STATISTICAL ANALYSIS PLAN

GWEP15100

A Randomized, Double-blind, Placebo-controlled Trial to Investigate the Efficacy and Safety of Cannabidiol (CBD; GWP42003-P) in Infants with Infantile Spasms Following an Initial Open-label Pilot Study

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Phase:	3
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Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom
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SIGNATURE PAGE

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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ABBREVIATIONS

Abbreviation	Definition
6-OH-CBD	6-hydroxy-cannabidiol
7-COOH-CBD	7-carboxy -cannabidiol
7-OH-CBD	7-hydroxy -cannabidiol
AE	Adverse event
AED	Antiepileptic drug
ATC	Anatomic therapeutic class
BMI	Body mass index
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CRF	Case report form
CSR	Clinical study report
DSMC	Data safety monitoring committee
ECG	12-lead electrocardiogram
EEG	Electroencephalography/electroencephalogram
GW	GW Research Ltd
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PGIC	Physician Global Impression of Change
POPPK	Population pharmacokinetics
PT	Preferred term
QTcB	QT interval corrected for heart rate with Bazett's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
VGB	Vigabatrin
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This document presents the abbreviated statistical analysis plan (SAP) for GW Research Ltd, Study GWEP15100: A Randomized, Double-blind, Placebo-controlled Trial to Investigate the Efficacy and Safety of Cannabidiol (CBD; GWP42003-P) in Infants with Infantile Spasms Following an Open-label Pilot Study. It contains the analysis details and methodology of the open-label pilot and extension phases of the study only.

This SAP is based on protocol V3 dated September 20, 2016 and is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP also will outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2. Objectives of Statistical Analysis

1.2.1. Pilot Phase

1.2.1.1. Primary Objective

- To determine the maximum safe, tolerable dose and dosing regimen of GWP42003-P in infants with IS, to be utilized in the pivotal phase and open-label extension (OLE).
- To assess the number and proportion of patients considered treatment responders, defined as those free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period.

1.2.1.2. Secondary Objectives

- **Key:** To assess the number and proportion of patients who are free of clinical spasms, as observed on video-electroencephalography (video-EEG) at the end of the treatment period.
- **Key:** To assess the number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period.
- To assess changes in spasms and seizure subtypes by caregiver observation during the treatment period.
- To determine time to cessation of spasms during the treatment period, as determined by caregiver diaries.
- To explore the effect of GWP42003-P on quality of life.

1.2.2. OLE Phase

1.2.2.1. Primary Objective

- To assess the long term safety of GWP42003-P in infants with IS.

1.2.2.2. Secondary Objectives

- **Key:** To assess the number and proportion of patients who are free of clinical spasms, as observed on video-electroencephalography (video-EEG) at the end of the treatment period.
- **Key:** To assess the number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period.
- To assess changes in spasms and seizure subtypes by caregiver observation during the treatment period.
- To determine time to cessation of spasms during the treatment period, as determined by caregiver diaries.
- To explore the effect of GWP42003-P on quality of life.
- To assess the number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, after 3, 6, 9 and 12 months of treatment.
- To assess the number and proportion of responders who relapse and the time to relapse.
- To explore the effect of GWP42003-P on growth, adaptive behavior and development.
- To determine the population POPPK of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD)

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a multisite trial to evaluate the efficacy and safety of GWP42003-P in patients with IS who have failed to become spasm- and hypsarrhythmia-free following treatment with 1 or more approved IS therapies (e.g., steroids and/or VGB). All approved therapies must be discussed with the patient's parent(s)/legal representative before the patient is considered for the trial (discussions regarding treatment options must be documented). The trial will comprise of a pilot safety phase, followed by a pivotal phase, with a 1 year OLE extension available to all patients who complete either phase. The pilot phase will be open-label with 2 sequential cohorts of 5 patients, the first cohort aged between 6 and 24 months and the second cohort aged between 1 and 24 months, who will receive GWP42003-P for 2 weeks. The pivotal phase will comprise 192 patients, aged 1–24 months, who will undergo a 2-week, randomized, placebo-controlled, double-blind treatment period.

