STATISTICAL ANALYSIS PLAN
Protocol GWEP1428
EudraCT Number: 2014-002942-33
A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE POSSIBLE DRUG-DRUG INTERACTIONS BETWEEN CLOBAZAM AND CANNABIDIOL (GWP42003-P)

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Name of Test Drug:	Cannabidiol (GWP42003-P)
Phase:	2
Methodology:	Double-Blind, Randomized, Placebo-Controlled
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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
AE	Adverse Event
AEDs	Antiepileptic Drugs
$AUC_{(0-\infty)}$	Area under the concentration time curve from to infinity with extrapolation of the terminal phase
$AUC_{(0-t)}$	Area under the concentration time curve, from time zero to 't' (where t = the final time of positive detection) as calculated by the linear trapezoidal method
CBD	Cannabidiol
CI	Confidence Interval
CLB	Clobazam
C_{max}	Maximum plasma concentration
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CYP	Cytochrome P450
DB	Double-Blind
ECG	12-Lead Electrocardiogram
EEG	Electroencephalography
GW	GW Research Ltd
GWP	GW Pharma Ltd
IMP	Investigational Medicinal Product
LEV	Levetiracetam
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
N-CLB	N-desmethylclobazam
OLE	Open Label Extension
PK	Pharmacokinetic
Q1	First Quartile
Q3	Third Quartile

Abbreviation	**Definition**
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SFU	Safety Follow Up
SOC	System Organ Class
STP	Stiripentol
$t_{½}$	Terminal half-life
TBL	Total bilirubin
THC	Δ^9-tetrahydrocannabinol
T_{max}	Time to maximum plasma concentration
TPM	Topiramate
VPA	Valproate
WHO	World Health Organization
λ_z	Terminal elimination rate constant

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

GWP42003-P is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of cannabidiol (CBD) as the principal phytocannabinoid. Clobazam (CLB) is a widely used antiepileptic drug (AED), prescribed with other medication(s) to control seizures in adults and children two years of age and older who have Lennox-Gastaut syndrome (a disorder that causes seizures and often developmental delays). CLB is in a class of medications called benzodiazepines. Similar to other benzodiazepine medications, CLB is metabolized by cytochrome P450 (CYP) enzymes (mainly in the liver). This metabolism results in the formation of an active metabolite N-desmethylclobazam (N-CLB), amongst others.

CBD can act as both a CYP inhibitor and inducer in human hepatocytes in vitro. Therefore, the potential for pharmacokinetic (PK) interactions with other drugs that are metabolized by CYP enzymes exists. The hypothesis is that the in vivo PK of CLB and its major metabolite (N-CLB) may be altered (increased or decreased) by the chronic administration of GWP42003-P.

GWEP1428 is a phase 2, double-blind (DB), randomized, placebo-controlled study to investigate possible drug-drug interactions between CLB and CBD (GWP42003-P) in patients with epilepsy.

1.2. Objectives of Statistical Analysis

Objectives of the study

Primary

To determine whether GWP42003-P affects the PK profile of CLB and its primary metabolite N-CLB.

Secondary

To assess the safety and tolerability of GWP42003-P in the presence of CLB.

Objectives of the statistical analysis plan

This statistical analysis plan (SAP) 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 study.

This SAP covers the two analyses planned, at the end of the DB period and the end of the study (see 4.3). The SAP describes analyses planned for both periods. For the first analysis, at the end of the DB period, all data from post-DB period will be absent from the outputs.

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

This SAP has been prepared in conjunction with the protocol version 04 (date: 04-February-2016).

2. STUDY DESIGN

2.1. Synopsis of Study Design

This phase 2, placebo-controlled study consists of a 34-day, DB phase followed by an optional maximum one year open label extension (OLE). Patients will continue to take CLB as advised by their physician for the duration of the study. GWP42003-P/placebo will be taken twice daily immediately after their CLB dose.

Patients will enter the study and begin a 10-day GWP42003-P or placebo titration phase. During this period patients will be up-titrated to a maintenance dose. Patients will continue to take this maintenance dose of GWP42003-P or placebo for 21 days (Days 12 to 32).

Upon completion of the treatment period (Day 34) patients will be invited to receive GWP42003-P during the OLE phase. If a patient enters the OLE they will take GWP42003-P as advised by the investigator. If a patient chooses not to enter the OLE, and/or the investigator does not feel it is in their best interests, they will taper off their GWP42003-P/placebo treatment by reducing their maintenance dose by 10% per day until dosing has ceased. For those patients not entering the OLE, dosing will end on Day 43 and they will receive a telephone follow-up visit four weeks after the end of GWP42003-P/placebo dosing (Day 71).

PK samples will be taken on two occasions during the blinded phase of the study:

- Day 1/2 (Visit 2) before beginning of treatment (patients will be taking CLB only).
- Day 33/34 (Visit 4) following 21 days of GWP42003-P or placebo maintenance (patients will be taking CLB and GWP42003-P or placebo).

Ten samples will be taken during each PK assessment. PK samples should be taken at time points in respect to the morning dose of CLB. The time points are as follows: Pre-dose, 15min, 30min, 1h, 1.5h, 2h, 4h, 6h, 12h and 24h. PK samples will be quantitatively analyzed for CLB, N-CLB, valproate (VPA), stiripentol (STP), levetiracetam (LEV) and topiramate (TPM) at Visit 2 and CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC (Δ^9-tetrahydrocannabinol) and THC major metabolites at Visit 4.

Upon entry into the OLE, the dose of GWP42003-P and other AEDs may be adjusted up or down to a maximum of 30 mg/kg/day. The OLE will last for a maximum of one year or until marketing authorization is granted; whichever is earlier.

Patients will be required to keep a paper diary to note the time and dose of IMP and CLB administration each morning and evening and to record any AEs that may occur whilst receiving IMP and any other medications. Patients will also be required to record the number and type of seizures for each day whilst on the study.

Study schemas depicting the overall study design are presented in Figure 7-1 and Figure 7-2, Appendix 7.3.

2.2. Randomization Methodology

This is a DB study. Patients will be randomized in a 4:1 ratio to receive 20 mg/kg GWP42003-P or placebo.

A total of 20 patients will be enrolled into the study.

2.3. Stopping Rules and Unblinding

A patient's treatment assignment must only be unblinded when knowledge of the treatment is essential to make a decision on the medical management of the patient. Unblinding for any other reason will be considered a protocol deviation.

2.4. Study Procedures

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

Table 1 Schedule of Assessments

Visit Number Day (Visit Window)	**Visit 1** Day -14 to -7	**Visit 2** Day 1 (+ 3 days)	**Visit 2** Day 2	**Visit 3** Day 12 (+ 3 days)	**Visit 4** Day 33 (± 3 days)	**Visit 4** Day 34	**Visit 5*** End of Taper	**Visit 6*** 4wk SFU (± 3 days)
Informed consent	X							
Eligibility criteria	X	X						
Enrolment		X						
Demographics	X							
Medical history	X							
Paper diary training	X		X					
Concomitant medications (including AEDs)	X	X	X	X	X	X	X	X
Physical examination (including height and body weight)♥	X	X	X	X	X	X	X	
ECG	X	X		X	X		X	
Vital signs	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X
Clinical laboratory blood sampling	X	X		X	X		X	
Clinical laboratory urine sampling (dipstick urinalysis)	X	X		X	X		X	
THC test	X							
Alcohol Test	X	X			X			

Visit Number Day (Visit Window)	**Visit 1** Day -14 to -7	**Visit 2** Day 1 (+ 3 days)	**Visit 2** Day 2	**Visit 3** Day 12 (+ 3 days)	**Visit 4** Day 33 (± 3 days)	**Visit 4** Day 34	**Visit 5*** End of Taper	**Visit 6*** 4wk SFU (± 3 days)
Pregnancy test (if appropriate)	X							
Pharmacokinetic blood sampling**		X	X		X	X		
Sample for Genetic Testing***		X						
C-SSRS	X	X		X	X		X	
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)		X		X	X		X	
IMP dispensing			X			X		
Collection of IMP				X	X		X	
IMP compliance review				X	X		X	
Study Medication Use and Behaviour Survey							X	

* Patients not entering the OLE

**PK Sampling time points are as follows: Pre-dose and 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours, 12 hours and 24 hours after dosing. For the second PK visit the patient should take the GWP42003-P/placebo immediately after their daily dose of CLB.

*** Samples for genetic testing will only be taken if additional consent is obtained.

♥ **Patients height measured at Visit 1 only.**

Open Label Extension Schedule of Assessments									
Visit Number Day (Visit Window)	**Visit 5** 2 Weeks (± 3 days)	**Visit 6** 1 Month (± 3 days)	**Visit 7** 2 Months (± 3 days)	**Visit 8** 3 Months (± 7 days)	**Visit 9** 6 Months (± 7 days)	**Visit 10** 9 Months (± 7 days)	**Visit 11** 12 Months (± 7 days)	**Visit 12** End of Taper	**Visit 13** 4wk SFU (± 3 days)
Paper diary training									
Concomitant medications (including AEDs)	X	X	X	X	X	X	X	X	X
Physical examination (including weight)	X	X	X	X	X	X	X	X	
ECG	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X
Clinical laboratory blood sampling	X	X	X	X	X	X	X	X	
Clinical laboratory urine sampling (dipstick urinalysis)	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)	X	X	X	X	X	X	X	X	
IMP dispensing	X	X	X	X	X	X	X		
Collection of IMP	X	X	X	X	X	X	X	X	
IMP compliance review	X	X	X	X	X	X	X	X	
Study Medication Use and Behaviour Survey								X	

2.5. Efficacy, Pharmacokinetic and Safety Variables

Primary Endpoint(s)

The primary endpoints of the study are the PK parameters of the following analytes:

- CLB
- N-CLB
- CBD
- CBD major metabolites

Blood samples will be collected as outlined in Table 1. The PK parameters will be determined as outlined in Table 2.

Table 2 Pharmacokinetic parameters

PK parameters	Description
C_{max}	Maximum measured plasma concentration
t_{max}	Time to the maximum measured plasma concentration
$AUC_{(0-\infty)}$	Area under the concentration time curve from zero to infinity with extrapolation of the terminal phase
$AUC_{(0-t)}$	The area under the plasma concentration versus time curve, from time zero to 't' (where t = the final time of positive detection) as calculated by the linear trapezoidal method
$t_{½}$	Terminal half-life

Secondary Endpoint(s)

To assess the safety and tolerability of GWP42003-P compared with placebo when taken in combination with CLB. Safety and tolerability will be assessed using the following parameters:

- Adverse Events (AEs)
- 12-lead electrocardiogram (ECG)
- Clinical laboratory parameters (clinical chemistry, hematology and urinalysis)
- Vital signs
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Seizure frequency
- Abuse liability
- CYP2C19 and CYP3A4 patient genotype analysis

PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{½}$) of the following analytes:

- THC
- THC major metabolites

3. PATIENT POPULATIONS

3.1. Population Definitions

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

Screened Population

All patients enrolled in the study (with an assigned patient number), irrespective of whether the patient completed the screening period or not, or was a screening failure.

The Screened Population is the primary analysis set for disposition.

Safety Population

All patients enrolled in the study who are treated and receive at least one dose of IMP will be included.

The Safety Population is the primary analysis set for all safety endpoints reported during the DB phase of the study. Analyses are done using actual treatment received (placebo or GWP42003-P) and not randomized treatment.

Pharmacokinetic Population

All patients enrolled in the study who are treated and receive at least one dose of IMP (GWP42003-P or placebo) and who provide some on-treatment data will be included. On-treatment data is defined as sufficient PK concentration data to derive PK parameters at day 1/2 (visit 2) and day 33/34 (visit 4).

The PK population is the primary analysis set for all PK endpoints.

Open Label Extension Population

The OLE population includes all patients enrolled in the extension phase of the study who took at least one dose of IMP from Visit 4 (Day 34) onwards. The OLE population will be used to provide long-term safety summaries of IMP use. Patients will be analyzed according to the treatment they actually received during the DB treatment period.

The analysis sets to be used for analyses are described in the table below. All listings will be presented using the screened population with flags indicating inclusion in other populations.

Analyses	Screened	Pharmacokinetic (Double-Blind)	Safety (Double-Blind)	Open-Label Extension
Patient Disposition	✓			
Demographics			✓	
Baseline (Prior Medications and Medical History)			✓	
Compliance and		✓	✓	✓

Exposure				
Pharmacokinetics		✓		
Adverse Events (AEs) and Serious Adverse Events (SAEs)			✓	✓
Laboratory Parameters			✓	✓
ECG			✓	✓
Physical Examination			✓	✓
Vital Signs			✓	✓
Concomitant Medications			✓	✓
C-SSRS			✓	✓
Genotype			✓	
Abuse liability			✓	✓
Seizure Frequency			✓	✓

3.2. Protocol Deviations/Violations

The sponsor, or designee, will be responsible for producing the final protocol deviation/violation file (formatted as an Excel file or SAS dataset). This file will be finalized prior to hard database lock.

4. STATISTICAL METHODS

4.1. Sample Size Justification

A total of 20 patients will be enrolled in this study. There is no formal sample size. Calculation and analysis are descriptive only.

4.2. General Statistical Methods and Data Handling

General Methods

All output will be incorporated into 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, PK 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, Q1, Q3, minimum and maximum values will be presented.

Summaries will be presented for data recorded pre-treatment, during the DB phase and during the OLE phase separately. Of note, tapering periods following DB or OLE are not included in the DB and OLE periods respectively, but as part of the safety follow-up.

In general, summaries for the Safety and the OLE populations will be presented by treatment group from the DB phase (placebo and GWP42003-P).

Listings will include all patients with flags for the populations and be sorted by actual treatment (normally randomized treatment), patient number, study period and time point (where applicable).

Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.2 or later), unless otherwise noted. Medical History and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1. Medications will be coded using World Health Organization (WHO) Drug Dictionary Enhanced, 01 June 2014.

Versions of dictionaries will be indicated in the footnote of the relevant tables.

Methods of Pooling Data

Not applicable to the present study.

Adjustments for Covariates

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

Multiple Comparisons/Multiplicity

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

Withdrawals, Dropouts, Loss to Follow-up

Patients who withdraw from the study will not to be replaced.

Missing, Unused, and Spurious Data

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

Visit Windows

No visit windows will be used. Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, or unscheduled measurements used to define worst outcome within a time period, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

Actual dates and times will be used for PK analyses rather than nominal days and times.

