic-clonic, tonic, clonic and atonic) that are countable.

5.1.3.8 Other Seizures

Other seizures are defined as absence, myoclonic, partial (focal) sensory seizures, and infantile or epileptic spasms.

5.1.3.9 Total Seizures

Total seizures are defined as the combination of TSC-associated seizures and other seizures.

5.1.3.10 Focal Seizures

Focal seizures are defined as Type 1, Type 2 or Type 3 as follows:

- Type 1: focal motor seizures without impairment of consciousness or awareness.
- Type 2: focal seizures with impairment of consciousness or awareness.
- Type 3: focal seizures evolving to bilateral convulsive seizures.

5.1.4 Interim Analysis

No formal interim analysis is to be conducted in this trial. However, interim reporting of the OLE may be required to support regulatory filings. This SAP contains details for the final reporting of the double-blind and OLE phases of the trial. For interim reporting of the OLE,

the rules described in the SAP will be followed. However, only a subset of outputs including OLE data may be required to support regulatory filings.

If interim reporting of the OLE is required, then only data available up to and including the date of the data cut will be included. The below section describes how data will be selected for the interim reporting.

5.1.4.1 Selection of Data and Handling of Partial Dates

For data that has an associated visit date or date of collection but does not have an associated start or end date, there is expected to be no partial date information. Therefore, data of this type that are collected after the date of data cut will not be included as part of the interim analysis. For non-medical history data that have an associated start date or end date, such as AEs or concomitant medications, the following rules will be followed in order to determine whether the records are included in the interim analysis.

Partial Start and/or End Dates

The following procedures will be followed in the event that a record has partial start or end dates:

Partial start date:

- If the start date is partial, then it will be assumed to have started at the earliest possible date based on the partial date provided, for the purposes of determining if the data should be included in the interim analysis only.

Partial end date:

- If the end date is partial, then it will be assumed to have ended at the latest possible date based on the partial date provided. However, if the patient withdrew from the trial, completed the trial or died prior to this imputed date, then the maximum of the last available visit date and the withdrawal/completion or death date will be used instead.

Once the dates have been suitably imputed, the processes for complete start or end dates, specified below, can then be followed to determine whether the record should be included in the data cut and how it should be adapted.

Complete Start or End Dates

The following procedures will be followed in the event that a record has complete start or end dates:

- If the start date falls on or before the date of data cut and the end date falls after the date of data cut, then the record will be included in the data cut but the end date will be set to missing and depending on the type of data, the following adjustments will be made:
  - For an AE record, the outcome will be set to “Continuing”.
  - For a concomitant medication record, the record will be set to “Ongoing at the End of the Trial”.
- If the start date falls after the date of data cut, then the record will not be included in the data cut.

5.2 Analysis Sets and Protocol Deviations

5.2.1 Safety Analysis Set

All randomized patients who received at least 1 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.

5.2.2 Intention to Treat Analysis Set

All randomized patients who received at least one dose of IMP will be included and analyzed according to their randomized treatment arm.

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

5.2.3 Per Protocol Analysis Set and Protocol Deviations

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

All patients who complete the trial with no protocol deviations deemed to compromise the assessment of efficacy, will be included and analyzed according to the treatment arm they were randomized. 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 BDRMs on 22nd and 25th March 2019. In addition to patients in the ITT analysis set who withdrew from the trial during the blinded 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.

5.2.4 OLE Safety Analysis Set

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

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 for the double-blind and OLE phases, including patients treated, completed the treatment and taper phases, 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, PP and OLE safety 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 arm and overall for the safety, ITT, PP and OLE safety analysis sets:

- Age (years);
- Age group (1–6 years, 7–11 years,12–17 years and 18–65 years);
- Sex;
- Race;
- Country;
- Region (US, 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 arm and overall for the safety, ITT, PP and OLE safety analysis sets:

- Average number of TSC-associated seizures per 28 days during baseline.
- Average number of total seizures per 28 days during baseline.
- Number of patients with seizures during the baseline period, by seizure type.
- Number of AEDs a patient has used, prior to the trial and is no longer taking.

- Number of AEDs a patient is currently taking.
- Total number of prior and current AEDs.
- 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 levetiracetam (Yes, No, and if no, Prior).
- Number of patients taking vigabatrin (Yes, No, and if no, Prior).

The number of prior AEDs no longer taking will be taken from the 'History of antiepileptic medications and therapies' CRF page. The number of AEDs 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 and the medication is considered concomitant (see Section 5.7.1) for the double-blind phase, then this will not be included in the number of prior AEDs no longer taking. AEDs starting after the last dose of IMP during the double-blind phase will not be counted.

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.

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 each of the other AEDs. The number of patients taking other AED types will also be presented if the overall frequency of patients taking the AED is >25%.

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

5.4.4 Epilepsy History

5.4.4.1 Genetic Testing History

Genetic testing history data will be listed only.

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

Data will be summarized by treatment arm and overall for the safety analysis set only, 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 data will be listed only.

For patients with more than one 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 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 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA v19.1).

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 arm. 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

Blinded Phase:

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 16 weeks of treatment there is no difference in effect between the 25 mg/kg/day GWP42003-P treatment arm and the placebo treatment arm in terms of the change in number of TSC-associated seizures during the treatment period compared to baseline.

The null hypothesis will be rejected if there is statistical evidence of a difference between the treatment arms 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 (25 mg/kg/day GWP42003-P vs. placebo and 50 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	25 mg/kg/day GWP42003-P vs. Placebo
2	1st key secondary endpoint	25 mg/kg/day GWP42003-P vs. Placebo
3	Primary endpoint	50 mg/kg/day GWP42003-P vs. Placebo
4	1st key secondary endpoint	50 mg/kg/day GWP42003-P vs. Placebo
5	2nd key secondary endpoint	25 mg/kg/day GWP42003-P vs. Placebo

6	3rd key secondary endpoint	25 mg/kg/day GWP42003-P vs. Placebo
7	2nd key secondary endpoint	50 mg/kg/day GWP42003-P vs. Placebo
8	3rd key secondary endpoint	50 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.