An independent DSMC will be used throughout the study; they will consider safety of the patients, and will confirm doses and dose regimens to be investigated in the pivotal phase, as well as the plans for dose titration. If required, following DSMC review, adjustment of doses and dose regimens will also take place following the first cohort of 5 patients in the pilot phase.

Patients will enter the pilot and pivotal phases at the respective screening visits (Visit 1, Day −7 to −1) for assessment of eligibility, which includes a prolonged video-EEG. Patients who satisfy all eligibility criteria will then be administered GWP42003-P (pilot phase) or randomized to GWP42003-P (1 of 2 dose levels) or placebo at a 1:1:1 ratio (pivotal phase) (Visit 2, Day 1 [+3 days]). The High Dose Level will be as recommended by the DSMC; the Low Dose Level will be defined as 50% of the High Dose Level. Patients in the placebo group will be split into 2 equivalent cohorts: half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes. Following baseline assessments, patients will titrate the investigational medicinal product (IMP) in 10 mg/kg/day increments to the target dose level (or equivalent volume of placebo in the pivotal phase) and will continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the 2-week treatment phase. Patients in the pilot phase will remain in the clinic as inpatients during the 4-day dose titration period. If deemed safe by the DSMC then it is planned for those in the pivotal phase to titrate in an outpatient setting. Further clinic-based assessments will take place after 3 days' dosing (Visit 3, Day 4 [+1 day]). All patients in the pilot and pivotal phases will return to the clinic after 2 weeks' dosing (Visit 4, Day 15 [+3 days]) or earlier if they withdraw prematurely. All patients who complete treatment will then have the opportunity to receive GWP42003-P during the subsequent OLE phase. The OLE phase will last for a maximum of 1 year.

Patients who enter the OLE phase will remain on the same dose (pilot phase) or will transition to their target dose of GWP42003-P over 4 days in a blinded manner (pivotal phase). Patients may continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the OLE phase. GWP42003-P may be discontinued at the discretion of the investigator. During the OLE phase, clinic visits will take place on Day 19 (Visit 5 [+1 day]), Day 29 (Visit 6 [±3 days]), Day 43 (Visit 7 [±3 days]), Day 71 (Visit 8 [±3 days]), Day 127 (Visit 9 [±7 days]), Day 211

(Visit 10 [±7 days]), and on Day 295 (Visit 11 [±7 days]). Patients will return to the site for an end of OLE treatment visit on Day 379 (Visit 12 [±7 days]) or earlier if they withdraw prematurely from the OLE phase. Following end of treatment, withdrawal, or discontinuation of IMP, all patients will taper the IMP over 10 days followed by safety follow-up. Patient diaries will be completed each day by the caregiver during the trial.

2.2. Randomization Methodology

The pilot and OLE phases of this study are single-arm and open-label with no randomization. After confirmation of eligibility at Visit 2, all patients are assigned GWP42003-P in the pilot phase and continue on this same treatment in the OLE phase.

2.3. Stopping Rules and Unblinding

The patient must be withdrawn from the trial if ANY of the following apply:

- Any issue with eligibility criteria that is considered to potentially compromise the safety of the patient.
- Administrative decision by the investigator, GW, or regulatory authority.
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- Withdrawal of the patient's parent(s)/legal representative consent.
- QTcB of 500 msec or greater on ECG, or a shift from baseline QTcB of 60 msec or greater.
- Lost to follow-up.
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.

ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5). The patient may also be withdrawn from the trial for ANY of the following:

- Any other issue with eligibility criteria (non-safety related).
- Any requirement to increase the dose of concomitant AED(s) or to add in new AED(s) during the pilot or pivotal phase.
- If a patient is not showing evidence of benefit during the OLE phase (the option of withdrawing from the trial will be discussed with the caregiver at each visit).
- Patient/caregiver non-compliance.
- AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the trial.

There is no blinding necessary for the pilot and OLE phases so unblinding procedures will not apply.

2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in **Table 1**.