Handling of Partially Missing Dates

For event dates relating to seizure information since diagnosis, history of epilepsy and prior AEDs, if the date is recorded as a complete date it will be used. If the date is recorded as an incomplete date, it will be imputed as follows: if the day and month are missing and the year is recorded, then the day and month are imputed to be 15 and June; if the day is missing and the month and year are recorded, then the day is imputed to be 15; if the day and year are recorded and the month is missing, then the month is imputed to be June. If the year is missing, then the date is left as missing.

Estimation of other event dates, such as AEs start and stop dates is given in the applicable section below.

Key Definitions

Baseline measurements are defined as the last available measurements obtained during the screening period, prior to first IMP dose administration.

DB period starts with the date/time of first dose (inclusive) and ends at the DB phase completion date or date of first dose in the OLE, whichever occurs later.

The date of first dose in the OLE is the start of the OLE period which ends at the OLE phase completion date.

For the purpose of study reporting, tapering period is considered as part of the safety follow-up.

4.3. Interim Analyses

The first analysis will be conducted at the end of the DB phase of the study. Final analysis will occur at the end of the study. Analysis may also be considered during the OLE phase, if long term data is required to support New Drug Application/Marketing Authorization Application submissions.

4.4. Patient Disposition

The number of patients enrolled by country and site will be summarized for the screened population. United Kingdom sites numbers are PPD other sites PPD are from Spain.

Patient disposition will be summarized overall and by treatment arm, for the screened population, including the following information:

- Number of patients screened
    - Number of patients not randomized (screen failure) and reasons
    - Number of patients randomized
    - Number of patients randomized and treated

- Number of patients who completed the DB period
    - Number of patients continuing in OLE period
    - Number of patients continuing to the taper period
    - Number of patients not continuing in OLE or Taper, and reasons

- Number of patients who did not complete the DB period and reasons
    - Number of patients continuing in the taper period
        - Number of patients who completed the taper period
        - Number of patients who did not complete the taper period and reasons
    - Number of patients not continuing in the taper period

- Number of patients that entered OLE period
    - Number of patients who completed the OLE period
        - Number of patients continuing to the taper period
        - Number of patients not continuing in taper period, and reasons

    - Number of patients who did not complete the OLE period and reasons
        - Number of patients continuing in the taper period
            - Number of patients who completed the taper period
            - Number of patients who did not complete the taper period and reasons

The number of patients at each visit will be summarized. An overview of the number of patients included in each population together with reason for exclusion will be produced.

A by-patient listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented. Information on informed consent for the study and genetic testing will also be included.

Protocol deviations identified in the study will be listed, including violation from entry criteria (inclusion/exclusion criteria). No per-protocol population will be used in this analysis.

4.5. Demographic and Baseline Characteristics

Demographic, prior medications, medical history and other baseline information will be summarized for the safety population using descriptive statistics.

Data will also be provided in listings.

Demographics

Demographic characteristics will be summarized using the following variables:

- Age at informed consent (years)
- Sex: male, female
- Race (CRF categories)
- Height (cm)
- Weight (kg) at Visit 1
- Body Mass Index (BMI in kg/m^2) at Visit 1

Note that if weight is missing at Visit 1, the first available weight taken after is to be used.

Age is derived as (date of informed consent – date of birth + 1)/365.25.

BMI is derived as the weight (kg)/(height[m] × height[m]).

Medical History

Data collected as part of the following CRF pages will be listed:

1. History of seizures no longer occurring (including also patient's age when seizure type last occurred)
2. History of current seizures (including also patient's age at onset of seizure type)
3. Electroencephalography (EEG) history
4. Neuroimaging history
5. Genetic testing history (including genetic testing informed consent)
6. History of antiepileptic medications and therapies
7. Non-epilepsy medical history

The following variables, from the domain above, will be summarized in a baseline disease characteristics table:

- Seizure type no longer occurring
- Current seizure types
- Number of patients who ever had abnormal EEG, and seizure type
- Number of patients who ever had an abnormal neuroimaging test (regardless of neuroimaging method)
- Number of patients who had genetic testing performed in the past

Number and percentages of patients having had at least one non-epilepsy medical history are presented by system organ class (SOC) and individual preferred term within each SOC. SOCs are sorted by descending order of frequency. If the frequencies of SOCs are the same, alphabetical order is used. The same rule applies for preferred terms within SOC.

Previous use of cannabis will be summarized in a table including the following variables: previous use (Yes, No), Time since last use (in months, continuous and categorical [≤ 3 months; > 3 months]) and frequency (once per year, up to 12 times per year, more than 12 times per year).

Time since last use (in months) is derived as the (date of informed consent – date of last use + 1)/30.5. In order to flag potential deviation from exclusion criteria 8 (worst case approach), the following imputation is done in case of partial/missing date of last use, for patients that reported previous use of cannabis:

- If the year is missing, the year of the informed consent is used.
- If the month is missing:
    - If the year is the same as the year of informed consent, the month of informed consent is used.
    - If the year is prior to the year of informed consent, the month of December is used.
- If the day is missing:
    - If the year and month are the same as the year and month of informed consent, the day of informed consent is used.
    - If the year is the same year of informed consent, but month is before the last day of the month is used.
    - If the year and month is prior to the year and month of informed consent, the last day of the month is used.

Prior Medications

See section 4.8 for a description of prior medications summaries.

Other Baseline Characteristics

Not applicable.

4.6. Efficacy Evaluation

Not applicable

4.7. Pharmacokinetic Evaluations

PK analyses will be conducted using the PK Population. All PK tables, listings and figures from this sub-section will be presented by treatment group (GWP42003-P/Placebo). Subgroup analyses might be performed on an ad-hoc basis.

The plasma concentration/time curves of CLB, N-CLB, VPA, STP, LEV and TPM will be assessed at Visit 2 (Day 1 and Day 2) and CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites at Visit 4 (Day 33 and Day 34). Patients will be given their daily dose of CLB at a scheduled time during Visit 2 and Visit 4 and the GWP42003-P/placebo immediately afterwards (Visit 4 only) to facilitate the accurate timing of blood samples required for PK analysis.

The PK assessments will therefore capture the following combinations of CLB and GWP42003-P:

- First PK Assessment: CLB only (*Visit 2: Days 1 and 2*)
- Second PK Assessment: CLB and GWP42003-P/Placebo (*Visit 4: Days 33 and 34*)

Blood samples will be taken at the following times: Pre-dose and, 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours, 12 hours and 24 hours after dosing. The timing of each PK sample will be relative to the morning dose of CLB.

PK variables listed in Table 2 will be calculated using standard non-compartmental methods and provided by an external partner.

Reporting of Pharmacokinetic Parameters (CLB/CBD/THC)

Plasma Concentration

Plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD), THC and THC major metabolites (11-OH-THC and 11-COOH-THC) will be displayed graphically, summarized and listed.

Plasma concentration will be summarized by visit, for CLB, CBD, THC and their major metabolites. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n (number of non-missing observations), arithmetic mean, SD, median, Q1, Q3, minimum, and maximum.

Nominal sampling times will be used in the table summaries and figures of plasma concentrations. Figures will plot the mean concentration by treatment group and assessment time (4 lines, GWP42003-P/Placebo × First/Second PK assessment period).

Handling of Values Below the LLOQ

For descriptive statistics, values below the lower limit of quantification of the assay (LLOQ) will be set to LLOQ/2.

All PK concentrations below the LLOQ will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis.

PK parameters

All PK parameters will be listed by patient and summarized by treatment group and PK assessment period.

Statistical Analysis of Drug-Drug Interaction

The following descriptive statistics will be presented in summary tables: n (number of non-missing observations), arithmetic mean, median, Q1, Q3, minimum, maximum, geometric mean, geometric CV, where GCV%=SQRT(e^{s^2}-1)*100 and s is the standard deviation of the log-transformed values.

In order to assess whether the presence of CBD alters the PK profile of CLB (or N-CLB), a standard 90% confidence interval (CI) approach for the between time point ratios of geometric means of $C_{max,}$ $AUC_{(0–t)}$, and $AUC_{(0–\infty)}$ will be carried on logarithmic scale using a linear mixed effect model. The no-effect boundary will be set between 0.5 and 2.0 and if the 90% CI for the ratio of the geometric means of a PK variable falls within the interval [0.5, 2.0], a lack of meaningful effect will be declared.

Estimates will be back transformed to provide summaries on the original scale.

The model will include a fixed effect term for PK assessment period. An unstructured covariance matrix will be used. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects.

The following SAS code can be used as reference:

```
PROC MIXED;
CLASS usubjid period;
BY treatment;
MODEL logvar= period /DDFM=KR;
REPEATED / Subject=usubjid type=un;
LSMEANS period / CL ALPHA=0.05;
ESTIMATE 'difference'   period 1 -1   / CL ALPHA=0.1;
RUN;
```

Data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, non-normality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the model(s) is observed.

For the descriptive statistics of PK parameters for Clobazam and N-desmethyl-Clobazam, Cmax and AUCs will be dose normalized as Cmax divided by the dose (expressed in mg/kg) and AUC divided by the dose.

Reporting of Pharmacokinetic Parameters (Other Drugs)

Plasma concentration and PK parameters for VPA, STP, LEV and TPM will be summarized descriptively similarly to CLB. However, the drug-drug interaction will not be formally assessed (PROC MIXED).

The plasma concentrations and PK parameters will be summarized by treatment using the following drug categories and patients:

- VPA alone vs. VPA + CBD for patients with at least one dose of VPA during DB period

- STP alone vs. STP + CBD for patients with at least one dose of STP during DB period
- LEV alone vs. LEV + CBD for patients with at least one dose of LEV during DB period
- TPM alone vs. TPM + CBD for patients with at least one dose of TPM during DB period

4.8. Safety Analyses

Safety analyses will be conducted using the Safety population for DB period and the OLE population for the extension period.

Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized for each phase of the study separately.

Compliance is taken from the CRF page IMP compliance review and reported by period as:

- "Compliant": if, for all assessments done in the period:
  - The response to the question 'Did the patient comply with the dosing scheduled' is answered 'Yes' and,
  - The response to the question 'Does the actual IMP usage reflect the expected amount used as per the dosing scheduled' is answered 'Yes' and,
  - The response to the question 'Were there some signals of potential abuse since last visit' is answered 'No'
- "Not compliant": if the response to the 2 first questions above was 'No' at least once or the response to the third question is 'Yes' at least once.
- "Unknown" otherwise

Duration of Treatment

Duration on DB treatment is defined as the difference between the last dose (as reported in the CRF page End of DB study outcome) minus the date of first dose of study medication (as reported in the Study medication CRF page) +1.

Similar definition is to be used for the duration of treatment in the taper and in the OLE periods.

Treatment compliance and exposure will be summarized in a table. All IMP drug usage data will be listed (CRF page: Study Medication, IMP compliance review).

Adverse Events

AEs will be coded using the MedDRA (Version 18.1) and displayed in tables and listings using SOC and Preferred Term.

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment emergent AE is defined as one that started, or worsened in severity or seriousness following the first dose of IMP.

AE classification

AEs which occurred during the study will be classified into three periods: pre-study, DB phase emergent, and OLE phase emergent.

The classification of each AE is performed by comparing the onset of the AE to drug intake as follows:

- **Pre-study:** AE with onset prior to the first dose of the study, or if no dose is taken, or stop date is before first dose
- **Treatment-emergent:** AE that occurred after the first dose or the same day as the first dose are considered treatment emergent AEs and further classified as:
    - **DB phase emergent:** if onset less than the first dose of the OLE period (if applicable).
    - **OLE phase emergent:** if onset greater than or equal to the first dose of OLE (if applicable).

For patients who did not enter the OLE phase, AE can only be assigned to pre-study or DB periods.

If the AE start date is missing or recorded as a partial date, the AE will be reported in the appropriate period using available start date information and stop date, if present.

AEs are summarized by patient incidence rates. The number of patients reporting at least one AE will be provided i.e. a patient contributes only once to the count for a given AE (overall, SOC or preferred term). Summaries will be provided for each phase of the study separately on the safety population and the OLE population respectively.

The following summaries will be produced:

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

In the tabulations by severity, each patient will contribute only once to each of the incidence rates by using the worse severity (within the period of interest).

All AEs occurring on study will be listed in patient data listings.

During the collection of AEs, if the patient reports an AE consistent with any of the following categories, then the investigator or study coordinator is required to complete an additional Supplemental AE Form and a Site Classification Form (investigator only) following further discussion of the event(s) with the patient or their caregiver. The categories 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.

Treatment-emergent AEs defined as "triggering events of interest" (see above) will also be tabulated and listed separately.

Character Presentation of Event Dates in Listings/datasets

The AE start/end date text (i.e., the character presentation) is the recorded AE start/end date if the AE start/end date is recorded as a complete date. If the AE start/end date is partially known, the partial date information that is available for the AE start/end day, start/end month, or the start/end year is used, where missing date parts are indicated with dashes (-).

If the AE start/end date is completely unknown, the AE start/end date text is left blank.

Note: within the dataset of adverse events, partial dates will be presented using the earliest start date possible and latest possible end date, with a flag detailing the level of imputation (day or month).

Laboratory Data

Clinical laboratory sample parameters are detailed in Table 3.

Table 3 Hematology, Biochemistry, Urinalysis and THC Screen

Biochemistry (serum)	**Hematology (whole blood)**	**Urinalysis (urine)**	**Pregnancy Test**	**THC screen (urine)**
Alanine aminotransferase	Hematocrit	Bilirubin	Serum	THC
Albumin	Hemoglobin	Blood		
Alkaline phosphatase	Mean cell volume	Glucose		
Aspartate aminotransferase	Mean corpuscular hemoglobin	Ketones		
Calcium	Platelets	Nitrites		
Creatinine	Red blood cell count	pH		
Estimates of glomerular filtration rate	White blood cell count with automated differential	Protein		
Gamma-glutamyl transferase		Specific gravity		

Table 3 Hematology, Biochemistry, Urinalysis and THC Screen

Biochemistry (serum)	Hematology (whole blood)	Urinalysis (urine)	Pregnancy Test	THC screen (urine)
Glucose		Urobilinogen		
HDL-cholesterol				
Potassium				
Prolactin				
Prothrombin time (plasma)				
Sodium				
Total bilirubin (TBL)				
Total protein				
Urea (BUN)				
Triglycerides				

Note: In addition, an alcohol test will be performed on Visit 1, Visit 2 and Visit 4 (refer to Table 1)

Clinical laboratory values will be expressed using conventional SI units.