Open-label Extension:

All endpoints will be summarized on the OLE safety analysis set, unless specified otherwise.

Endpoints will be summarized by treatment received during the double-blind phase (GWP42003-P or Placebo, i.e. not split by dose) and overall.

For seizure endpoints, the OLE treatment phase will be split into 12 week periods, for example:

- OLE Week 1 (OLE Day 1) to OLE Week 12 (Day 84)
- OLE Week 13 (OLE Day 85) to OLE Week 24 (OLE Day 168)
- OLE Week 25 (OLE Day 169) to OLE Week 36 (OLE Day 252)
- OLE Week 37 (OLE Day 253) to OLE Week 48 (OLE Day 336)
- OLE Week 49 (OLE Day 337) to OLE Week 60 (OLE Day 420)
- Etc.

In addition, seizure data will be presented for the full OLE treatment phase as well as the last 12 weeks of the OLE treatment phase (see Section 5.1.3.3).

5.5.2 Primary Efficacy Endpoint

Blinded Phase:

The primary endpoint is the change in number of TSC-associated seizures (see Section 5.1.3.7) during the treatment period (see Section 5.1.3.4) compared to baseline period (see Section 5.1.3.1) in patients taking GWP42003-P compared with placebo.

The primary endpoint will be analyzed using a negative binomial regression model with the total number of TSC-associated seizures during the baseline period and treatment period as the response variables.

A mixed effect model with repeated measures will be performed modelling the observed total number of TSC-associated 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 (1–6 years, 7–11 years, 12–17 years and 18–65 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 seizure data 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 no seizures during the baseline or treatment period then all patients will have their baseline and treatment period seizure count adjusted by adding a value of 1.

The estimated least squares mean seizure rate for each period and 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 arm 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 the ITT analysis set.

TSC-associated seizure frequency (28-day average) and percentage change in seizure frequency will also be presented using summary statistics. Percentage change from baseline in TSC-associated 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 the TSC-associated seizure endpoints only, if patients are randomized with no TSC-associated seizures during the baseline period then the percentage change from baseline will be calculated as:

(Frequency during the treatment period + 1) × 100

Open-label Extension:

The primary endpoint for the OLE is the safety of GWP42003-P, evaluated by assessing the incidence, type and severity of AEs. Data will be presented as per Section 5.6.2.

However, percentage change from baseline in TSC-associated seizure frequency is considered a key secondary endpoint for the OLE.

In the OLE, seizures are recorded on a weekly basis rather than daily. Caregivers/patients are expected to call the IVRS system to record the number of seizure subtypes experienced every 7 days during the OLE. TSC-associated seizure frequency per 28 days will be calculated for each of the periods described in Section 5.5.1. 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 only.

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 IVRS 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 OLE 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.

Summary statistics will be presented for raw seizure frequencies and percentage change from baseline (from the blinded phase).

5.5.2.1 Sensitivity Analyses for the Primary Efficacy Endpoint

Blinded Phase:

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

- Primary endpoint analysis repeated using the PP analysis set.
- Wilcoxon rank-sum test on percentage change from baseline in TSC-associated seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P arm 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 TSC-associated seizure frequency during the treatment period.

  The ranks of the percentage change from baseline and the baseline TSC-associated 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 TSC-associated seizure frequency and stratified age group as covariates and treatment arm 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 TSC-associated seizure frequency during the treatment period.

  The TSC-associated seizure frequency during the treatment period and the baseline TSC-associated seizure frequency will be log transformed prior to analysis. The log transformed TSC-associated seizure frequency during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline TSC-associated seizure frequency and stratified age group as covariates and treatment arm 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 TSC-associated seizures during the baseline or treatment periods, then 1 will be added to the TSC-associated seizure frequency for all patients prior to log transformation.
- ANCOVA on percentage change from baseline in TSC-associated seizure frequency during the treatment period including baseline and stratified age group as covariates

and treatment arm 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 5.1.3.6) 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 the titration period (see Section 5.1.3.5) each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12-week maintenance period).
  These analyses will include only patients who have at least 7 days of seizure data within each corresponding 4 week period.

- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the 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 TSC-associated 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

- Primary endpoint analysis repeated using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption (see Section 5.5.2.1.1).

Open-label Extension:

Open-label summaries 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 5.1.3.3).
- 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.

5.5.2.1.1 Sensitivity Analysis of Missing Data

Missing data in this trial could potentially arise from the mechanism of MNAR. Hence, a sensitivity analysis is required to assess the potential impact that missing data under the mechanism of MNAR may have on the estimated results for the primary endpoint.

To facilitate multiple imputation techniques for missing data due to patients who withdraw from the treatment period, it is necessary to divide the treatment period into smaller periods for which missing seizure data can be imputed. Hence, sensitivity analysis of the primary endpoint will be carried out based on periods corresponding to each 14 days of the

treatment period, by multiple imputations on the average daily TSC-associated seizure frequency. The final period will consist of 15 days to include Day 113, where applicable. Following imputation, the imputed periods will be recombined for each patient in order to repeat the primary analysis.

For each 14 calendar days of the treatment period (15 days for the final period), the average daily TSC-associated seizure frequency will be calculated as:

(Number of TSC-associated seizures in the period ÷ Number of reported days in IVRS in the period)

For patients with <6 days in a period, the frequency will be set to missing and will be imputed as part of this analysis.

For intermittent missing data, in which subjects have missing values for intermediate periods but have available data at subsequent periods, imputation will be based on the MCMC methodology. Assumptions underlying this partial imputation step are that patients will follow a similar outcome trajectory as patients in their respective treatment arm that have complete data. Intermittent missing values will be imputed using the MCMC method in PROC MI with an IMPUTE=MONOTONE statement for 200 times for each treatment arm separately. To avoid negative results, a minimum of 0 will be specified in the PROC MI statement. As a result, missing intermediate visits will be imputed and the resulting 200 partially imputed datasets will have a monotone missing pattern.