Table 1 Schedule of Assessments

	Pilot or Pivotal phase				**Open-Label Extension Phase**									
Visit Number Day (Visit Window)	**Visit 1** Day -7 to -1	**Visit 2**[1] Day 1 (+3 days)	**Visit 3** Day 4 (+1 day)	**Visit 4**[2] Day 15 (+3 days)	**Visit 5** Day 19 (+1 day)	**Visit 6** Day 29 (±3 days)	**Visit 7** Day 43 (±3 days)	**Visit 8** Day 71 (±3 days)	**Visit 9** Day 127 (±7 days)	**Visit 10** Day 211 (±7 days)	**Visit 11** Day 295 (±7 days)	**Visit 12** Day 379 (±7 days)	**End of Taper Period Visit**[3] (+3 days)	**Safety Follow-up Visit**[4] (+3 days)
Informed consent	X													
Patient number	X													
Eligibility criteria	X	X[5]												
Start of IMP dosing		X												
Inpatient stay (pilot phase only)		X	X											
Demographics	X													
Medical history	X													
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X		X	X	X	X	X	X	X	X	

Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X	X[6]	X[7]	X[7]	X	X	X	X	X	X	X	X	X	
Video-EEG (8-24 hours)	X			X		X	X		X	X	X	X		
Clinical laboratory sampling (blood/urine)	X		X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling[8]		X		X	X									
Caregiver paper diary issue/training	X													
CGIC		X[9]		X		X	X	X	X	X	X	X		
PGIC		X[9]		X		X	X	X	X	X	X	X		
Vineland-II		X								X		X		
IMP dispensing[10]		X		X		X	X	X	X	X	X			
IMP compliance review				X		X	X	X	X	X	X	X	X	
Caregiver diary review		X	X	X	X	X	X	X	X	X	X	X	X	X
Spasm/seizure information		X	X	X	X	X	X	X	X	X	X	X	X	X

IMP usage[11]			X	X	X	X	X	X	X	X	X	X	X	
Changes in concomitant AEDs		X	X	X	X	X	X	X	X	X	X	X	X	X
Usage of rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X

[1]All patients in the pilot phase will titrate GWP42003-P in an inpatient setting. In both phases (pilot and pivotal), daily safety checks will be made during the first week of IMP dosing (can be conducted by telephone). Each safety check will conduct the same assessments as listed for safety follow-up visit.
[2]Daily safety checks will be made during the first week of OLE IMP dosing (can be conducted by telephone). Each safety check will conduct the same assessments as listed for safety follow-up visit.
[3]IMP is to be tapered over 10 days following discontinuation of IMP, end of treatment, or withdrawal (unless continued dosing is not possible due to an AE).
[4]Safety follow-up visit is to occur 28 (+3) days after date of final dose (including tapered dose); weekly (±3 days) telephone calls must be made during the follow-up period. Each safety telephone call will conduct the same assessments as listed for safety follow-up visit.
[5]Based on assessment of clinical laboratory and video-EEG results.
[6]ECG to be performed between 3 and 5 hours after the day's first dose of IMP only.
[7]ECG to be performed both prior to the day's first dose of IMP and between 3 and 5 hours after this dose.
[8]Only for patients involved in the pivotal phase, and progressing to the OLE from the pivotal phase. To be conducted only if the risk/benefit outcome is favorable, in the investigator's opinion.
[9]Memory aid only (worksheet completed).
[10]If necessary, IMP will also be dispensed for taper period.
[11]IMP usage to be recorded on a dosing schedule which will form part of the paper diary

2.5. Primary Endpoints

The following endpoints will be analyzed descriptively only:

2.5.1. Pilot Phase

- Safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period
- The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG.

2.5.2. OLE Phase

- To assess the long term safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period.

2.6. Secondary Endpoints

2.6.1. Pilot Phase

For the pilot phase, the following secondary endpoints will be analyzed descriptively only:

- The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period.
- The number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period.
- Changes in spasms and seizure subtypes by caregiver observation during the treatment period.
- Time to cessation of spasms during the treatment period, as determined by caregiver diaries.
- CGIC.
- PGIC.