The actual value and change from baseline to each on study evaluation will be summarized for biochemistry, hematology and urinalysis for the Safety (DB period) and the OLE (OLE period) populations. For all post-baseline time points, the original assessment for any given time point will be used in the data summaries. In the event of repeat values, the last non-missing value per study day/time will be used.

All other laboratory values (baseline pregnancy, baseline THC screen test, and alcohol test results at each time point) will be presented within the listing only.

Categorical shift tables to all visits will also be presented, showing the numbers of patients with values outside the normal range for the Safety (DB period) and the OLE populations.

All laboratory data will be provided in data listings.

Vital Signs, Physical Examinations and Blood Pressure

For vital signs (pulse rate, respiratory rate and temperature), physical examination (weight) and blood pressure, the actual value and change from baseline to each on study evaluation will be summarized for the Safety (DB period) and the OLE (OLE period) populations in one table.

By-patient listings of measurements will be presented.

12-lead Electrocardiogram

ECG results and change from baseline will be summarized descriptively at each study visit. All ECG data for each patient will be provided in data listings.

Concomitant Medications

Concomitant AED (as reported in the Concomitant AED dosing CRF page) are summarized in a table and listing.

Prior and concomitant medications will be coded using the WHO Drug Dictionary Enhanced. Results will be tabulated for each period of use (see below) by Anatomic Therapeutic Class (ATC) level 2 and preferred term.

The use of concomitant medications will be included in by-patient data listing.

Medications taken during the study will be classified according to the start/end dates. Concomitant medications that were administered on or after the first study dose date or that were administered before the first study dose date and are ongoing are considered on treatment concomitant medications (other medications are considered prior medications) and further categorized as:

- **Baseline ongoing:** A concomitant medication with a start date prior to the date of the first study dose date.
- **DB Treatment Period:** A concomitant medication with a start/end date on or after the date of the first study dose date and with a start/end date before the start of OLE or with a start date before the date of the first study dose date and is ongoing.
- **Extension Phase:** A concomitant medication with a start date on or after the start of OLE or with a start date before the start of OLE and an end date after the start of OLE or is ongoing.

C-SSRS

The Columbia–Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior.

The following outcomes are C-SSRS categories and have binary responses (yes/no).

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Suicidal ideation is defined as a 'yes' answer to any one of the five suicidal ideation questions (categories 1-5).

Suicidal behavior is defined as a 'yes' answer to any one of the five suicidal ideation questions (categories 6-10).

Suicidal ideation or behavior is defined as a 'yes' answer to any one of the 10 categories.

The 10 C-SSRS categories, Self-injurious behavior, Suicidal ideation, Suicidal behavior and Suicidal ideation or behavior will be summarized for each period separately. For each item and period, the number of patients with at least once a response 'yes' will be presented.

Genotype

A listing of available genotype analyses will be provided.

Abuse liability

The following listings will be provided:

- Study Medication Use and Behavior Survey
- Supplemental AE Form
- Supplemental Drug Accountability Form
- Site Classification Form

Patient Diary

Unless already listed elsewhere, data from patient diaries will be listed.

Seizure Frequency

Seizure frequency during a period is defined as the total number of seizures divided by the total number of reported days in the diary. Any intermittent missing data for the number of seizures arising from unreported days in diary will not be imputed.

Summary statistics for the seizure frequency, absolute and percentage change from screening will be presented for the DB period only using the safety population. The number of patients experiencing percent changes >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in seizure frequency will also be displayed.

Data from all periods will be listed.

5. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan.

6. REFERENCES

Not Applicable

7. APPENDICES

7.1. Statistical Tables to be Generated, CRF data

This list is only indicative and might be modified.

1. Subject disposition, visit attendance, protocol violations	1.1 Patients screened by country and site		Screened population
	1.2 Patient disposition		Screened population
	1.3 Number of patients by visits		Screened population
2. Summary of analysis sets	Screened population		Screened population
3. Summary of demographics	Safety population		Safety population
4. Baseline disease characteristics	4.1 Epilepsy characteristics		Safety population
	4.2 Previous use of cannabis		Safety population
5. Non-epilepsy medical history			Safety population
6. Concomitant medications	6.1 Medications ongoing at baseline		Safety population
	6.2 Medications concomitant to DB treatment period		Safety population
7. Compliance			Safety population
8. PK	Note: 2 tables per PK assessment (1 descriptive of PK concentration, 1 for analysis of PK parameters)		PK population
9. PD	NA		
10. Exposure			Safety population
11. Adverse events	11.1 Treatment-emergent AEs		Safety population
	11.2 Treatment-emergent related Aes		Safety population
	11.3 Treatment-emergent AEs by maximum severity		Safety population
12. Serious and other significant adverse events	11.4 Treatment-emergent SAEs		Safety population
	11.5 Treatment-emergent related SAEs		Safety population
	11.6 Treatment-emergent AEs reported as leading to permanent cessation of study treatment		Safety population
	11.7 All fatal AEs		Safety population
	11.8 Triggering adverse events		Safety population
13. Laboratory evaluations	13.1 Biochemistry	13.1.1 Values and changes by visit	Safety population
		13.1.2 Shift based on reference ranges	Safety population
		13.1.3 Shift based on toxicity limits	Safety population
	13.2 Hematology	13.1.1 Values and changes by visit	Safety population
		13.1.2 Shift based on reference ranges	Safety population
		13.1.3 Shift based on toxicity limits	Safety population
	13.3 Urinalysis	13.1.1 Values and changes by visit	Safety population
		13.1.2 Shift based on reference ranges	Safety population

14. Vital signs, other physical findings and other observations related to safety	14.1 Vital signs	14.1.1 Value by visit	Safety population
		14.1.2 Change by visit	Safety population
	14.2 ECG	14.2.1 Value by visit	Safety population
		14.2.2 Change by visit	Safety population
	14.3 C-SSRS	Safety population	
	14.4 Seizure data	Safety population	

7.2. Toxicity criteria for laboratory parameters

The toxicity criteria that will be used to identify abnormal laboratory parameters are presented in Table 4 and Table 5.

Table 4 Toxicity Criteria for Biochemistry Parameters

Parameter	Toxicity Decrease	Toxicity Increase
Chloride	≤0.96xLL	≥1.04xUL
Calcium	≤0.89xLL	≥1.16xUL
Sodium	≤0.96xLL	≥1.04xUL
Potassium	≤0.90xLL	≥1.10xUL
Glucose (mmol/L)	≤3.2	≥16
Phosphate	≤0.79xLL	
Cholesterol	≤0.85xLL	≥1.6xUL
ASAT (SGOT)		≥2.6xUL
ALAT (SGPT)		≥2.6xUL
Lactate Dehydrogenase (LDH)		≥2.6xUL
Alkaline phosphatase		≥2.6xUL
Gamma GT		≥2.6xUL
Bilirubin		≥1.26xUL
Albumin	≤0.84xLL	
Total protein	≤0.84xLL	≥1.16xUL
Urea		≥2.6xUL
Blood urea nitrogen (BUN)		≥2.6xUL
Creatinine		≥2.6xUL
Uric acid		≥1.16xUL

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

Table 5 Toxicity Criteria for Hematology Parameters

Parameter	Toxicity Decrease	Toxicity Increase
Hemoglobin (g/dL)	≤9.4	
Hematocrit (%)	≤28	
Red cell count	≤0.84xLL	
Mean corpuscular volume	≤0.84xLL	≥1.11xUL
Mean corpuscular hemoglobin	≤0.84xLL	
Mean corpuscular hemoglobin concentration	≤0.84xLL	
Platelets (x10^9/L)	≤74	
Prothrombin time		>1.5xUL
Prothrombin ratio		>1.5xUL
Total white blood cell count (x10^9/L)	≤2.9	≥21
Total neutrophil count (x10^9/L)	≤1.36	≥14.7
Segmented neutrophil count (x10^9/L)	≤0.75	≥12.3
Eosinophils (x10^9/L)		≥1.5
Basophils (x10^9/L)		≥0.31
Monocytes (x10^9/L)		≥2.1
Lymphocytes (x10^9/L) for patients <18 years (auto hematology)	≤1.0	
Lymphocytes (x10^9/L) for patients <18 years (manual hematology)	≤0.2	
Lymphocytes (x10^9/L) for patients ≥18 years	≤0.2	
Promyelocytes		≥1.1
Metamyelocytes (x10^9/L)		≥1.1
Myclocytes (x10^9/L)		≥1.1

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

7.3. Study Design

Figure 7-1 Study Design and Treatment Schema (first part)

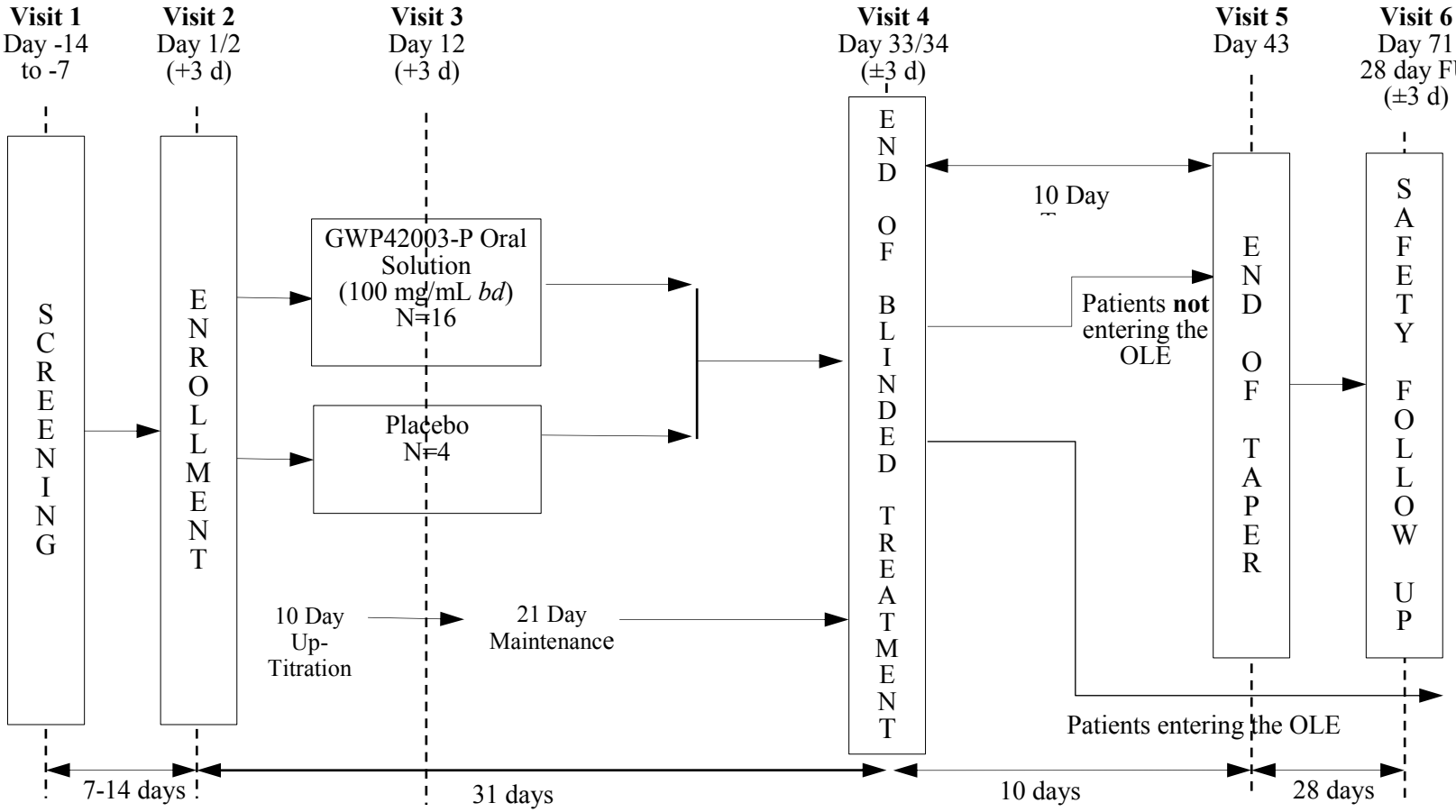
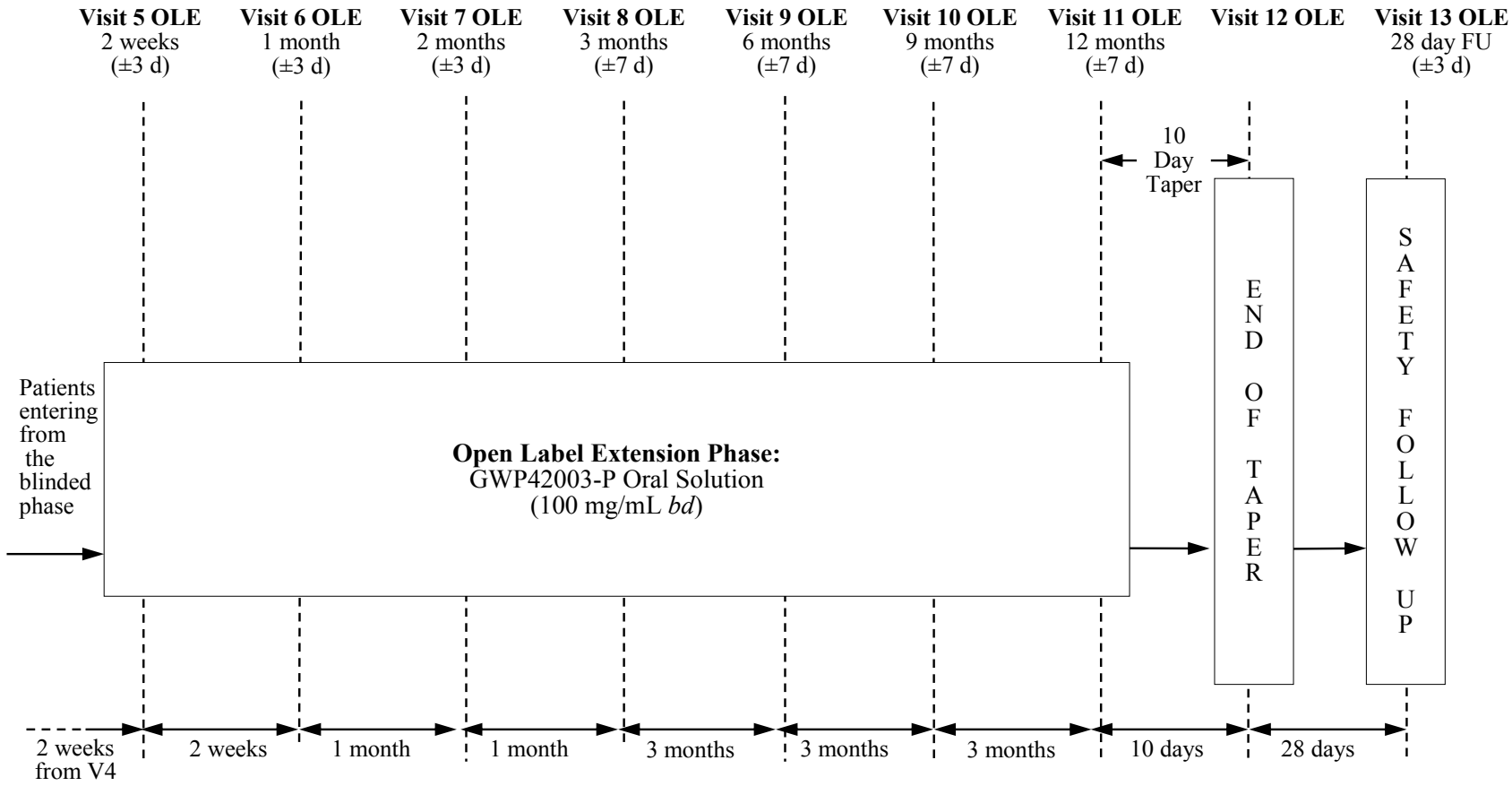