The remaining monotone missing data will then be imputed using predictive mean matching in which missing observations are imputed with an observed value from another patient whose predicated value is close to the predicated value of the patient with the missing observation. The predictive mean matching is performed using the steps below, in which imputation will be carried out on each of the 200 imputed datasets using the SAS MI procedure (with the 200 imputed datasets included in the 'BY' statement of the MI procedure):

Step 1 – Missing at random (MAR) based multiple imputation for the placebo arm:

- Monotone missing data under the MAR assumption at period t will be imputed using predictive mean matching method from the observed daily TSC-associated seizure frequency at baseline and at each period up to period t (in chronological order)
- The imputation will be realized using the MI procedure with the 'MONOTONE REGPMM' option.
- The imputation model will include baseline daily TSC-associated seizure frequency and each period up to period t (in chronological order).

Step 2 – MNAR based multiple imputation for the GWP42003-P arms (MNAR is assumed for missing values resulting from discontinuation due to any reason or any other monotone missing data):

- With the data imputed from Step 1, monotone missing data under the MNAR at period t will be imputed using predictive mean matching method.
- At each period t, the input dataset for the MI procedure will include all placebo patients and those patients from each GWP42003-P arm (implemented separately by arm) that have values at that period.
- The imputation will be realized using the MI procedure with the 'MONOTONE REGPMM' option.

- The imputation model will include daily TSC-associated seizure frequency at baseline and each period up to period t (in chronological order).

Once all missing values at all periods have been imputed, the TSC-associated seizure count for each period will be calculated as:

(Daily frequency for the period × Number of days in the period for the non-imputed period or 14 for an imputed period), rounded to the nearest whole number

The result will be 200 fully imputed datasets ready to be analyzed using the same analysis method as the primary endpoint, producing 200 analysis results.

The estimated ratio, 95% CI and p-value from analyses of the 200 imputed datasets will be combined using PROC MIANALYZE.

To test the robustness of the analysis to the MNAR imputations a tipping point analysis will be performed. This will be conducted by adding or subtracting a sensitivity parameter, k × standard error of the observed average daily TSC-associated seizure frequency in the placebo arm at each period, to the MNAR imputations only at the corresponding period (where k = 0, ± 0.5, ± 1.0, ± 1.5, etc.).

The tipping point analysis 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.

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: TSC-associated Seizure Treatment Responders (≥50% Reduction in TSC-associated Seizure Frequency)

Blinded Phase:

The proportion of patients considered treatment responders, defined as those with a ≥50% reduction in TSC-associated seizure frequency from baseline during the treatment period, for patients who have not withdrawn from the trial during the treatment period, will be summarized by treatment arm 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 arms 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 arm 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, the titration period and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration 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.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE periods. However, for the OLE periods, withdrawn patients may be considered responders.

5.5.3.1.2 2nd Key Secondary Endpoint: Subject/Caregiver Global Impression of Change

Blinded Phase:

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.

The responses above are based on comparison with a brief description of the patient's overall condition used as a memory aid from Visit 3.

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 arm.

It is anticipated that only a small percentage of patients will complete the subject version of the questionnaire. Hence, no analyses will be performed for the SGIC.

A combined score will be used as the primary analysis for this endpoint. The combined score 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.

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 arm as a factor. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, 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 primary 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.

Since this analysis uses a combination of caregiver and subject ratings, a sensitivity analysis will be performed using only the CGIC score and using the same analyses as above.

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

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.3.1.3 3rd Key Secondary Endpoint: Total Seizures

Blinded Phase:

Summaries and analyses of total seizures (see Section 5.1.3.9) 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, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration 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.

Open-label Extension:

Summaries will be performed for the OLE periods as described in the OLE portion of the primary endpoint section (Section 5.5.2).

5.5.3.2 Other Secondary Efficacy Endpoints

5.5.3.2.1 TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom

Blinded Phase:

The 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 TSC-associated seizure frequency from baseline during the treatment period will be summarized by treatment arm.

In addition to the key secondary endpoint, the proportion of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in TSC-associated seizure frequency from baseline and the proportion of patients who are TSC-associated seizure free, defined as those with a 100% reduction in TSC-associated seizure frequency from baseline, during the treatment period, for patients who have not withdrawn from the trial

during the treatment period will be summarized by treatment arm and analyzed using a CMH test stratified by age as described in Section 5.5.3.1.1.

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 only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration 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.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

5.5.3.2.2 Number of TSC-associated Seizure Free Days

Blinded Phase Only:

The number of TSC-associated 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 TSC-associated seizure free days per 28 days will be analyzed for the treatment period using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm 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.

5.5.3.2.3 Other Seizures

Blinded Phase:

For other seizures (see Section 5.1.3.8), 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.

Other seizure and total seizure 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 and titration periods and during each 4 weeks of the maintenance period will be produced for total seizures only. Patients with no corresponding other seizures during the baseline period will be excluded from the analysis for other seizures.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

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

Blinded Phase:

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 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.[1], 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 arm. The change from baseline 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 analysis of covariance (ANCOVA). The model will include baseline and stratified age group as covariates and treatment arm as fixed factor.

The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented. Exploratory analyses may also be performed on other subscale scores.

Missing data will be handled according to Section 5.1.1.2.1.

The QOLCE was to be completed for patients aged 2-18 years old only. The primary analysis will be based on all patients who have a completed questionnaire, regardless of age. Summaries and analyses will be repeated using questionnaires only from patients who were aged 2 to 18 years old at the time of informed consent.

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

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

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

Blinded Phase:

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] (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 treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the weighted subscale scores and the total score, will be analyzed using the same ANCOVA approach as specified in Section 5.5.3.2.4.

Missing data will be handled according to Section 5.1.1.2.2.

The QOLIE-31-P was to be completed for patients aged 19 years and above only. The primary analysis will be based on all patients who have a completed questionnaire, regardless of age. Summaries and analyses will be repeated using questionnaires only from patients who were aged 19 years or older at the time of informed consent.

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

5.5.3.2.6 Physician Global Impression of Change

Blinded Phase:

The PGIC comprises the following questions to be rated on a 7-point scale:

- Please assess the change in the patient's general functional abilities since Visit 3 (prior to the commencement of study medication).

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 3.