2.6.2. OLE Phase

For the OLE phase, the following secondary endpoints will be analyzed descriptively only:

- The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period.
- The number and proportion of patients who have resolution of hypsarrhythmia as, observed on video-EEG at the end of the treatment period.
- Changes in spasms and seizure subtypes by caregiver observation during the treatment period.
- Time to cessation of spasms during the treatment period, as determined by caregiver diaries.
- The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, as determined by video-EEG after 3, 6, 9 and 12 months of treatment.

- The number and proportion of responders with relapse of spasms, and the time to relapse, as determined by caregiver diaries.
- Changes from baseline in length (height), body weight, and head circumference.
- CGIC.
- PGIC.
- Change from baseline in Vineland-II score.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following analysis sets will be evaluated and used for presentation and analysis of the data:

- Pilot Phase Safety: All patients exposed to at least 1 dose of IMP during the pilot phase will be used for summaries of the safety endpoints during the pilot phase.
- OLE Phase Safety: All patients exposed to at least 1 dose of IMP during the OLE phase will be used for summaries of the safety endpoints during the OLE phase.

3.2. Protocol Deviations

All protocol deviations will be listed and reasons for exclusion from the analysis sets will be summarized.

4. STATISTICAL METHODS

4.1. Sample Size Justification

The pilot phase of the study is not powered and comprises of 9 patients.

4.2. General Statistical Methods and Data Handling

4.2.1. General methods

All output will be incorporated into Microsoft Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented.

Given that only the pilot and OLE phases will be analyzed in this study, there will be no formal hypothesis testing. Descriptive statistics will be used in the analyses. Data from the pilot and OLE phases will be presented together in the same outputs, unless otherwise noted. All tabulations will display one treatment column since the pilot and OLE phases only consist of one open-label treatment group.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 or higher), unless otherwise noted. Medical History and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD, Q2.2016).

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates and Stratification

No formal statistical analysis that adjusts for possible covariate effects is planned.

4.2.5. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

4.2.6. Subpopulations

No analyses of subgroups of subjects are planned.

4.2.7. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdraw from the study will not be replaced.

4.2.8. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the CRF will be included in data listings that will accompany the clinical study report.

4.2.8.1. Adverse Events Onset Date

In the case an AE onset date is missing or partially missing, an imputation needs to be done to determine if the event is to be classified as occurring during the treatment period.

If an onset date is completely **missing** (or the year is missing), the **derived onset date** will be calculated as the first non-missing valid (actual) date from the following list (in order of precedence):

- First active study medication date
- Consent date
- If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.

If an onset date is incomplete, the derived onset date will be calculated using the following algorithm:

Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):

- First active study medication date
- Consent date
- If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.

Based on the information provided, set the initial derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

If the surrogate date is non-missing then:

- If the derived date is on or after the surrogate date use the derived date as calculated
- If the derived date is prior to the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date
- If the derived date is prior to the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

If all dates used to determine the surrogate date are missing, then based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

4.2.8.2. Adverse Events End Date

A missing or incomplete end date of an AE will be imputed according to the following conventions:

- If an end date is missing, the derived end date will be set to missing
- If an end date is incomplete, set the derived end date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

4.2.8.3. Adverse Events Severity and Relationship

The missing AE severity will be imputed to be "severe" and the missing AE relationship to study drug will be imputed to be "definitely related".

4.2.9. Baseline Definition

Unless otherwise noted, baseline (for both the pilot and OLE phases) is defined as the data most recently collected prior to the first IMP dosing start date/time in the pilot phase. If the timing of some data collection is not recorded, it will be assumed that the assessment at the first dosing date is performed as planned, i.e. prior to dosing in the pilot phase.

4.2.10. Visit Windows

Any clinical domains that are displayed by visit will be shown by nominal study visit.

4.3. Interim Analyses

An interim analysis is not planned for this study.

4.4. Subject Disposition

All patients (enrolled, screened, treated, entering the OLE, prematurely terminating IMP) will be accounted for in the enrollment and disposition summary tables.