Figure 7-2 Study Design and Treatment Schema (second part)



7.4. Examples of outputs

1. Subject disposition, visit attendance, protocol violations
1.1 Disposition by periods
Screened population

Country Site	Placebo N=xx Subjects n %	GWP N=x Subjects n %	All patients N=xx Subjects n %
All countries	xx (xxx.x)	x (xxx.x)	xx (xxx.x)
Spain	x (xx.x)	x (xx.x)	xx (xx.x)
PPD	x (xx.x)	x (xx.x)	x (xx.x)
	x (xx.x)	x (xx.x)	x (xx.x)
United Kingdom	x (xx.x)	x (xx.x)	xx (xx.x)
PPD	x (xx.x)	x (xx.x)	x (xx.x)
	x (x.x)		x (x.x)
	x (xx.x)	x (xx.x)	x (xx.x)
	x (xx.x)	x (xx.x)	x (xx.x)

Output ID: T-DISP1 DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-DISP1.sas

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1. Subject disposition, visit attendance, protocol violations
1.1 Disposition by periods
Screened population

Statistics	Placebo (N=xx) n (%)	GWP (N=xx) n (%)	Total (N=xx) n (%)
Screened subjects	xx (xxx.x)	x (xxx.x)	xx (xxx.x)
Screen failure		x (xx.x)	x (x.x)
-> Withdrew Consent PPD WAS AFRAID OF POSSIBLE SIDE EFFECTS.)		x (xx.x)	x (x.x)
Randomized	xx (xxx.x)	x (xx.x)	xx (xx.x)
Randomized and treated subjects	xx (xxx.x)	x (xx.x)	xx (xx.x)
Completed the DB period	xx (xx.x)	x (xxx.x)	xx (xx.x)
Did not complete the DB period	x (xx.x)		x (xx.x)
Patient,legal representative withdrew consent to participate	x (xx.x)		x (xx.x)
Other	x (xx.x)		x (xx.x)

Output ID: T-DISP2 DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-DISP2.sas

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1. Subject disposition, visit attendance, protocol violations
1.1 Number of patients by visits
Screened population

Parameters	Placebo (N=xx) n (%)	GWEP (N=x) n (%)	Total (N=xx) n (%)
V1 (Day -14 to -7)	xx (xxx.x)	x (xxx.x)	xx (xxx.x)
V2 (Day 1)	xx (xxx.x)	x (xx.x)	xx (xx.x)
V2 (Day 2)	xx (xxx.x)	x (xx.x)	xx (xx.x)
V3 (Day 12)	xx (xxx.x)	x (xx.x)	xx (xx.x)
V4 (Day 33)	xx (xxx.x)	x (xx.x)	xx (xx.x)
V4 (Day 34)	xx (xx.x)	x (xx.x)	xx (xx.x)
V5 DB (End of Taper after DB period)			
V6 DB (SFU after DB period)	x (xx.x)		x (x.x)
V5 (OLE Week 2)	x (xx.x)	x (xx.x)	x (xx.x)
V6 (OLE Month 1)	x (x.x)		x (x.x)
V7 (OLE Month 2)	x (x.x)	x (xx.x)	x (x.x)
V8 (OLE Month 3)			
V9 (OLE Month 6)			
V10 (OLE Month 9)			
V11 (OLE Month 12)	x (x.x)		x (x.x)

Output ID: T-DISP3 DDMMMYY
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1. Subject disposition, visit attendance, protocol violations
1.1 Number of patients by visits
Screened population

Parameters	Placebo (N=xx) n	(%)	GWEP (N=x) n	(%)	Total (N=xx) n	(%)
V12 (End of Taper after OLE period)						
V13 (SFU after OLE period)						

Output ID: T-DISP3 DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-DISP3.sas

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2. Summary of analysis sets
Screened population

Statistics	Placebo (N=xx) n (%)	GWEP (N=x) n (%)	Total (N=xx) n (%)
Screened	xx (xxx.x)	x (xxx.x)	xx (xxx.x)
Safety Population	xx (xxx.x)	x (xx.x)	xx (xx.x)
Pharmacokinetic Population			
OLE Population	x (xx.x)	x (xx.x)	xx (xx.x)

Output ID: T-DISP4 DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-DISP4.sas

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3. Summary of demographics
Safety population

Parameters	Statistics	Placebo (N=xx)	GWEP (N=x)	Total (N=xx)
Age	N (missing)	xx (x)	x (x)	xx (x)
	Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)	xx.xx (x.xx)
	Median	xx.xx	xx.xx	xx.xx
	Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
Sex	N (missing)	xx (x)	x (x)	xx (x)
	Male	x (xx.x)	x (xx.x)	xx (xx.x)
	Female	x (xx.x)	x (xx.x)	xx (xx.x)
Race	N (missing)	xx (x)	x (x)	xx (x)
	White	xx (xx.x)	x (xxx.x)	xx (xx.x)
	Other	x (x.x)		x (x.x)
Height (cm)	N (missing)	xx (x)	x (x)	xx (x)
	Mean (SD)	xxx.xx (xx.xx)	xxx.xx (x.xx)	xxx.xx (x.xx)
	Median	xxx.xx	xxx.xx	xxx.xx
	Q1 ; Q3	xxx.xx ; xxx.xx	xxx.xx ; xxx.xx	xxx.xx ; xxx.xx
	Min ; Max	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x
Weight (kg) at Visit 1	N (missing)	xx (x)	x (x)	xx (x)
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.xx	xx.xx	xx.xx
	Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx
	Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x

Output ID: T-DM DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-DM.sas

3. Summary of demographics
Safety population

Parameters	Statistics	Placebo (N=xx)	GWEP (N=x)	Total (N=xx)
Body Mass Index (kg/m2) at Visit 1	N (missing)	xx (x)	x (x)	xx (x)
	Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)	xx.xx (x.xx)
	Median	xx.xx	xx.xx	xx.xx
	Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x

Output ID: T-DM DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-DM.sas

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4. Baseline disease characteristics
4.1 Epilepsy characteristics
Safety population

Statistics	Placebo N=xx Subjects n %	GWEP N=x Subjects n %	All patients N=xx Subjects n %
Ever Had Abnormal EEG? ->Yes	xx (xx.x)	x (xx.x)	xx (xx.x)
Ever Had Abnormal Neuroimaging History? ->Yes	x (xx.x)	x (xx.x)	x (xx.x)
Ever Had Genetic Testing? ->Yes	x (x.x)	x (x.x)	x (x.x)
History Of Current Seizures	xx (xx.x)	x (xx.x)	xx (xx.x)
Absence or Atypical absence	x (x.x)	x (xx.x)	x (x.x)
Atonic	x (x.x)	x (x.x)	x (x.x)
Complex Partial Seizure (Focal Dyscognitive)	x (xx.x)	x (xx.x)	xx (xx.x)
Generalized Tonic Clonic Convulsion	x (x.x)	x (x.x)	x (x.x)
Other	x (x.x)	x (xx.x)	x (x.x)
Secondarily Generalized Tonic Clonic (Evolving to bilateral convulsive seizure from partial (focal) seizure)	x (xx.x)	x (x.x)	x (xx.x)
Tonic	x (x.x)	x (x.x)	x (x.x)
History Of Seizures No Longer Occurring	x (xx.x)	x (x.x)	x (xx.x)
Atonic	x (x.x)		x (x.x)
Complex Partial Seizure (Focal Dyscognitive)	x (x.x)		x (x.x)
Generalized Tonic Clonic Convulsion	x (x.x)		x (x.x)
Secondarily Generalized Tonic Clonic (Evolving to bilateral convulsive seizure from partial (focal) seizure)	x (x.x)	x (x.x)	x (x.x)

Output ID: T-EPIL DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-EPIL.sas

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11. Adverse events
11.1 Treatment-emergent AEs
Safety population

Statistics	Placebo N=xx Subjects n %	GWEP N=x Subjects n %	All patients N=xx Subjects n %
Subject with at least one adverse event	xx (xx.x)	x (xx.x)	xx (xx.x)
Gastrointestinal disorders	x (xx.x)	x (xx.x)	x (xx.x)
Diarrhoea	x (xx.x)	x (xx.x)	x (xx.x)
Nausea	x (xx.x)	x (xx.x)	x (xx.x)
Vomiting	x (x.x)	x (xx.x)	x (xx.x)
Abdominal pain	x (x.x)		x (x.x)
Dyspepsia		x (xx.x)	x (x.x)
Nervous system disorders	x (xx.x)	x (xx.x)	x (xx.x)
Dizziness	x (x.x)	x (xx.x)	x (xx.x)
Sedation	x (x.x)	x (xx.x)	x (xx.x)
Somnolence	x (x.x)	x (xx.x)	x (xx.x)
Aphasia		x (xx.x)	x (x.x)
Dysarthria		x (xx.x)	x (x.x)
Headache	x (x.x)		x (x.x)
Hypersomnia		x (xx.x)	x (x.x)
Lethargy	x (x.x)		x (x.x)
Memory impairment	x (x.x)		x (x.x)
Seizure cluster	x (x.x)		x (x.x)
Speech disorder		x (xx.x)	x (x.x)
Skin and subcutaneous tissue disorders	x (xx.x)	x (xx.x)	x (xx.x)
Dermatitis	x (xx.x)		x (xx.x)
Petechiae		x (xx.x)	x (x.x)
Rash		x (xx.x)	x (x.x)
Rash maculo-papular	x (x.x)		x (x.x)
Rash pruritic		x (xx.x)	x (x.x)

Output ID: T-AE DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-AE.sas

Page 1 of xx

14. Vital signs, other physical findings and other observations related to safety
14.1 Vital signs
14.1.1 Value by visit
Safety population

Parameter	Visit	Statistics	Placebo (N=xx) n (%)	GWEP (N=x) n (%)	Total (N=xx) n (%)
VS/BP/PE indicative of medical condition?	Anytime post baseline	N	xx	x	xx
		Yes		x (xx.x)	x (xx.x)
		No	xx (xxx.x)	x (xx.x)	xx (xx.x)
Weight (kg)	V1: Day -14 to -7	N	xx	x	xx
		Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
		Median	xx.xx	xx.xx	xx.xx
		Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx
		Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x
	V2: Day 1	N	xx	x	xx
		Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
		Median	xx.xx	xx.xx	xx.xx
		Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx
		Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x
	V2: Day 2	N	xx	x	xx
		Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
		Median	xx.xx	xx.xx	xx.xx
		Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx
		Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x
etc…	etc…	N	xx	x	xx
		Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
		Median	xx.xx	xx.xx	xx.xx
		Q1 ; Q3	xx.xx ; xx.xx	xx.xx ; xx.xx	xx.xx ; xx.xx
		Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x

Parameter	Visit	Statistics	Placebo (N=xx) n (%)	GWEP (N=x) n (%)	Total (N=xx) n (%)

VS=Vital Signs; BP=Blood Pressure; PE=Physical Examination
Output ID: T-VS DDMMMYY
Z:\GWPHARMA\GWEP1428\DB\BIOSTATISTICS\PRODUCTION\TABLES\PGM\T-VS.sas

GWEP1428

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE POSSIBLE DRUG-DRUG INTERACTIONS BETWEEN CLOBAZAM AND CANNABIDIOL (GWP42003-P)

DATA MANAGEMENT PLAN

Author: PPD

Job Title: PPD

1 Approval Form

QUANTICATE AUTHOR
Name: PPD
Position: PPD
PPD

Signature — 02 NOV 2016. Date

QUANTICATE REVIEW
Name: PPD
Position: PPD
PPD

Signature — 01 NOV 2016. Date

QUANTICATE REVIEW
Name: PPD
Position: PPD
PPD

Signature — 01 NOV 2016 Date

GW RESEARCH LTD APPROVAL
Name: PPD
Position: PPD
PPD

Signature — 02-NOV-2016 Date

GW RESEARCH LTD APPROVAL
Name: PPD
Position: PPD
PPD

02 NOV 2016

2 Table of Contents

3 Version Controlled Document Log

Effective Date	Version	Change
29Feb2016	Approved 1.0	Approved Version
20Sep2016	Approved 2.0	Personnel updates
01Nov2016	Approved 3.0	Updated Section 8.9 Discrepancy Management

4 Glossary of Abbreviations

ACRF	Annotated Case Report Form
AE	Adverse Event
AED	Antiepileptic Drugs
CAB	Cognitive Assessment Battery
CDASH	Clinical Data Acquisition Standards Harmonization
CDC	Clinical Data Co-ordinator
CDISC	Clinical Data Interchange Standards Consortium
CDM	Clinical Data Management/Manager
CGIC	Caregiver Global Impression Of Change
CGICSD	Caregiver Global Impression Of Change in Seizure Duration
CM	Concomitant Medication
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CSR	Clinical Study Report
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CWS	Cannabis Withdrawal Scale
DBA	Database Administrator
DCF	Data Clarification Form
DCI	Data Collection Instrument
DEC	Data Entry Clerk