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

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

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 arm as a factor. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, 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 primary 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.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4 Exploratory Efficacy Endpoints

5.5.4.1 Composite Focal Seizure Score

Blinded Phase:

Composite focal seizure score will be calculated as the sum of:

- 1 × Number of focal motor seizures without impairment of consciousness or awareness.
- 2 × Number of focal seizures with impairment of consciousness or awareness.
- 3 × Number of focal seizures evolving to bilateral convulsive seizures.

Summaries and analyses of composite focal seizure score will be performed as per the primary endpoint (Section 5.5.2).

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the

maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration 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.

Open-label Extension:

Summaries will be performed for the OLE periods as described in the OLE portion of the primary endpoint section (Section 5.5.2).

5.5.4.2 Individual Seizure Types

Blinded Phase:

For each individual seizure type (focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, tonic-clonic, tonic, clonic, atonic, absence, myoclonic and partial sensory seizures, and infantile or epileptic spasms), summaries will be performed as per the primary endpoint (Section 5.5.2). However, analyses will only be performed for the following seizure types:

- Focal motor seizures without impairment of consciousness or awareness;
- Focal seizures with impairment of consciousness or awareness;
- Focal seizures evolving to bilateral generalized convulsive seizures;
- Tonic-clonic; and
- Tonic.

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 analyses using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Analyses on the maintenance period, titration 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.

Individual seizure type responders and freedom will also be summarized and analyzed using the methods described in Section 5.5.3.2.1, for the following seizure types only:

- Focal motor seizures without impairment of consciousness or awareness;
- Focal seizures with impairment of consciousness or awareness;
- Focal seizures evolving to bilateral generalized convulsive seizures;
- Tonic-clonic; and
- Tonic.

The summaries and analyses during the maintenance and titration periods and during each 4 weeks of the maintenance period will be produced. Patients with no corresponding seizures, for a particular seizure type, during the baseline period will be excluded from the analysis for that seizure type.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE periods.

5.5.4.3 Rescue Medication Use

Blinded Phase:

The number of days that rescue medication (RM) was taken since the previous visit will be collected throughout the trial at scheduled visits and safety telephone calls.

To standardize between patients, the total number of days RM was taken will be calculated as the sum of all reported records within a period. Hence, the average number of days RM was taken per 28 days within a period will be calculated as follows:

(Total number of days RM was taken during the period ÷ Number of days in the period) × 28

This will be calculated for both the baseline period and treatment period. The number of days in a period will be calculated as the number of days from the visit prior to the first recorded value in the period to the day of the last recorded value in the period. The baseline period refers to the period between Visit 2 and Visit 3. The treatment period refers to the period between Visit 3 and Visit 10.

The number of days RM was taken per 28 days will be summarized by period and treatment arm. The change from the baseline period will also be included.

The change from the baseline period to the treatment period will be analyzed using an ANCOVA approach. The model will include the baseline period and stratified age group as covariates and treatment arm as fixed factor.

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

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for the OLE period. The OLE period refers to the period between Visit B1 and the last available visit in the OLE phase.

5.5.4.4 Status Epilepticus

The number of episodes of status epilepticus will be collected daily via IVRS for the blinded phase and weekly via IVRS for the open-label extension.

The number of patients with status epilepticus will be presented for the baseline, treatment and OLE periods.

5.5.4.5 Subject/Caregiver Global Impression of Change in Seizure Duration

Blinded Phase:

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 3 (prior to commencement of IMP) as a memory aid for assessment further visits.

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 by treatment arm.

It is anticipated that only a small percentage of patients will complete the subject version of the questionnaire. Hence, no analyses will be performed for the SGICSD.

A combined score will be used as the primary analysis for this endpoint. 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.

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

Since this analysis uses a combination of caregiver and subject ratings, a sensitivity analysis will be performed using only the CGICSD score and using the same analyses as above.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.6 Vineland Adaptive Behavior Scales, Second Edition

Blinded Phase:

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 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 arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, 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 5.5.3.2.4.

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 arm.

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 arms 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.

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.7 Wechsler Tests

Blinded Phase:

The Wechsler tests are age specific and will only be administered at a sub-group of centers that have the expertise to conduct the assessments. The age of the patient at entry is used when choosing the items to be administered. The following Wechsler Subtests will be used:

Age 2–6:

- Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-4) Vocabulary and Matrix Reasoning

Age 6–Adult:

- Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2) Vocabulary and Matrix Reasoning
- Wechsler Intelligence Scale for Children – Fourth Edition (WISC-4) and Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-4) Digit Span and Coding.

The T scores (Vocabulary and Matrix Reasoning), scaled scores (Coding) and forward, backward, longest forward and longest backward scores (Digit Span) will be summarized by visit including the change from baseline.

The change from baseline will be analyzed using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor.

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

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.8 Achenbach Child Behavior Checklists and Adult Behavior Checklist

Blinded Phase:

The Achenbach CBCL is a caregiver questionnaire assessing both behavioral and emotional symptoms in children. Depending on the patients' age, 1 of 2 versions of the Achenbach CBCL is used. The CBCL/1½-5 is used for children 18 months old to 5 years and 11 months old. For patients ≥6 and ≤17 years old the CBDL/6-18 is used. An adult version of the checklist, the Achenbach ABCL (ABCL/18-59), is used for patients ≥18 and ≤59 years old.

The CBCL/1½-5 comprises of 100 items, the CBCL/6-18 comprises of 113 items and the ABCL/18-59 comprises of 123 items. Response options are 0=not true; 1=somewhat or sometimes true; 2=very true or often true. Similar items are grouped and summed to produce syndrome scale scores, which are further grouped into problem scales as specified in Table 7. Other scales for CBDL/6-18 and ABCL/18-59 are also derived.

Derivation instructions for the Achenbach scales are given in Appendix 5. For each questionnaire, the individual item responses will not be listed, only the raw scores for the scales given in Table 7 and Table 8 will be listed. For the Achenbach CBCL/1½-5, no scoring will be performed for the language development survey. For the Achenbach ABCL/18-59, no scoring will be performed for the spouse/partner functioning scale or the tobacco, alcohol and drugs substance use scales.