A tabulation of subject disposition will be displayed, including the number enrolled, the number screened, reasons for screen failure, the number randomized, the number that completed the pilot phase and the number that entered the open label extension phase.

A listing of screen failures and a listing of study completion information, including the primary reason for study withdrawal, if applicable, will be presented by cohort and subject.

4.5. Demographic and Baseline Characteristics

Demographic data, including gestational age, birth weight, age at informed consent, sex and race, will be summarized using descriptive statistics. For continuous variables, mean, standard deviation, median, minimum, and maximum will be presented. For categorical variables, N and % will be presented.

Demographic and baseline data will also be provided in data listings by cohort and site.

4.6. Medical History

Previous and current significant non-epilepsy medical history will be summarized using System Organ Class (SOC) and Preferred Term (PT).

Non-epilepsy medical history data will also be provided in data listings by cohort and site.

4.7. Efficacy Analyses

Efficacy analysis will be conducted using the Safety Analysis Set.

4.7.1. Primary Efficacy Variables

4.7.1.1. Treatment Responders

The number and proportion of patients who are considered treatment responders will be summarized descriptively separately for each phase. Treatment responders are defined as those free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG. Resolution of hypsarrhythmia requires reduction of the EEG background below 300 μV and elimination of any electrodecrements or epochs of discontinuity. Persistence of some background slowing and interictal epileptiform discharges may be seen and still be consistent with resolution of hypsarrythmia.

4.7.2. Key Secondary Efficacy Variables

4.7.2.1. Clinical Spasms

The number and proportion of patients who are free of spasms, as observed on video-EEG at the end of the treatment period, as observed on video-EEG at the end of the treatment period, and after 3, 6, 9, and 12 months of treatment will be summarized separately for each phase.

4.7.2.2. Hypsarrhythmia

The number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period, and after 3, 6, and 12 months of treatment will be summarized separately for each phase.

4.7.3. Secondary Efficacy Variables

4.7.3.1. Changes in Spasms and Seizure Subtypes

Caregivers will be instructed to record whether the patient had any episodes of spasms and/or other subtypes of epileptic seizure on a daily basis. The number and percentage of subjects who experienced spasms and other seizure subtypes (ie-Tonic, Clonic, Tonic-Clonic, Atonic, Myoclonic, Focal, Absence) during the treatment period will be summarized for each phase by visit.

4.7.3.2. Caregiver Global Impression of Change (CGIC)

The CGIC comprises a single question to be rated on a 7-point scale: “Since the patient started treatment, please assess the status of the patient’s overall condition (comparing their condition now to their condition before treatment) using the scale below.”

The markers are: “Very Much Improved”; “Much Improved”; “Slightly Improved”; “No Change”; “Slightly Worse”; “Much Worse”; “Very Much Worse”.

The caregiver will be asked to record the status of the patient’s overall condition at Visit 2 (Day 1, prior to commencement of IMP) as a memory aid for subsequent visits.

The number and percentage of subjects in each response category will be presented by visit for both phases combined.

4.7.3.3. Physician Global Impression of Change (PGIC)

The PGIC comprises the same single question as the CGIC to be rated on the same, 7-point scale by the investigator. The investigator will be asked to record the status of the patients' overall condition at Visit 2 as a memory aid for subsequent visits.

The number and percentage of subjects in each response category will be presented by visit for both phases combined.

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

The Vineland-II is an individually administered instrument for assessing adaptive behaviors and is widely used in pediatric clinical trials due to its applicability to children of all ages and developmental levels. The Vineland-II will be completed by the caregiver using a rating scale. Due to the possibility of cognitive/developmental delay, caregivers should start the assessment at the lowest age, irrespective of the patient's actual age. The Vineland-II consists of 5 domains (communication, daily living skills, socialization, motor skills, and maladaptive behavior) with items that are rated as 0=Never, 1=Sometimes or Partially, or 2=Usually. The Vineland-II scores will be calculated as the sum of all individual item scores across all scales.