DEG	Data Entry Guidelines
DMP	Data Management Plan
DS	Dravet Syndrome
DSD	Database Specification Document
DSMC	Data Safety Monitoring Committee
DVG	Discrete Value Groups
DVP	Data Validation Plan
DVS	Data Validation Specification
EDTS	Electronic Data Transfer Specifications
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GW	GW Research Ltd
HLGT	Higher Level Group Term
HLT	Higher Level Term
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IS	Information Systems
IWRS	Interactive Web Response System
LCDM	Lead Clinical Data Manager
LLT	Lowest Level Term
MEDDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
OC	Oracle Clinical
PCWS	Pediatric Cannabis Withdrawal Scale
PK	Pharmacokinetics
PDF	Portable Document Format
PDM	Project Data Manager
PI	Principal Investigator
PT	Preferred Term
PVD	Pharmacovigilance Department
QC	Quality Control

QOLCE	Quality of Life in Childhood Epilepsy
QOLIE	Quality of Life in Epilepsy
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SEC	Self Evident Corrections
SF	Screen Failure
SGIC	Subject Global Impression of Change
SGICSD	Subject Global Impression of Change in Seizure Duration
SMF	Study Master File
SMUBS	Study Medication Use and Behavior Survey
SOC	System Organ Class
SOP	Standard Operating Procedure
UAT	User Acceptance Testing
TMS	Thesaurus Management System
WHO-DD	WHO Drug Dictionary

5 Outline Description of the Protocol

This is a phase 2, double-blind, randomized, placebo-controlled study in 20 patients. Patients will be randomized in a 4:1 ratio to receive 20 mg/kg GWP42003-P or placebo from days 2 to 33. At the end of the treatment period, patients will be given the option of continuing onto an open label extension (OLE) period if the investigator and patient both agree that it is in their best interests. Doses may be adjusted up or down, dependent on investigator opinion, to a maximum of 30 mg/kg/day GWP42003-P. The OLE will last for a maximum of one year or until marketing authorization is granted; whichever is earlier. Patients that do not continue onto the OLE will taper off of GWP42003-P over a 10 day period and will have a telephone follow-up visit four weeks after the end of taper day on Day 71.

5.1 Distribution List

- GW Clinical Project Manager (CPM)
- GW Lead Clinical Data Manager (CDM)
- Quanticate Project Data Manager (PDM)
- Quanticate Lead Clinical Data Manager (LCDM)

A copy of the signed Data Management Plan (DMP), amendments, and related documents will be filed in the Study Master File (SMF) by the LCDM or designee, the Quanticate project team will be informed of the location. A copy will be forwarded to GW Research Ltd. These are the authorised copies. Any copies taken of these documents are not authorised or version controlled.

5.2 Data Management Plan Objectives and Administration

This DMP is intended to document, describe and define all Clinical Data Management (CDM) processing activities for the project. It will provide a detailed description of all data related procedures and processes. Quanticate CDM staffs are responsible for the initiation, production, review and maintenance of the DMP.

Quanticate has been contracted to perform the CDM tasks for this project that are listed in section 6 of this DMP. These include data review and validation of data with a final project endpoint of a clean database.

Data processing activities will not be started on a project until the DMP has been authorised by GW.

5.3 Project Outline

This project will be conducted from the planning phase through database close over the course of approximately 2 years. The estimated patient enrolment is 20 patients. The first patient was enrolled in the third week of Jan 2016. The first CRF pages should arrive at Quanticate by the last week of February 2016. The last CRF should arrive in-house by last week of June 2016. Database lock is planned to occur 4 weeks after last CRF data for each part is received in house.

5.4 Project Personnel

The CDM team will be lead by a LCDM who, in conjunction with the PDM are responsible for the accuracy and timelines of the project. The LCDM is responsible for ensuring that the data management activities throughout the project are adequately resourced and that the resource on the project has been trained on the study requirements, the systems used and the Standard Operating Procedures (SOP) appropriately.

6 Scope of Work Defined Within the Data Management Plan

- CRF Design
- Database Design
- CRF Receipt
- CRF Logging/Tracking
- CRF Storage
- Data Entry
- Data Validation
- Laboratory Data Handling
- External Data Handling (e.g. PK)
- Medical Coding
- Serious Adverse Events (SAE) Reconciliation
- Discrepancy Management
- Data Clarification Form (DCF) Process
- Database Editing

- File Notes
- Quality Control
- Control of the DMP

7 Timelines

Timelines and assignments will be reviewed by the project team and will be discussed at regular team meetings. All deliverables will be sent to GW unless otherwise specified. It is essential that modifications to activities, such as responsibilities and timings, be communicated as soon as they are known as this could affect current project scope thus potentially resulting in out of scope activities.

Timelines will be discussed by the PDM and the GW Lead Data Manager and the CPM on a regular basis, and will be stored electronically in the project area S:\Q_048\Q_02553\GWEP1428\Data Management\Documents\Timelines.

The clinical monitoring of the project will be performed by GW. It is their responsibility to provide the LCDM with the patient enrolment list and the monitoring schedule on a monthly basis to allow accurate estimates of CRF workflow.

The CRF design will be finalised and available for data to be entered into before the first patient is enrolled.

Once the CRF is finalised, the database will be built.

Once the CRF is finalised the creation of the following documents will commence:

- Data Validation Plan (DVP)
- Final Data Quality Control (QC) Plan
- Electronic Laboratory Data Transfer Specifications
- Data Entry Guidelines (DEG)

The DEG must be approved prior to the start of data entry. The DVP must be authorised by GW prior to commencing programming of the data validation checks. The QC Plan must be authorised by GW prior to the start of database lock procedures.

GW's SAE Reconciliation and Coding Plan will be referenced for SAE Reconciliation and Coding activities.

Transfer specifications for external data received electronically will be produced prior to the first load of data being received by Quanticate. For GWEP1428 electronic data will

be transferred to Quanticate from ACM-pivotal Global Central Laboratory, LGC Group, Covance and Parexel.

8 Project-Specific Guidelines for the Completion of Tasks

The project specific guidelines for this project are written in accordance with Quanticate SOPs.

8.1 CRF Design

The CRF has been designed by Quanticate on receipt of the final, signed protocol in accordance with CDM-SOP-004.

8.2 Database Design

The database will be built by Quanticate in Oracle Clinical (OC) v4.5. This application is compliant with ICH GCP and 21 CFR part 11. This is a system based in Oracle which has been validated according to Quanticate CMP-SOP-012 'Validation of Computerised Systems'.

Database naming conventions will be based on CDISC CDASH standards unless otherwise specified by the customer.

Access will only be granted to personnel specifically assigned to this project, with access authorised by the LCDM or designee. Specific access is assigned by the CDM programmer via the study access form. The access level is specified on the form and granted as per the role requirement.

An annotated CRF (aCRF) and a Database Specification Document (DSD) will be prepared to define the database format, and these will document the database structure. The aCRF and DSD will form part of the SMF.

Full quality control of the database will be performed prior to release of the database for testing. This will be performed by 100% QC of the Discrete Value Groups (DVG), Questions, Question groups, and Data Collection Instruments (DCI) in the database against the aCRF. The database will not be released for testing until all issues identified during the QC have been resolved as per CDM-SOP-001 ’Database Design’.

User Acceptance Testing (UAT) of the database will be carried out by entering test patient data. During entry, the data entry screens will be checked to ensure the collection of all required data and that all variables are of adequate length and appropriate type and have been correctly assigned. Any database updates identified will be actioned and QC’d before the database is released for production data entry.

8.3 CRF Transport

CRFs will be couriered from the Site/Clinical Research Associate (CRA) to the designated Quanticate office at the following address:

For All sites:

PPD
Quanticate
Bevan House
Bancroft Court
Bancroft
HITCHIN
Herts
SG5 1LH
T. PPD

PPD
Quanticate
Bevan House
Bancroft Court
Bancroft
HITCHIN
Herts
SG5 1LH
T. PPD

Each batch of CRFs will be accompanied by an inventory document listing the contents of the container (site ID, patient ID, visits, pages or DCF numbers, and any non-CRF related study documents such as laboratory reports). GW's Transmittal Form will be used for this purpose.

The CRA will notify the PDM and LCDM of the expected arrival of the data by email.

It is the responsibility of the CRAs to ensure that any CRFs sent to Quanticate have been signed by appropriately authorised site staff.

The Clinical Data Co-ordinator (CDC) will acknowledge the arrival of the CRFs with the CRA

The LCDM will inform the CRA if the pages are not received.

8.4 CRF Receipt

Quanticate will expect to receive the top copies (originals) only of the Main CRF pages and bottom copies of the questionnaire pages.

The CDC will check the CRFs against the inventory provided on the GW transmittal form. Any discrepancies between the inventory and the documents received will be noted and the appropriate CRA informed. A signed and dated inventory will be returned to the sender by fax or scanned image/PDF and emailed within two working days of receipt of the CRFs. The original inventory will be filed in the SMF.

If more than one copy of the CRF is received (original and working copy) then both copies will be noted in the inventory form that is sent back to the CRA. The pages will

be split, and the copy/copies that should not have been sent will be returned to the CRA.

8.5 CRF Tracking

The CDC will set up and maintain the logging and tracking spreadsheet in Microsoft Excel.

The study number, site number and patient number will be checked manually on all pages received to ensure all the correct pages are with the correct CRF. Any errors in the header data will be noted GW's Transmittal Form.

Each CRF should also be manually checked to ensure the pages are in the correct order, and any other documents (laboratory reports, DCFs) are at the front of the CRF. Missing page reports will be run periodically and issued to the CPM. If patient confidential information (i.e. name, telephone number, national insurance number) are recorded on the CRF or associated documents, a copy of the page will be taken, the confidential information will be blacked out on the copy with permanent marker and the page scanned. The scanned page will replace the scan of the original page. The LCDM will inform GW and the person who sent the documents to inform them of the action taken. The original page will be returned to the CRA for redacting.

Any scanned copies of the original CRF or associated documents will be deleted from CRF storage or electronic systems (including any back up process in place). The CRF or associated documents which have had the confidential information removed will be scanned again and the usual process will be followed to enter the data into the database.

If the confidential information from CRF or associated documents has already been entered into the database (or any other electronic systems) then the data must be deleted from the database (including audit trail and any back up process in place) immediately once it is noted.

The LCDM will inform GW in writing either in an email or a file note to confirm the above steps have been taken.

Any additional information not recorded on the CRF e.g. on any form of sticky note will be ignored (not tracked or data entered). Any additional information must be recorded on the actual CRF or DCF.

CRFs should be logged as follows:

X received

XB received blank page (also used for received blank pages that are not expected

PC received photocopy page

PCB received photocopy of page that contains no data

M missing page (noted as sent but not received)

There may be more than 1 line per patient, in the Excel tracker. A new line is created each time a new batch of data is received.

The first page of all unused visits should be provided to Quanticate for all patients who terminate the study early. The page should have the header details completed with the rest of the page struck through. In addition the page should be initialled and dated. A comment along the lines of: “the patient did not complete visit X no further CRF pages completed for this visit” or similar should be annotated onto the CRF page.

Where multiple visits are not completed the sites will be instructed to record a comment stating “the patient did not complete visits X, Y and Z, no further CRF pages will be completed”.

In all cases at least one AE, Concomitant Medication (CM) and general comments page must be sent to Quanticate. If the pages do not contain any data, the header should be completed, the page struck through and a comment along the lines of “no data expected for this page” or similar should be annotated onto the CRF page.

If additional pages are used (Non- Epilepsy Medical History, Concomitant Medications, Adverse Events, Comments etc.), these will be numbered as 2.1 for first repeat for Non-Epilepsy Medical History, AE.1 for first repeat for Adverse Event, AED.1 for Concomitant Antiepileptic Medications, MED.1 for first repeat for other concomitant medications etc. Only completed additional pages are should be sent to Quanticate.

The CRF modules that have an additional page contain a check box that should be completed if an additional page is used (located at the bottom of the page). Quanticate will reconcile this field with the actual pages received from the site.

Scanned CRF pages should only be sent to Quanticate prior to an Interim Analysis (to support New Drug Application and Marketing Authorization Application filing). Original pages should still be collected and issued to Quanticate. Quanticate will reconcile the original page against the scanned page and update the database if required.

The tracking spreadsheet will be located on the Quanticate network, and can be accessed by all Quanticate sites as required. Tracking reports will be sent to GW on a weekly basis.

8.6 Expected Pages

For GWEP1428, the following pages are expected for randomized patients as mandatory minimum for the Blinded and OLE phases:

8.6.1 Blinded Phase:

Study period Visit 1	Page 1-16
Study period Visit 2	Page 17-29
Study period Visit 3	Page 30-34
Study period Visit 4	Page 35-48
Study period Visit 5 *	Page 49-57
Study period Safety Telephone Call (Visit 6)*	Page 58
Site Classification Form**	SCF_
Supplemental Drug Accountability Form**	SDAF_
Supplemental Adverse Event Form**	SAEF1_ , SAEF2_
Study Medication Dose Adjustment Log	DAL_
Concomitant Antiepileptic Medications	AED_
Concomitant Antiepileptic Rescue Medications	RM_
Other Concomitant Medications	MED_
Concomitant Antiepileptic Therapies	AET_
Adverse Events	AE_
Investigator's Signature Page	SIGN

* Study period visit 5 and study period safety telephone call (visit 6) needs to be updated for Non-OLE patients only.
** Page required only if the trigger question on study medication pages indicate that the page is needed.
*** The following non mandatory pages may also be received if applicable: unscheduled visit (U1-U5); general comments page (GC_)

8.6.2 Blinded Diary Pages:

Epilepsy Daily Diary Record	Pages 9-10; 15-16; 22-27; 32-33*

*None OLE patients only.