The derived raw scores for the syndrome scales and problem scales as indicated in Table 7, recorded at each visit, will be summarized, on a continuous scale, by questionnaire version and treatment arm. The change from baseline will also be included.

The change from baseline to the end of treatment visit, for the internalizing, externalizing and total problems scales only, will be analyzed for each of the questionnaire versions using the same ANCOVA approach as specified in Section 5.5.3.2.4.

The raw scores for other scales as indicated in Table 8 will also be summarized.

Table 7 Achenbach CBCL and ABCL Syndrome and Problem Scales

Questionnaire Version	Problem Scales	Syndrome Scales
CBCL/1½-5	Internalizing	Emotionally Reactive
		Anxious/Depressed
		Somatic Complaints
		Withdrawn
	Externalizing	Attention Problems
		Aggressive Behavior
	Other	Other Problems
		Sleep Problems

	Total	
CBDL/6-18	Internalizing	Anxious/Depressed
		Withdrawn/Depressed
		Somatic Complaints
	Externalizing	Rule-breaking Behavior
		Aggressive Behavior
	Other	Social Problems
		Thought Problems
		Attention Problems
		Other Problems
	Total	
ABCL/18-59	Internalizing	Anxious/Depressed
		Withdrawn
		Somatic Complaints
	Externalizing	Aggressive Behavior
		Rule-breaking Behavior
		Intrusive
	Other	Thought Problems
		Attention Problems
		Other Problems
	Total	

Table 8 Achenbach CBCL and ABCL Other Scales

Questionnaire Version	Other Scales	Other Sub-Scales
CBDL/6-18	Total Competence	Activities
		Social
		School
ABCL/18-59	Friends	
	Critical Items	

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.9 Social Communication Questionnaire

Blinded Phase:

The current version of the SCQ will be completed by the caregiver for all patients above the age of 4 years with a mental age of at least 2 years. The scale assesses behavior over the most recent three month period using 40 questions, each to be answered ‘yes’ or ‘no’.

The answer to Item 1 ‘Is she/he now able to talk using short phrases or sentences?’ is not scored and is instead used to determine which of the remaining items relating to abnormal language will contribute to the total score. If the answer to Item 1 is ‘yes’, then the six items relating to abnormal language will be used and the total score will range from 0 to 39 points from items 2 to 40. If the answer to Item 1 is ‘no’ then the six items relating to abnormal language will not be used and the total score will range from 0 to 33 points from items 8 to 40 only.

For Items 2, 9, 19 and 20–40, 'yes' will be assigned a score of 0 and 'no' a score of 1. For all other items, 'yes' will be assigned a score of 1 and 'no' a score of 0. The total score is calculated by taking the sum of the scores for each item.

In addition to the total score, the following domain scores will be derived:

- Reciprocal Social Interaction: Items 9, 10, 19, 26-33, 36, 37, 39 and 40.
- Communication: Items 2-6, 20-25, 34 and 35.
- Restricted, Repetitive and Stereotyped Patterns of Behavior: Items 7, 8 and 11-16.

The total score and domain scores will be summarized by visit including the change from baseline. The change from baseline for each score will be analyzed using an ANCOVA approach. The model will include baseline and stratified age group as covariates and treatment arm as fixed factor. Sex will also be included as a covariate in the model only if the p-value of the estimate is <0.05.

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

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

Open-label Extension:

Descriptive summaries described above for the blinded phase will be repeated for OLE visits.

5.5.4.10 Time to Baseline TSC-associated Seizure Frequency

Blinded Phase only:

Time to baseline TSC-associated seizure frequency is defined as the number of reported days in IVRS, from Day 1, that it takes for the cumulative number of TSC-associated 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 trial without experiencing greater than or equal to the number of seizures (per 28 days) experienced during the baseline period, or who withdraw from the trial, will be censored at the earliest 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 TSC-associated seizure frequency will be summarized on a continuous scale, by treatment arm, 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 TSC-associated seizure frequency will be presented along with 95% CIs for the median and p-values from log-rank tests comparing each GWP42003-P arm with placebo. A Kaplan-Meier plot will also be produced.

The above will be repeated using Day 29 instead of Day 1 as the start day for counting the cumulative number of TSC-associated seizures.

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 TSC-associated 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 TSC-associated 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 (1-6 years, 7-11 years,12-17 years and 18-65 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).
- . Levetiracetam use (Yes, No).
- Vigabatrin use (Yes, No).
- Baseline average TSC-associated seizures 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 (<5, ≥5).
- Number of prior and concurrent AEDs (<8, ≥8).

Effects of patients taking other AED types will also be tested if the overall frequency of patients taking the AED is >25%.

5.6 Safety Evaluation

5.6.1 Exposure to IMP

Blinded Phase:

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 trial medication 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 trial medication was taken at least once (AM or PM) will be summarized and calculated as:

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

The number of days in which trial medication 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 ÷ 8 and rounded to the nearest 0.1]

for patients randomized to the 25 mg/kg/day dose level and:

2 × [Weight (kg) at Day 1 ÷ 4 and rounded to the nearest 0.1]

for patients randomized to the 50 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)

Open-label Extension:

The total number of dosing days will be calculated for the OLE and presented along with a categorical summary of patients whose largest dose was 25 mg/kg/day or less and patients whose largest dose was over 25 mg/kg/day during the OLE treatment phase.

5.6.2 Adverse Events

All reported AEs will be classified by system organ class (SOC), preferred term and lower level term using Version 19.1 of MedDRA.

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

A blinded phase treatment emergent AE (TEAE) is defined as an AE with a start date on or after the first dose of IMP during the blinded phase up to and including the date of first dose of the OLE phase (OLE Day 1). An OLE phase TEAE is defined as an AE with a start date on or after the OLE Day 1. 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 and if it is unclear which phase the event started, it will be assigned to both phases. If the start date of the AE is the same as the date of first dose of IMP from the blinded phase 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 trial medication is recorded on the CRF as 'yes'. If the data on plausibility relationship to trial medication 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 separately for the blinded and OLE phase (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 arms and where the incidence is greater than the placebo treatment arm.
- List of patients experiencing TEAEs by SOC and preferred term.
- Summary of pre-treatment AEs (blinded phase only).