Observed and change from baseline in Vineland-II scores will be summarized descriptively by visit for the OLE phase only.

4.8. Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set.

4.8.1. Extent of Exposure and Compliance to Study Treatment

Descriptive statistics will be produced to describe the exposure and compliance to the IMP. The duration of exposure, and percent of treatment compliance will be summarized separately by phase.

Duration of exposure in the will be calculated for each subject by counting days where the study medication was actually taken (i.e., overall treatment duration - number of days a subject missed all doses of study medication). If a subject took at least one dose of study medication on a study day, then the subject will be counted as having received study medication on that day.

Overall percent compliance will be calculated and summarized as follows: duration of exposure / overall treatment duration x 100.

4.8.2. Adverse Events

Adverse events will be coded using the latest version of MedDRA and displayed in tables and listings using SOC and PT.

Analyses of AEs will be performed for those events that are considered treatment emergent AEs (TEAEs), where treatment emergent is defined as any adverse event that started, or worsened in severity or seriousness, following the first dose of IMP.

The number and percentage of subjects with the following AEs will be summarized:

- All-causality TEAEs
- Treatment-related TEAEs

- All-causality TEAEs by severity
- All-causality TEAEs by sex
- All-causality non-serious TEAEs
- All-causality serious TEAEs
- Treatment-related serious TEAEs
- TEAEs reported as leading to permanent cessation of study treatment
- Treatment-related TEAEs reported as leading to permanent cessation of study treatment
- Fatal TEAEs.

In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes. No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed by cohort and subject. Listings will also be provided for the following: subject deaths; SAEs; and adverse events leading to withdrawal of study drug.

4.8.3. Laboratory Data

For each phase of the trial, clinical laboratory data (hematology and biochemistry) at screening, during and at the end of treatment, and the change from baseline to end of treatment will be summarized for the safety analysis set using descriptive statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range and values outside of toxicity limits for hematology and biochemistry data.

All hematology, biochemistry and urinalysis laboratory data will be provided in data listings. The values that are below the lower limit or above the upper limit of the reference range and values that are outside of toxicity ranges will be flagged.

GW Toxicity criteria will be summarized for the following lab tests only:

- >3xULN for ALT and AST;
- >2xULN for TBL.

4.8.4. Vital Signs and Physical Examinations

Vital signs measurements (systolic and diastolic blood pressure, pulse rate, body temperature, respiratory rate, height, weight, BMI, and head circumference), taken in a supine position at rest for 5 minutes, will be completed alongside the physical examination.

Physical examinations will include length (height), body weight, and head circumference measurements.

Vital signs and physical examination data will be summarized at screening, baseline, and at each time point during the treatment period using descriptive statistics. Changes in the vital signs from baseline to end of treatment will also be summarized.

All vital sign and physical examination measurements will be presented in data listings.

4.8.5. Electrocardiogram

ECG recordings (ventricular rate, PR duration, QRS duration, QT duration, and QTCB) will be performed after 5 minutes in a supine position. A physician must review the ECG immediately (annotated, signed and dated) and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately on the CRF. Additional ECG measurements can be taken at any time during the trial, if clinically indicated.

ECG data will be summarized at screening, baseline, and at each time point during the treatment period using descriptive statistics.

All ECG measurements will be presented in a data listing.

4.8.6. Prior and Concomitant Medications

Prior medications are those the subject used prior to the start date/time of IMP administration. Concomitant medications are those the subject used on or after the start date/time of IMP administration. No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a concomitant medication.

Prior antiepileptic medications and therapies along with concomitant antiepileptic therapies and medications, rescue medications, and all other medications will be coded using the WHO-DD. Results will be tabulated by Anatomic Therapeutic Class (ATC) and PT.

The use of prior and concomitant medications will be included in data listings by cohort and subject.

5. CHANGES TO PLANNED ANALYSES

Since this trial only included patients from the open-label pilot study, the details and analyses of the pivotal phase of the study mentioned in the protocol were omitted from this SAP.

6. CLINICAL STUDY REPORT APPENDICES

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