8.6.3 OLE Phase:

Study period Visit 5	Page 1 – 6
Study period Visit 6	Page 7 – 12
Study period Visit 7	Page 13 – 18
Study period Visit 8	Page 19 – 24
Study period Visit 9	Page 25 – 30
Study period Visit 10	Page 31 – 36
Study period Visit 11	Page 37 – 43
Study period Visit 12	Page 44 – 52
Study period Visit 13	Page 53
Site Classification Form*	SCF_
Supplemental Drug Accountability Form*	SDAF_
Supplemental Adverse Event Form**	SAEF1_ , SAEF2_
Concomitant Antiepileptic Medications	AED_
Concomitant Antiepileptic Rescue Medications	RM_
Other Concomitant Medications	MED_
Concomitant Antiepileptic Therapies	AET_
Adverse Events	AE_
Investigator's Signature Page	SIGN

* Page required only if the trigger question on study medication pages indicate that the page is needed.
** The following non mandatory pages may also be received if applicable: unscheduled visit (U1-U5); general comments page (GC_)

8.6.4 OLE Diary Pages:

Epilepsy Daily Diary Record	Pages 9-11; 16-18; 26-30; 38-43; 57-71; 85-99; 113-127; 132-133

8.6.5 Questionnaires

The following questionnaires will be used in this study for both blinded and OLE phase:

Columbia Suicide Severity Rating Scale [Adult (C-SSRS)]	Blinded: Visit 1, Visit 2, Visit 3, Visit 4,Visit 5, OLE: Visit 5 , Visit 6, Visit 7, Visit 8 Visit 9, Visit 10, Visit 11, Visit 12
Study Medication Use & Behaviour Survey (SMUBS)	SMUBS Page 1 & 2, Blinded: visit 5; OLE: Visit 12

8.6.6 Screen Failure Patients

For patients who are not randomized (screen-failures) only the following pages are expected:

- Study period Visit 1 (page 1)
- Screen Failure page (SF)
- Adverse Events (AE.1) the “None” box should be ticked if no AEs were reported
- Investigator signature page

Any other pages received will be tracked but the data will not be entered. Missing page queries for screen failure patients will only be issued if any of the pages mentioned above are not received.

8.7 CRF Storage

CRFs maintained by Quanticate will be kept in a secure, limited-access, storage area. CRF pages will be filed such that all data for each patient will be stored together in page order. Laboratory reports and other related project documents will be stored at the front of the CRF. CRFs will be stored in the project-specific section of the storage area in patient numerical order.

Removal of the CRFs or any project related file will be documented in the CRF tracking log, kept in the storage area, to ensure they can be easily found if required.

All CRF pages will be scanned, and the scanned images stored on the designated project area on the Quanticate network. The pages will be grouped by patient as they are scanned and will be scanned upon arrival at the designated Quanticate office. The file will be named according to patient number and the pages received e.g. If pages 11-20 are received for patient 002 from site 0001 for visits 3 and 4 the file name will be CRF0001002_p11 to 20.

8.8 Data Entry and Verification

Once data have been tracked the data entry team are informed that the CRFs are ready for entry.

The first pass Data Entry Clerk (DEC) will perform first pass entry using the 'Initial Log-In and Entry' option.

All data in the CRF will be double data entered in Oracle Clinical v4.5 (OC) with 'DCI book on' as described in the project-specific DEG. The DEG includes conventions for missing/partial dates, times, other variables, or if a whole page/visit is "Not Done" or blank. Data Entry will not commence until the DEG is finalised and approved by the LCDM and GW.

Personnel using the system have an individual username and password. The system logs the data entry personnel (Pass 1 User and Pass 2 User) for each module. Changes made to the database during editing are clearly indicated by an electronic audit trail and is available to all personnel assigned to the project with access to the OC project database.

The CRF data are entered as seen, without interpretation or modification (unless directed by the DEG or Self Evident Corrections [SEC]), into the data entry system (Pass 1 User), then a second entry with verification is entered by another, independent data entry clerk (Pass 2 User) into the system.

Reconciliation of Pass 1 and Pass 2 data entry will be carried out by an independent user within OC. Data points with a discrepancy between Pass 1 and Pass 2 will be highlighted within OC and can be corrected during reconciliation of the Data entry.

If the investigator has entered extraneous comments on the CRF page, these will be entered as seen by the first pass data entry clerk using 'Investigator comments'.

If the data are unclear the first pass data entry clerk will raise an 'Operator Comment' to create a manual discrepancy for the CDM to review.

The LCDM will run a listing periodically to identify if two CRF pages with identical header information are entered into the project database. It will then be the LCDM's (or designee's) responsibility to review the issue and, under Key Changes, delete/amend the duplicate record, as applicable.

Once a batch of data entry has been completed, the LCDM (or designee) will check for any CRF pages which have a status of either 'Received',' Pass 1 started', 'Pass 1 complete' or 'Pass 2 started' any outstanding data entry issues and will be actioned and confirmation of any blank pages received obtained if required.

The OC database is automatically updated to show the entry status of each CRF.

If repeated errors are encountered in the CRFs during data entry, the DEC must inform the LCDM so that GW can be informed, the database can be changed, or the DEGs can be updated. Site staff will be instructed on the changes to the guidelines by the GW project team, to facilitate a smoother data entry process.

The LCDM or designee will perform a 100% QC of the first patient entered for each DEC (number of CRF pages to be selected for QC depends on the project size). The LCDM will inform the DECs of any consistent errors.

8.8 Data Validation

Once a batch of data has been double entered, electronic checks will be run across the whole database on a daily basis.

Data validation is performed as detailed in the 'Data Validation Plan' (CDM-ATT-068). This details all of the validation checks that will be performed on the data, the discrepancy message that the investigator/user will see and the type of check (univariate, multivariate, SAS check, listing) and these are agreed between GW and Quanticate prior to the start of validation check programming.

The DVP will consist of:

Univariate Checks:

- Electronic (Univariate) Checks (U): these checks are created at database build and will fire for missing data, or indicator questions that have been specified in the DVP or for data entered in the incorrect format (text in numerical fields or incorrect field length etc.). These will fire at the data entry stage.

Validation Procedures:

- Electronic (Multivariate) Checks (E): Automated checks (validation procedures) programmed in PL/SQL within Oracle Clinical. These are for checking data within datasets and for simple cross-dataset checks. These will be run overnight during the scheduled batch validation sessions or as required by study personnel with the relevant access.

- Programmed Manual Checks (M): Programs producing discrepancies for manual review where programming of edit checks would not be possible. These will be run overnight during the scheduled batch validation sessions or as required by project personnel with the relevant access.

- Listings (L): These are run across data where the programming of checks will be too complex, e.g. comparison of Concomitant Medication start dates with Medical History and Adverse Events. These are run at intervals throughout the duration of the project.

The DVP will be approved by before programming of validations and listings begins.

Validation checks are written in OC. Programs are validated with test data. The purpose of the test data is to enter both valid and invalid data values to ensure that the validations catch all errors and are only seen by the site when expected. The test data will be single data-entered and the validations will be run on the data. Once the validations are executed, errors are generated for each patient. These errors will be reviewed for any potential programming errors which will be fixed prior to the validations being used in production mode

Once in production, the validation checks are run on the whole master database. An error message will be created for any items that fail a validation check. This message is stored in the OC discrepancy management system, together with information to identify the record (site, patient, visit and field name etc.). The system is designed so that should an item that fails a validation check be edited and it is still invalid, a new error message will be generated the next time the validations are run because the value of the item has changed.

- SAS checks/listings/programmed manual checks: Checks across different types of data or CRF pages that are not possible to cross-check electronically and/or require manual interpretation of the data before a query can be raised.
- Electronic checks: Programmed by the CDM Programmer, which are run at intervals during the project, to check for any missing data, data inconsistencies and out-of-range values etc.
- Self-Evident Corrections (SEC): These will be actioned when an obvious error has been made and does not require any interpretation of the data on the CRF by the observer or the error can be resolved by referring to other CRF pages.

The DVP will be approved by GW before programming of checks and listings begins. The list of SECs requires approval from the Principal Investigator (PI).

Validation procedures will be tested against test data, created by a CDM (or designee) to confirm that each check is accurate and generates appropriate discrepancies.

Batch validations will be set to run periodically throughout the project. Additional batch validations may be performed until no new discrepancies are generated and all existing discrepancies have been resolved.

8.9 Discrepancy Management

Discrepancies can be generated several different ways. All discrepancies will be stored in the discrepancy database regardless of how they are generated. The methods of generating discrepancies are as follows:

- Univariate: Created by OC during data entry when the entry in the field is not as expected, e.g. the field length or format of the entry is incorrect.
- Indicator: Created as part of the Database build - normally set up for key questions on repeating groups i.e. yes/no on Medical History – when a response is expected but not present, or vice versa.
- Manual: Created by data entry as an operator comment or by a CDM after review of SAS output, listings, data QC etc.
- Multivariate: Created by running the validation checks over the database in a batch validation session. Batch validations run on data which have been double data entered and have a page status of 'Complete'.
- TMS (Thesaurus Management System): Created from the Coding application when the coder designates a term as un-codable and requiring a discrepancy. The discrepancies created in this way will be transferred to the discrepancy database during batch validation.

The OC discrepancy database will be used to store and track discrepancies. OC will assign a unique identification number to each discrepancy (i.e. DISC ID). All new discrepancies in the discrepancy database will have a status of 'Unreviewed' (i.e. requires action by a CDM) and these will all be reviewed by a CDM or designee to decide the action required. Once the action is decided, the status of the discrepancy will be amended:

- Investigator Review: Requires review and resolution by Investigator DCF sent to site.
- DM Review: Requires review by LCDM.
- Resolved: Discrepancy is no longer open, resolution has been provided by either an allowable change or change/confirmation provided by a resolved discrepancy by the Investigator. (This status will not be allocated until after the database update has been performed).
- Closed: Data has changed and is no longer discrepant.
  Quanticate will not raise any queries for Concomitant Medications and Adverse Events where both the stop date and on-going are blank until the original pages are received.

DCFs will be created from the discrepancy database and will contain discrepancies which require Investigator review. Please note that a DCF may contain more than one discrepancy. Once created DCFs will have a unique number and have the status of 'Created'. The DCFs will be sent to the CRA as a PDF, and the DCF status will be amended to 'Sent'.

Original, resolved, signed DCFs will be returned to Quanticate Hitchin office on an on-going basis prior to the end of the project. In any circumstance where the original 'wet-

ink', resolved, signed DCFs are not available, scanned copies will be accepted in place of the originals.

It is the responsibility of the CRAs to ensure that any DCFs returned to Quanticate have been signed by appropriate, authorised site staff.

On receipt of the DCFs they will be checked to ensure that they have been signed and answered, and then the DCF status will be updated to 'Received'. If the DCF has not been signed or answered, it will be returned to CRA.

It will be the responsibility of the LCDM to notify GW and/or the CRA of receipt of any unresolved DCFs or DCFs outstanding for more than 28 days. Monthly standard DCF status reports will be sent to GW.

8.10 Translation

Quanticate will work with TransPerfect to obtain translations of the comments recorded on the questionnaires (and CRFs/diaries if required).

TransPerfect and Quanticate will follow the process outlined below:

1. Pages requiring translation will be identified during the CRF tracking process
2. Quanticate to upload photocopied documents on to Trial Interactive
3. TransPerfect will translate, edit, and proofread the indicated handwritten portions of text
4. Formatting and Redacting of content in scope will take place
5. Quality Review and Certification (if necessary)
6. Final Deliverable in Microsoft word or PDF format uploaded to Trial Interactive
7. CRF data entered into the clinical database
8. Project Feedback

TransPerfect contact details:

PPD
PPD
TransPerfect Life Sciences
45 Moorfields
5th Floor
London
EC2Y 9AE
Tel: PPD
Email: PPD

8.11 Data Editing

Edits to the data in the database may be necessary as an action to a DCF, operator comment, data entry error, self evident correction or quality control finding.

SECs will be actioned when an obvious error has been made and does not require any interpretation of the data on the CRF by the observer, or the error can be resolved by referring to other CRF pages. The SEC document requires approval from the PI from each site. No SECs will be actioned from a site until the approved list has been received from that site by the Quanticate CDM.

Edits to the data in the database have a full electronic audit trail, allowing a complete record of amendments to the database to be recorded.

A reason for change is required every time an update to the data is made. If the update was actioned from a discrepancy, the DCF ID will be recorded in the comments field as the reason for the update. If the update was actioned from a SEC, the SEC ID will be recorded in the comments field as the reason for the update.

A sample of edits to the data in the database will be QC'd. Depending on the number of errors found in the edits, approximately 10% of updates to the database from DCF answers will be QC'd. The first batch of DCFs updated will be QC'd and a random sample of DCFs will be QC'd over the duration of the project. If more than 1% of errors are found in the edits, further QC of edits will be performed.

8.12 Protocol Deviations

Information on Protocol Deviations (PD) will be collected by both the CRAs and Quanticate CDM.

- CRAs will record any PD into the monitoring visit reports; the report reviewer collates this information into a central log.
- The log will be shared with Quanticate at regular intervals during the study.
- Quanticate will review the log and use it to close the queries that are related to PD.
- Quanticate will capture any PDs mentioned on the DCF e.g. approved out of window visit dates in a log. This log will be reviewed against the PDs log from CRAs and ensure that duplicate PDs are not collected (i.e. remove any PDs from DM log if they are already present in CRA log).
- Quanticate will produce a listing of PDs from the comments page, where PD is ticked upon GW request.

GW will combine PDs received from CRAs and Quanticate CDM at the end of the study, any duplicates will be removed and a final log will be created.

8.13 Laboratory/ External IWRS and Quality of Life Data Handling

In addition to CRF data, central laboratory data, external IWRS data, Diary Pages and Questionnaire data are expected for each patient. Questionnaire data will be received as paper copies and will be double entered into the OC database as specified in the DEG. The laboratory data including PK will be received as datasets from Covance,

ACM-Pivotal Global Central Laboratory and LGC Group. IWRS data will be received as datasets from Parexel.

Central lab data and external IWRS data will be received electronically in GW compliant format. This data will not be entered into OC database. The process for receipt and handling electronic data will be documented in the Electronic Data Transfer Specifications (EDTS).

Questionnaire:
Minimal queries will be raised on questionnaire data. Missing and inconsistent data within the forms will not be queried; the only issues to be queried will be missing questionnaire pages, and inconsistent header data.

Electronic Data Transfer:
Details of the process of laboratory data handling and IWRS data handling will be discussed with GW, ACM-Pivotal Global Central Laboratory, LGC Group, Parexel and Covance and upon agreement will be documented in the EDTS.