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 to 2 (Day 1 to 14).
- Weeks 3 to 4 (Day 15 to 28).
- Weeks 5 to 8 (Day 29 to 56).
- Weeks 9 to 12 (Day 57 to 84).
- >12 weeks (> Day 84).

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 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.

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

Summaries will be presented by treatment arm 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:

eGFR (mL/min) = [(140 - age) × weight × k] / 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:

eGFR (mL/min/1.73m2) = eGFR (mL/min) × 1.73/BSA

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

weight 0.425 × height 0.725 × 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 × height) / 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.

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 m^2

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.

For the blinded phase, 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 for the blinded phase only, 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 arm and visit, presenting the incidence of patients with urinalysis or blood results indicative of a medical condition at Visit 1 and indicative of an adverse event 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.

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 arm and visit.

5.6.4 Vital Signs, Other Physical Findings and Other Safety Data

5.6.4.1 Vital Signs

At Visit 1, 3 and B3, 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 arm for each vital sign parameter at each visit. Change from baseline to each post-baseline visit will also be presented.

Body mass index will be calculated, for each visit in which height and weight are recorded, as:

$$\text{Weight (kg)} \div \text{height (m)}^2$$

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

Based on the criteria presented in Section 8, 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 clinically significant change from baseline will be summarized by parameter, visit and treatment arm. The number of patients with at least one post-baseline flagged vital sign parameter value will be summarized by parameter, flagged criteria and treatment arm for the blinded phase and repeated for the OLE phase.

5.6.4.2 Electrocardiogram

Summaries will be presented by treatment arm 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 arm and visit, presenting the incidence of patients with an ECG indicative of a medical condition at Visit 1 and indicative of an adverse event 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 arm for the blinded phase and repeated for the OLE phase.

5.6.4.3 Physical Examination

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 adverse event after Visit 1 will be summarized by treatment arm and visit.

5.6.4.4 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 by treatment arm 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.

5.6.4.5 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.

The number of patients with inpatient epilepsy-related hospitalizations will be presented by visit, including OLE visits.

5.6.4.6 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 arm.

For the blinded phase only, 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).

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

5.6.4.7 Menstruation

Menstruation details will be summarized as appropriate, including any changes in normal cycles, by treatment arm.

5.7 Other Measures

5.7.1 Concomitant Medication

Medications will be coded using the World Health Organization Drug Dictionary, Version September 2016.

A medication will be considered concomitant for each phase if it has a start date on or after the first dose of IMP for the corresponding phase 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 (%), separately for the blinded and OLE phase (unless stated otherwise):

- History of AEDs (blinded phase only);
- Concomitant AEDs;
- 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 Pharmacokinetics of CBD and its Major Metabolites

Samples for PK analysis are taken on Visit 3 (first dose, Day 1) and Visit 10 (last maintenance dose of the blinded phase, Day 113) for patients weighing more than 20 kg. For patients recruited under Protocol Version 2, PK samples were taken at the following time-points:

- Prior to administration of IMP, ≤0.0 hours pre-dose on Visit 3 or C_{trough} at steady state (Visit 10).
- ≥4.0 hours to ≤5.0 hours.
- ≥6.0 hours to ≤7.0 hours.
- ≥8.0 hours to ≤10.0 hours, for patients 18 years or older.

Patients recruited under Protocol Version 3 onwards, PK samples were taken at the following time-points:

- Prior to administration of IMP, ≤0.0 hours pre-dose on Visit 3 or C_{trough} at steady state (Visit 10).
- ≥2.0 hours to ≤3.0 hours.
- ≥4.0 hours to ≤6.0 hours.
- ≥8.0 hours to ≤10.0 hours, for patients 18 years or older.

The nominal mid-point time of 0, 2.5, 4.5, 5, 6.5 and 9 hours will be used for summaries of plasma concentrations. Plasma concentrations and PK parameters will be summarized showing the number of non-missing values (n), arithmetic mean, standard deviation, coefficient of variation (%), median, minimum and maximum. Where samples are reported as BLQ, a value of zero will be used in the summaries. Summary statistics will be presented to 3 significant figures.

Where data allow, the PK parameter AUC_{0-t}, will be derived at each visit by the PK vendor. A dose-normalized AUC_{0-t} will be calculated as AUC_{0-t} divided by the randomized dose per administration (12.5 or 25 mg/kg). This will include Visit 3, for consistency, where the first dose of IMP will be 2.5 mg/kg.

Plasma concentrations of CBD and its major metabolites 7-hydroxy-CBD (7-OH-CBD) and 7-carboxy-CBD (7-COOH-CBD) will be summarized by nominal mid-point time, visit and GWP42003-P arm. In addition, a dot plot of plasma concentrations for each patient, by nominal mid-point time will be created for each visit and GWP42003-P arm. The arithmetic mean will be highlighted on the plot. Additionally, a line plot of the arithmetic mean plasma concentration will be created with standard error bars by nominal mid-point time for each visit and GWP42003-P arm. These plots will be presented both a linear and semi-logarithmic scale for plasma concentration.

AUC_{0-t} and dose normalized AUC_{0-t}, for CBD and its major metabolites 7-OH-CBD and 7-COOH-CBD, will be summarized by visit and GWP42003-P arm. In addition, the ratio of 7-OH-CBD AUC_{0-t} to CBD AUC_{0-t} and the ratio of 7-COOH-CBD AUC_{0-t} to CBD AUC_{0-t} will be summarized. Box plots of AUC_{0-t} will be produced comparing visit on the x-axis, by parent and metabolite, and GWP42003-P arm. This will be repeated with parent and metabolite on the x-axis, by visit and GWP42003-P arm. Summaries and plots of AUC_{0-t} will be repeated by stratified age group.

Plasma concentration and AUC_{0-t} summaries may exclude individual time-points or visits for patients deemed to meet certain criteria that could affect exposure. These criteria include:

- Patients vomiting on or 1 day prior to the PK visit.
- Missed doses prior to the PK visit.
- IMP dose reduction.
- Cases of severe diarrhoea.
- Use of disallowed concomitant medication.

All exclusion will be detailed in a separate document finalized prior to unblinding. All data will be listed with data excluded from summaries flagged along with the reason for exclusion.

5.7.3 Plasma Concentrations of Concomitant AEDs

Blood sampling for AEDs will be performed at Visit 3 (Day 1), Visit 5, Visit 7, Visit 9 and Visit 10 (end of treatment) of the blinded phase. For each AED, plasma concentrations will be summarized by treatment arm at each visit for patients in the safety analysis set.

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 trial coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit.

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

Each question will be summarized, on a categorical scale, by treatment arm. Percentages will be based on the number of patients completing the survey, in each treatment arm. 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 with a completed form will be summarized separately for the blinded phase and OLE phase. 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 with a completed form will be summarized separately for the blinded phase and OLE phase. 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 with a completed form a will be summarized, along with the form associated to, separately for the blinded phase and OLE phase. 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

For the blinded phase only, the number of unreported days in IVRS, during the baseline and treatment periods, will be summarized, on a continuous and categorical scale, by treatment arm 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

5.8 Changes in the Conduct of the Trial or Planned Analysis

During the OLE, seizure counts are collected every 7 days rather than daily. Hence, the endpoint of TSC-associated seizure free days has been defined for the blinded phase only.

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 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. 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
24Apr2019	5.5.1	The hierarchy for analysis was updated to be consistent with protocol version 8, dated 23rd April 2019.

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 9.

Table 9 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: < -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 10.

Table 10 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 11.

Table 11 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 12 and

Table 13.

Table 12 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 13 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 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 Derivation Instructions for Achenbach Child Behavior Checklists and Adult Behavior Checklist

CBCL/1½–5

The syndrome scale and problem scale grouping of items is shown in Table 14. If data are missing for more than 8 items (not counting item 100) then the syndrome and problem scales will not be calculated.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 14.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.

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Table 14 Syndrome Scale Items for Achenbach CBCL/1½–5

Problem Scales	Syndrome Scales	Items
Internalizing	Emotionally Reactive	21, 46, 51, 79, 82, 83, 92, 97, 99
	Anxious/Depressed	10, 33, 37, 43, 47, 68, 87, 90
	Somatic Complaints	1, 7, 12, 19, 24, 39, 45, 52, 78, 86, 93
	Withdrawn	2, 4, 23, 62, 67, 70, 71, 98
Externalizing	Attention Problems	5, 6, 56, 59, 95
	Aggressive Behavior	8, 15, 16, 18, 20, 27, 29, 35, 40, 42, 44, 53, 58, 66, 69, 81, 85, 88, 96
Other	Other Problems	3, 9, 11, 13, 14, 17, 25, 26, 28, 30, 31, 32, 34, 36, 41, 49, 50, 54, 55, 57, 60, 61, 63, 65, 72, 73, 75, 76, 77, 80, 89, 91, 100
	Sleep Problems	22, 38, 48, 64, 74, 84, 94

CBCL/6–18

The syndrome scale and problem scale grouping of items is shown in Table 15. If data are missing for more than 8 items (not counting items 56h or 113) then the syndrome and problem scales will not be calculated.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 15.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.

Table 15 Syndrome Scale Items for Achenbach CBCL/6–18

Problem Scales	Syndrome Scales	Items
Internalizing	Anxious/Depressed	14, 29, 30, 31, 32, 33, 35, 45, 50, 52, 71, 91, 112
	Withdrawn/Depressed	5, 42, 65, 69, 75, 102, 103, 111
	Somatic Complaints	47, 49, 51, 54, 56a-g
Externalizing	Rule-breaking Behavior	2, 26, 28, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 99, 101, 105, 106
	Aggressive Behavior	3, 16, 19, 20, 21, 22, 23, 37, 57, 68, 86, 87, 88, 89, 94, 95, 97, 104
Other	Social Problems	11, 12, 25, 27, 34, 36, 38, 48, 62, 64, 79
	Thought Problems	9, 18, 40, 46, 58, 59, 60, 66, 70, 76, 83, 84, 85, 92, 100
	Attention Problems	1, 4, 8, 10, 13, 17, 41, 61, 78, 80
	Other Problems	6, 7, 15, 24, 44, 53, 55, 56h, 74, 77, 93, 98, 107, 108, 109, 110, 113

The activities scale is made up of 6 scores and the total score for the activities scale is the sum of these 6 scores. If more than 1 of the 6 scores is missing then the total score for the activities scale will not be calculated. If 1 score is missing, then the mean of the other 5 scores will be used for the missing score in calculating the total. However, if the missing score is an answer for question IB, IIB or IVB (see below) and the mean of the other 5 scores is greater than 2, then the missing score will be set to 2. The total activities score should be rounded to the nearest 0.5. The 6 scores used for the total score for the activities scale are derived as follows:

- Question I, IA:
  - 0 if 'None' is ticked.
  - 1 if 1 sport is listed under a, b or c.
  - 2 if 2 sports are listed under a, b or c.
  - 3 if 3 or more sports are listed under a, b and c.
- Question I, IB:
  - 0 if 'None' is ticked for IA.
  - Otherwise, for each sport under a, b and c, and for both time and skill the below scores will be assigned and then the mean of these scores (excluding "Don't know" or blank responses) will be the score for IB:
    - 0 for "Less than average" or "below average".
    - 1 for "Average".
    - 2 for "More than average" or "above average".
- Question II, IIA:
  - 0 if 'None' is ticked.
  - 1 if 1 activity is listed under a, b or c.
  - 2 if 2 activities are listed under a, b or c.
  - 3 if 3 or more activities are listed under a, b and c.
- Question II, IIB:
  - Calculated as per IB.
- Question IV, IVA:
  - 0 if 'None' is ticked.
  - 1 if 1 job is listed under a, b or c.

    - 2 if 2 jobs are listed under a, b or c.
    - 3 if 3 or more jobs activities are listed under a, b and c.
- Question IV, IVB:
    - Calculated as per IB.