8.13.1 External Vendors

The following laboratory groups will be responsible for collecting, analysing and reporting results accordingly:

ACM-Pivotal Global Central Laboratory
PPD
ACM Global Central Laboratory
23 Hospital Fields Road
York
YO10 4DZ
UK
Direct Dial: PPD
Office: PPD Fax: PPD
PPD
ACM Global Central laboratory will be supplying the Biochemistry, Haematology, Urinalysis, Pregnancy test and Urine drug screen data. The blinded data will be reconciled before the database lock.

LGC Group

PPD
Newmarket Road
Fordham
CB7 5WW
UK
Tel: PPD (Office)
Tel PPD (Direct)
PPD

LGC Group will provide the Plasma Cannabinoid data. The unblinded data will be received once the database is locked (i.e. when the access to database is revoked or set to read-only for all users). This data should only be sent to GW upon confirmation from GW statistician that the trial has been unblinded.

Covance

PPD
Covance Laboratories Limited
Otley Road,
Harrogate,
North Yorkshire,
HG3 1PY,
UK
Tel: PPD
PPD

Covance will provide the Plasma AED and THC data. The unblinded data will be received once the database is locked (i.e. when the access to database is revoked or set to read-only for all users). This data should only be sent to GW upon confirmation from GW statistician that the trial has been unblinded.

PAREXEL:

PPD
Castle Wharf,
4 Canal Street,
Nottingham,
NG1 7EH
Tel: PPD
PPD

Parexel will be providing the IWRS, and patient enrolment data. The unblinded data will be received once the database is locked (i.e. when the access to database is revoked or set to read-only for all users). This data should only be sent to GW upon confirmation that the trial has been unblinded.

Transfer specifications and transfer schedules will be created and authorised by Quanticate and the relevant external vendor prior to receipt of the first live data transfer being issued to Quanticate.

The external data sources will be responsible for the quality and completeness of their data. Cumulative transfers will be received.

Quanticate will be responsible for:

- Reconciliation of external header data (patient number/visit date and time where collected) against CRF data.
- Reconciliation of external demography data (date of birth/sex) against CRF data.
- Ensuring external data are present for every sample date/time indicated on the CRF.

Quanticate will not be responsible for:

- Checking that all protocol specified parameters are present.
- Amending database structure if not received in the format specified in the Transfer Specifications.

Discrepancies between the external data and the CRF data will be queried to the investigator. If the CRF data are incorrect, these will be updated. If the external data are incorrect the query resolution will be forwarded to the external data source vendor for resolution. The original DCF resolution will be retained by Quanticate.

No hardcopy printouts of any kind are expected for tracking. No investigator comments, flags or CS/NCS attributions on laboratory data are expected for data entry.

8.14 Medical Coding

Adverse Events, Medical History (MH) and Concomitant Medications will be coded using TMS v4.6 in OC.

Detailed coding conventions are provided in the GW SAE Reconciliation and Coding Plan.

The coding will be performed using the following dictionaries:

- WHODD version June 2014 for CM. ATC coding will be performed as part of the CM coding. Up to fourth level ATC coding will be provided as well as the ATC Code level breakdown.

- MedDRA version 18.1 for AE and MH. Coding will be performed using the 5 coding levels in MedDRA (Lowest Level Term [LLT], Preferred Term [PR], Higher Level Term [HLT], Higher Level Group Term [HLGT] and System Organ Class [SOC]).

If the dictionaries are updated to an updated version during the study lifetime, any differences found between previous and current versions of the dictionary shall require to be reviewed.

It is anticipated that the majority of terms will be coded automatically in TMS. Terms requiring manual coding will be handled as specified in GW SAE Reconciliation and Coding Plan.

All query resolutions requiring update will be updated in the OC database using a modified verbatim term field. The updated modified terms will then appear for coding in a later coding cycle. No changes to the verbatim term will be made on the OC database unless confirmed by the investigator. All queries raised in TMS are linked to OC and exported during the nightly scheduled batch validation sessions.

Coding will be performed on an on-going basis but at a minimum after 75% and 100% of the data has been double data entered.

Listings will be generated during the coding process for the LCDM to check for appropriate coding consistency. The following listings may be generated for each type of term coded:

- Listing by unique verbatim terms
- Listing by unique coded terms
- Listing by body system or drug classification

Quanticate will QC the manual coding for consistency and reasonability prior to forwarding to GW for medical review. Medical review of the coding will be the responsibility of GW. During medical review of the coding, changes may be requested. These will be updated within the coding application. The revised coding will then be available for re-review. The changes are recorded using a paper and electronic audit trail.

Medical review of the coding by a medical monitor and approval of the coding will be required from GW and designated medically qualified reviewer, prior to database lock.

8.15 Serious Adverse Event/ Reconciliation

Details of the process of the SAE reconciliation have been discussed with the GW Pharmacovigilance Department (PVD) and are recorded in the GW SAE Reconciliation and Coding Plan.

Any SAEs reported to GW PVD during the study will be reconciled with the CRF database according to the GW SAE Reconciliation and Coding Plan.

The SAE forms will be received by GW PVD and the data on these forms will be entered by GW PVD onto the SAE database. The SAE forms will not be entered into the Quanticate clinical database.

8.16 File Notes

File Notes are records of data handling issues which were not anticipated at the planning stage of the trial, and their solutions.

8.17 Investigator Comments

Any additional information such as free-standing notes on the CRF or comments in the query replies that cannot be entered into the data fields database will be documented in the Investigator Comments during the course of the project. These will be captured in the database but will not be reviewed by clinical data management and will only be used by the CDM department as a tool to reduce query numbers.

8.18 Quality Control

At the start of the processing phase of the project the LCDM or designee will select CRF pages on which to perform a 100% QC on entered data and the LCDM will inform the DECs of any consistent errors.

The end of project QC that will be performed on the database is described in detail in the QC Plan and will be approved by GW. This plan must be finalised prior to database lock.

The end of project QC process can begin when a patient's data are deemed clean (all data for that patient is entered, validation completed, database edits completed, no medical coding queries outstanding, and no SAE reconciliation queries outstanding).

The database QC is performed by competent members of CDM who have had little or no involvement in the project, where possible.

CDM Programmers are responsible for producing the list of randomly-selected patient numbers for the QC sample and for producing the QC listings.

Quanticate will assess discrepancies in terms of their possible cause in order to identify whether they are systematic, and therefore require a specific course of action. All findings will be documented on the 'Final Data Quality Control Form' (CDM-ATT-022) and all errors will be corrected on the database. Any corrections will be QC'd before database lock. Please refer to the QC Plan for a definition of an error.

The QC findings will be summarised in a 'Final Data Quality Control Report' (CDM-ATT-021) which will be sent to GW for approval. If for any reason it fails the QC process (with an error rate above the agreed rate specified in the QC Plan) GW will be notified and a plan of action will be proposed.

8.19 Database Lock

The following criteria must be met prior to database lock. (Please refer the 'Database Lock Checklist' [CDM-ATT-035] for a full list of procedures to be completed prior to database lock).

- All patient data has been double-data-entered and validated.
- All queries have been resolved or signed off.
- All electronic checks and SAS listings have been re-run against the data and no new queries were generated.
- All external electronic data has been imported with no new errors.
- All coding has been reviewed and approved by GW.
- All SAE reconciliation has been reviewed and approved by GW.
- All the Investigator signature pages (signed and dated by the Investigator) have been received for all patients.
- GW has authorised the database lock.

The final database QC will be performed to calculate the final error rate. Once the final database QC has been completed and the error rate is acceptable, the LCDM will request the lock of the database, upon which write-access will be removed from all CDM personnel. Written confirmation of database lock, including date and time of lock, will be sent to GW.

The locked raw data will be extracted and mapped, where necessary, to GW standards prior to transfer to GW.

8.20 Database Unlock

A database which was locked and released for analysis will usually only be unlocked if an error is identified which would:

- Significantly affect the statistical outcome of the analysis of key efficacy parameters.
- Change the safety profile of the study data.

If a request is received to unlock a clinical database or amend locked datasets, the Head of CDM and the GW CPM must document their authorisation to re-open the database/amend the data in clinical database using 'Database Unlock Authorisation Form' (CDM-ATT-037). The request and approval must include the reason and rationale for unlocking the database/amending the data in clinical database. The request and approval must be maintained in compliance with GEN-SOP-024 ('Study Master File').

The database will be unlocked by the Database Administrator (DBA) by changing the access profile on receipt of 'Database Unlock Authorisation Form' (CDM-ATT-037).

- Study folders will be unlocked by the Quanticate Information Systems (IS) department on receipt of the 'Database Unlock Authorisation Form' (CDM-ATT-037).
- Data corrections will be made in accordance with CDM-SOP-008 ('Editing Data'). A QC check will be performed to ensure that only approved changes to the data were actioned. This will be documented by the LCDM in compliance with GEN-SOP-024 ('Study Master File'). Changes that are made must be documented in an audit trail.

The database will be re-locked following completion of 'Database Lock Authorisation Form' (CDM-ATT-036)

8.21 Export

Exports of data will occur at the following time points:

- Test transfer following initial data entry into production database. In the event of any errors, further test transfers may be required.
- 5 transfers of the exported data from the clinical database will be provided to GW. Each transfer will be sent only following a documented request from GW.
- Upon written request from GW, the final database, following database lock. The data extracts include data extracted from the clinical database and any external data.

Data extracts include data extracted from the clinical database and any external data.

All exported datasets will be in PC SAS v9.1 in the Quanticate format as per the aCRF/DSD. The datasets will be made available to GW via Quanticate's online portal (QuantiCliQ). The CRFs and SMF will be sent to GW within 3 months of the completion of the final Clinical Study Report (CSR) and once all CDM invoices have been settled.

8.22 Screen Failures

The following pages will be collected and databased for screen failure patients: Page 1, Screen failure page (SF), AE page (if any occurred) and the Investigator signature page. These pages will be tracked and stored with the completed CRF's in the designated

project storage area. Limited checks will be performed for screen failure patients are defined in the DVP.

8.23 Control of the DMP

Each new version of the DMP will be reviewed by a suitably qualified member of CDM and authorised before it is issued to the individuals defined in the distribution list (section 5). A copy of the updated authorised document will be stored in the SMF in addition to the original copy.

9 Appendix 1

9.1 SOPs to be Followed

9.1.1 Quanticate SOPs:

Number	Title	Version
CDM-SOP-001	Database Design	5.0
CDM-SOP-002	Data Management Plan	4.0
CDM-SOP-003	Data Entry	5.0
CDM-SOP-004	Case Report Form Design	4.0
CDM-SOP-005	Medical Coding	4.0
CDM-SOP-006	Data Validation	5.0
CDM-SOP-007	Discrepancy Management	5.0
CDM-SOP-008	Editing Data	4.0
CDM-SOP-010	Final Data Quality Control	4.0
CDM-SOP-011	CRF Logging and Tracking	6.0
CDM-SOP-012	Database Lock and Unlock	6.0
CDM-SOP-013	Serious Adverse Event Reconciliation	4.0
CDM-SOP-014	Laboratory Data Handling	3.0
CDM-SOP-017	Database Administration	5.0
GEN-SOP-004	Document Management and Version Control	5.0
GEN-SOP-013	Data Transfer	2.0
GEN-SOP-015	Good Document Practice	2.0
GEN-SOP-017	Company Communication	3.0
GEN-SOP-018	Escalation and Documentation of Project Issues	1.0
GEN-SOP-019	Records Retention and Return to Customer	3.0
GEN-SOP-022	Final Inspection of Quality Control Documentation Prior to Release of Product to the Customer	4.0
GEN-SOP-024	Study Master File	1.0

The current version of these SOPs will be adhered to throughout the duration of the project. An SOP deviation will be created to explain why updated versions of SOPs are not being adhered to (if applicable).

Updated versions of these SOPs (if applicable) will be adhered to and the customer will be informed of changes between previous and updated SOPs. New versions of SOPs will be inserted in to the SOP table above.

GWEP1428

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE POSSIBLE DRUG-DRUG INTERACTIONS BETWEEN CLOBAZAM AND CANNABIDIOL (GWP42003-P)

FINAL DATA QUALITY CONTROL PLAN

Author: PPD
Job Title: PPD

1 Approval Form

QUANTICATE AUTHOR
Name: PPD
Position: PPD

PPD

Signature

23-Sep-2016
Date

QUANTICATE REVIEW
Name: PPD
Position: PPD

PPD

Signature

26-Sep-2016
Date

QUANTICATE REVIEW
Name: PPD
Position: PPD

PPD

Signature

23-Sep-2016
Date

GW RESEARCH LTD APPROVAL
Name: PPD
Position: PPD

PPD

Signature

23-SEP-2016
Date

2 Table of Contents

3 Version Controlled Document Log

Effective Date	Version	Change
29 Aug 2016	1.0	First Issued.
13 Sep 2016	2.0	Datasets GNIC, EX, EXADEX, EXAD were added to Critical QC Datasets SMUBQS, SMUB, SF, DIDI, CHK, DASCDASC, DASC, DASP, AESP were added to Random QC.
23 Sep 2016	3.0	From Page 11 'Was the dose of IMP adjusted by the Investigator?" was removed as not applicable for this study Added CONCOMITANT ANTIEPILEPTIC MEDICATIONS (Page AED._) Added additional datasets names to Random Selection QC

4 Glossary of Terms

CRF	Case Report Form
DCF	Data Clarification Form
DCM	Data Collection Module
QC	Quality Control

5 Final Data Quality Control

The following Quality Control will be performed on the data in the database in accordance with CDM-SOP-010 ('Final Data Quality Control') and prior to database lock being declared.

5.1 Critical Item QC

100% of the data indicated below as being critical items, including query updates and any other relevant documentation, will be checked against the data in the database. All findings will be documented on the 'Final Data Quality Control Form' (CDM-ATT-022) and corrected. All updates will be checked by an appropriately qualified member of Quanticate Clinical Data Management independent of the person who performed the update.