The social scale is made up of 6 scores and the total score for the social scale is the sum of these 6 scores. If more than 1 of the 6 scores is missing then the total score for the social scale will not be calculated. If 1 score is missing, then the mean of the other 5 scores will be used for the missing score in calculating the total. However, if the missing score is IIIB, V2, VIA or VIB (see below) and the mean of the other 5 scores is greater than 2, then the missing score will be set to 2. The total activities score should be rounded to the nearest 0.5. The 6 scores used for the total score for the social scale are derived as follows:

- Question III, IIIA:
    - 0 if 'None' is ticked.
    - 1 if 1 organization is listed under a, b or c.
    - 2 if 2 organizations are listed under a, b or c.
    - 3 if 3 or more organizations are listed under a, b and c.
- Question III, IIIB
    - Calculated as per IB for the activities scale.
- Question V, V1:
    - 0 if 'None' is ticked.
    - 1 if '1' is ticked.
    - 2 if '2 or 3' is ticked.
    - 3 if '4 or more' is ticked.
- Question V, V2:
    - 0 if 'less than 1' is ticked.
    - 1 if '1 or 2' is ticked.
    - 2 if '3 or more' is ticked.
- Question VI, VIA:
    - For a to c, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VIA:
        - 0 for "Worse".
        - 1 for "Average".
        - 2 for "Better".
- Question VI, VIB:
    - For item d:
        - 0 if 'Worse' is ticked.
        - 1 if 'Average' is ticked.
        - 2 if 'Better' is ticked.

The school scale is made up of 4 scores and the total score for the school scale is the sum of these 4 scores. If any of the 4 scores are missing or the child does not attend school then the total score for the school scale will not be calculated. The total school score should be rounded to the nearest 0.5. The 4 scores used for the total score for the school scale are derived as follows:

- Question VII, VII1:
    - For a to g, the below scores will be assigned and then the mean of these scores (excluding blank responses) will be the score for VII1:
        - 0 for "Failing".
        - 1 for "Below Average".
        - 2 for "Average".

        - 3 for “Above Average”.
- Question VII, VII2:
    - 0 if ‘Yes’ is ticked.
    - 1 if ‘No’ is ticked.
- Question VII, VII3:
    - 0 if ‘Yes’ is ticked.
    - 1 if ‘No’ is ticked.
- Question VII, VII4:
    - 0 if ‘Yes’ is ticked for any academic or other problems in school.
    - 1 if ‘No’ is ticked for any academic or other problems in school.

The total competence score will be calculated as the sum of the activities, social and school scale scores. However, if any of these 3 scales are missing then the total competence score will be set to missing.

ABCL/18–59

The syndrome scale and problem scale grouping of items is shown in Table 16. If data are missing for more than 8 items (not counting items 2, 4, 15, 49, 73, 80, 88, 98, 106, 109, 110 and 123) then the syndrome and problem scales will not be calculated. If items 56a to 56g are missing then they will be scored as 0.

Each of the items is scored 0, 1 or 2 as indicated on the questionnaire. The individual items associated with each syndrome scale are presented in Table 16.

The syndrome scale scores will be calculated as the sum of the individual items associated with that scale. The problem scale scores will then be calculated as the sum of the corresponding syndrome scale scores as per Table 7 in Section 5.5.4.8. The total problem scale score will be calculated as the sum of the internalizing, externalizing and other problem scales.

Table 16 Syndrome Scale Items for Achenbach ABCL/18–59

Problem Scales	Syndrome Scales	Items
Internalizing	Anxious/Depressed	12, 13, 14, 22, 31, 33, 34, 35, 45, 47, 50, 52, 71, 91, 103, 107, 112, 113
	Withdrawn	25, 30, 42, 48, 60, 65, 67, 69, 111
	Somatic Complaints	51, 54, 56a-i, 100
Externalizing	Aggressive Behavior	3, 5, 16, 28, 37, 55, 57, 68, 81, 86, 87, 95, 97, 116, 118
	Rule-breaking Behavior	6, 20, 23, 26, 39, 41, 43, 76, 82, 90, 92, 114, 117, 122
	Intrusive	7, 19, 74, 93, 94, 104
Other	Thought Problems	9, 18, 36, 40, 46, 63, 66, 70, 84, 85
	Attention Problems	1, 8, 17, 53, 59, 61, 64, 78, 101, 102, 105, 108, 119, 121
	Other Problems	10, 21, 24, 27, 29, 32, 38, 44, 58, 62, 72, 75, 77, 79, 83, 89, 96, 99, 110, 115, 120

The critical items scale score will be calculated as the sum of the following 19 problem items scores:

- 6, 8, 9, 10, 14, 16, 18, 21, 40, 55, 57, 66, 70, 84, 90, 91, 92, 97, 103.

The friends scale is made up of 4 scores and the total score for the friends scale is the sum of these 4 scores. If any of the 4 scores are missing then the total score for the friends scale will not be calculated. The 4 scores used for the total score for the friends scale are derived as follows:

- If 'None' is ticked for item IA then 0 will be used for IB and IC.
- Question I, IA:
  - 0 if 'None' is ticked.
  - 1 if '1' is ticked.
  - 2 if '2 or 3' is ticked.
  - 3 if '4 or more' is ticked.
- Question I, IB:
  - 0 if 'Less than 1' is ticked.
  - 1 if '1 or 2' is ticked.
  - 2 if '3 or 4' is ticked.
  - 3 if '5 or more' is ticked.
- Question I, IC:
  - 0 if 'Not well' is ticked.
  - 1 if 'Average' is ticked.
  - 2 if 'Above average' is ticked.
  - 3 if 'Far above average' is ticked.
- Question I, ID:
  - 0 if 'Less than 1' is ticked.
  - 1 if '1 or 2' is ticked.
  - 2 if '3 or 4' is ticked.
  - 3 if '5 or more' is ticked.

Appendix 6 List of Tables, Listings and Figures

Table 17 List of Blinded Phase Tables

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Table Number	Title	Analysis Set
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Table Number	Title	Analysis Set
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OLE Figure 9.1.3	Percentage Change in TSC-associated Seizure Frequency Over Time (Patients with Data in OLE Week 37 to 48)	OLE Safety Analysis Set
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