Section	DCM	OC SAS Name	GW SAS Name
INFORMED CONSENT (Page B1)			
Date of informed consent	SV[1]	INFORDN	INFORMDN
GENETIC TESTING INFORMED CONSENT (Page B1)			
Was informed consent for genetic testing obtained?	GNIC	ICGYN	ICGYN
Date of informed consent for genetic testing	GNIC	ICGDT	ICGDT
DEMOGRAPHICS (Page B1)			
Date of birth	DM[1]	DOB	DOB
Sex	DM[1]	SEX	SEX
Race	DM[1]	RACE	RACE
Other, Specify:	DM[1]	RACETX	RACETX

GENETIC TESTING HISTORY(Page B6)

Has the patient had genetic testing performed in the past?	MHGN	MH_YN	MH_YN
Test name	MHGN	MHTERM	MHTERM
Was a mutation found?	MHGN	MUTNYN	MUTNYN
If yes, list the specific mutation(s)	MHGN	MUTNSPC	MUTNSPC
Did either parent have the mutation?	MHGN	PRMUTN	PRMUTN
Were they mosaic for the mutation?	MHGN	MSCMUTN	MSCMUTN
Additional genetic testing history page	MHGN	MHADD	MHADD
If tested off-site, has the report from the genetic testing center been received and filed?	MHGN	GENTYN	GENTYN
Was a genome wide SNP array performed?	MHGN	SNPYN	SNPYN
If yes, please record any abnormal results below	MHGN	SNPSPC	SNPSPC
Was an epilepsy gene panel performed?	MHGN	EPLSYN	EPLSYN
If yes, please record any abnormal results below	MHGN	EPLSSPC	EPLSSPC
Was a whole exome sequencing performed?	MHGN	EXOMYN	EXOMYN
If yes, please record any abnormal results below	MHGN	EXOMSPC	EXOMSPC

PHYSICAL EXAMINATION (Pages B18, B26, B31, B36, B44, B50, O2, O8, O14, O20, O26, O32, O38, O45)

Were any of the results of Physical examination indicative of a medical condition?	PE	PEMC	PEMC
Height	PE	HEIGHT	HEIGHT
Weight	PE	WEIGHT	WEIGHT

INCLUSION CRITERIA (Page 14)

Inclusion Criteria	INC	INC # 1-13	INC 1-13

EXCLUSION CRITERIA (Page 15,16)

Exclusion Criteria	EXC	EXC # 1-23	EXC 1-23

VITAL SIGNS (Pages B10,B18, B26, B31, B36, B44, B50, O2, O8, O14, O20, O26, O32, O38, O45,)

Pulse rate	VS	PULSE	PULSE
Respiratory rate	VS	RESP	RESP
Temperature	VS	TEMP	TEMP

BLOOD PRESSURE (Pages B10,B18, B26, B31, B36, B44, B50, O2, O8, O14, O20, O26, O32, O38, O45)

Arm used	VS	VSARM	VSARM
Sitting Blood Pressure	VS	VSSISYS	VSSISYS
Sitting Blood Pressure	VS	VSSIDIA	VSSIDIA
Supine Blood Pressure	VS	VSSPSYS	VSSPSYS
Supine Blood Pressure	VS	VSSPDIA	VSSPDIA
Standing Blood Pressure	VS	VSSTSYS	VSSTSYS
Standing Blood Pressure	VS	VSSTDIA	VSSTDIA
Are any of the vital signs or blood pressure results indicative of a medical condition?	VS	VSMC	VSMC

12-LEAD ELECTROCARDIOGRAM (Pages B11, B19, B32, B37, B51, O3, O9, O15, O21, O27, O33, O39, O46)

Date of 12- Lead ECG	ECG	ECGDN	ECGDN
Rhythm	ECG	EGABN	EGABN
Comments	ECG	ABNCOM	ABNCOM
Ventricular Rate	ECG	EGVR	EGVR
PR Interval	ECG	EGPR	EGPR
QRS duration	ECG	EGQRS	EGQRS
QT Interval	ECG	EGQT	EGQT
QTcB	ECG	EGQTCB	EGQTCB
ST or T-wave changes	ECG	EGST	EGST
Comments	ECG	ECGCOM	ECGCOM
Abnormality	ECG	EGCND	EGCND
Infarct pattern / R-wave progression	ECG	EGINF	EGINF
Are any of the results indicative of a medical condition?	ECG	ECGMC	ECGMC

STUDY MEDICATION (Pages B29, B40, B46)

Date of administration	EX	EXDT	EXDT
Time of administration (morning dose)	EX	EXAMTM	EXAMTM
Time of administration (evening dose)	EX	EXPMTM	EXPMTM
Time of First dose of Study Medication	EX	EXTM	EXTM

CLINICAL LABORATORY BLOOD AND URINE SAMPLING (Pages B12, B20, B33, B38, B52, O4, O10, O16, O22, O28, O34, O40, O47)

Have blood samples been taken?	LB	LBBLOOD	LBBLOOD
If no, reason	LB	BLDSPC	BLDSPC
Has a urine sample for urinalysis been taken?	LB	LBURINE	LBURINE
If no, reason	LB	URNSPC	URNSPC
Are any of the urinalysis or blood results indicative of a medical condition?	LB	LBRESMC	LBRESMC
Are any of the urinalysis or blood results indicative of an Adverse Event?	LB	LBRESMC	LBRESMC
Was a urine sample collected for THC?	LB	LBTHC	LBTHC
Is a repeat blood sample required?	LB	LBREPYN	LBREPYN
Date repeat blood sample taken	LB	LBREPDN	LBREPDN
Is a repeat urine sample required?	LB	REPURYN	REPURYN
Date repeat urine sample taken	LB	REPURDN	REPURDN
Is the patient of child bearing potential?	LB	LBPOTYN	LBPOTYN
Was a urinalysis sample sent for further analysis to central lab?	LB	LBURCL	LBURCL
Results of serum pregnancy test (for patient of child bearing potential)	LB	PRGRES	PRGRES
Was a blood sample collected for serum alcohol testing?	LB	LBALCYN	LBALCYN
Result of serum alcohol test	LB	ALCRES	ALCRES
Was a blood sample collected for genetic testing?	LB	LBGENYN	LBGENYN

COMPLETION OF QUESTIONNAIRES (COLUMBIA –SUICIDE SEVERITY RATING SCALE (C-SSRS) (Page B13, B21, B34, B39, B53, 05, O11, O17,O23, O29, O35, O41, O48)

Has the C-SSRS been completed?	QSYN	CSSR_YN	CSSR_YN

STUDY MEDICATION DOSE ADJUSTMENT LOG (Page DAL)

Study medication dose adjustments made during the study?	EXAD	EXYN	EXYN
Date of adjustment	EXADEX	EXADDT	EXADDT
Dose adjusted to	EXADEX	EXDOSE	EXDOSE
Dose units	EXADEX	EXDOSU	EXDOSU
Reason for dose adjustment	EXADEX	EXADJ	EXADJ
Reason for dose adjustment: Other specify	EXADEX	EXSPC	EXSPC
AE number	EXADEX	AENUM	AENUM
Additional study medication dose adjustment page	EXAD	EXADD	EXADD

PHARMACOKINETIC BLOOD SAMPLING (Page B23,B27,B41,B45,)

Time-point	LBPK	LBTPT	LBTPT
Collection date	LBPK	LBDT	LBDT

Collection time	LBPK	LBDM	LBDM
Not done	LBPK	LBND	LBND
Comments	LBPK	LBCOM	LBCOM

STUDY MEDICATION (Pages B29, B40, B46, B54, O6, O12, O18, O24, O30, O36, O42, O49)

Was medication dispensed?	DA	MEDDIS	MEDDIS
Number packs (bottles) dispensed at this visit	DA	DADISP	DADISP
Was the first dose of study medication administered on site?	DA	FSTDOS	FSTDOS
If no, specify	DA	FSTSPC	FSTSPC
Time of first dose of study medication	DA	DOSETM	DOSETM
Was IMP returned?	DA	DARETURN	DARETUN
Was IMP returned? (Blinded medication)	DA	BLDRYN	BLDRYN
If yes, how many packs/bottles (used and unused) were returned?	DA	BLDRET	BLDRET
Was IMP returned? (OLE medication)	DA	OLERYN	OLERYN
If yes, how many packs/bottles (used and unused) were returned?	DA	OLERET	OLERET
Does the actual IMP usage reflects the expected amount used as per dosing schedule??	DA	DAUSED	DAUSED
If no please record	DA	DACOM	DACOM
Were there some signals of potential abuse since last visit?	DA	DASPAB	DASPAB

Were the two doses of study medication administered on site?	DA	DAADM	DAADM
If no, specify	DA	FSTSPC	FSTSPC
Was medication dispensed?	DA	MEDDIS	MEDDIS
Number of packs (bottles)dispensed at this visit	DA	DADISP	DADISP

IMP COMPLIANCE REVIEW (Pages B30, 35, 49, O1, O7, O13, O19, O25, O31, O37, O44)

Did the patient comply with the dosing schedule?	IMP	DACOMP	DACOMP

CONCOMITANT RESCUE MEDICATIONS (Page RM._)

Has the patient taken any rescue medication in the 14 days prior to screening Visit or during the course of the study?	CM	CM_YN	CM_YN
Generic name	CM	CMTRT	CMTRT
Brand name	CM	CMBRDNM	CMBRDNM
Dose	CM	CMDSTXT	CMDSTXT
Units	CM	CMDOSU	CMDOSU
Route	CM	CMROUTE	CMROUTE
Frequency	CM	CMDOSFR	CMDOSFR
Start date	CM	CMSTDT	CMSTDT
Stop date	CM	CMENDT	CMENDT
Continuing at the end of the study?	CM	CMONGO	CMONGO
Reason	CM	CMREAS	CMREAS
Additional other concomitant medication page	CM	CMADD	CMADD

OTHER CONCOMITANT MEDICATIONS (MED._)

Has the patient taken any other concomitant medications in the 14 days prior to the screening visit or during the course of the study?	CM	CM_YN	CM_YN
Medication name(Generic name)	CM	CMTRT	CMTRT
Indication	CM	CMINDC	CMINDC
Dose	CM	CMDSTXT	CMDSTXT
Units	CM	CMDOSU	CMDOSU
Route	CM	CMROUTE	CMROUTE
Frequency	CM	CMDOSFR	CMDOSFR
Start date	CM	CMSTDT	CMSTDT
Stop date	CM	CMENDT	CMENDT
Continuing at the end of the study?	CM	CMONGO	CMONGO
Additional other concomitant medication page	CM	CMADD	CMADD

CONCOMITANT ANTIEPILEPTIC MEDICATIONS (Page AED._)

Has the patient taken any concomitant antiepileptic medications (excluding rescue medications) in the 14?	CM	CM_YN	CM_YN
Generic name	CM	CMTRT	CMTRT
Brand name	CM	CMBRDNM	CMBRDNM
Dose	CM	CMDSTX	CMDSTX
Units	CM	CMDOSU	CMDOSU

Route	CM	CMROUT	CMROUT
Frequency	CM	CMDOSFR	CMDOSFR
Start date	CM	CMSTDT	CMSTDT
Stop date	CM	CMENDT	CMENDT
Reason	CM	CMREAS	CMREAS
AE number	CM	AENUM	AENUM
Specify Comment	CM	CMSPC	CMSPC
Continuing at the end of study	CM	CMONGO	CMONGO
Additional other concomitant medication page	CM	CMADD	CMADD

CONCOMITANT ANTI EPILEPTIC THERAPIES (Page AET._)

Has the patient used a ketogenic diet in the 4 weeks prior to Visit 1 or during the course of the study?	CM	CM_YN	CM_YN
If yes, start date:	CM	CMSTDT	CMSTDT
If yes, stop date:	CM	CMENDT	CMENDT
Ongoing	CM	CMONGO	CMONGO
Has the patient used VNS in the 4 weeks prior to Visit 1 or during the course of the study?	CM	CM_YN	CM_YN
If yes, start date:	CM	CMSTDT	CMSTDT
If yes, stop date:	CM	CMENDT	CMENDT
Ongoing	CM	CMONGO	CMONGO
Additional other concomitant medication page	CM	CMADD	CMADD

ADVERSE EVENTS (Page AE.1 and AE._)

Adverse Event	AE	AETERM	AETERM
Start date	AE	AESTDT	AESTDT
Stop date	AE	AEENDT	AEENDT
Duration	AE	AEDURTM	AEDURTM
Outcome	AE	AEOUT	AEOUT
Severity	AE	AESEV	AESEV
Plausible relationship to Study Medication	AE	AEREL	AEREL
Action taken with Study Medication	AE	AEACN	AEACN
Serious Adverse Event	AE	AESER	AESER
Additional Adverse Event page	AE	AEADD	AEADD

END OF BLINDED PHASE STUDY OUTCOME (Page B48)

Date of blinded phase completion or withdrawal	DSTR	DSSTDT	DSSTDT
Did the patient complete the blinded phase as planned?	DSTR	TRTYN	TRTYN
Date of last dose	DSTR	DSLSTDT	DSLSTDT
Is the patient continuing to the open label extension?	DSTR	CONTOPN	CONTOPN
If no, state reason	DSTR	CONTSPC	CONTSPC
Is the patient continuing to taper period?	DSTR	CONTAP	CONTAP
If No, state reason	DSTR	TAPSPC	TAPSPC

Specify the treatment option the patient will receive	DSTR	TRTOPT	TRTOPT
If other, specify	DSTR	TRTSPC	TRTSPC
Primary Reason for Withdrawal	DSTR	DSTERM	DSTERM
Corresponding AE number(s)	DSTR	OCAEITX	OCAEITX
Patient and/or legal representative withdrew consent to participate, specify	DSTR	OCCOSTX	OCCOSTX
Patient met (protocol specified) withdrawal criteria, Specify criteria	DSTR	OCPROTX	OCPROTX
Patient was withdrawn from participation by the Investigator , Specify	DSTR	OCINVTX	OCINVTX
Specify	DSTR	DSSPEC	DSSPEC

STUDY OUTCOME – TREATMENT PHASE (Page O43)

Date of treatment phase completion or withdrawal	DSTR	DSSTDT	DSSTDT
Did the patient complete the treatment phase as planned?	DSTR	TRTYN	TRTYN
Date of last dose	DSTR	DSLSTDT	DSLSTDT
Is the patient continuing to taper period?	DSTR	CONTAP	CONTAP
If No, state reason	DSTR	TAPSPC	TAPSPC
Is the patient going to receive a Treatment option?	DSTR	TRTOPT	TRTOPT
If yes,	DSTR	TRTSPC	TRTSPC
Primary Reason for Withdrawal	DSTR	DSTERM	DSTERM
Corresponding AE number(s)	DSTR	OCAEITX	OCAEITX

Patient or parent/legal representative withdrew consent to participate Specify	DSTR	OCCOSTX	OCCOSTX
Patient met (protocol specified) withdrawal criteria Specify criteria	DSTR	OCPROTX	OCPROTX
Other, Specify	DSTR	DSSPEC	DSSPC

END OF TAPER STUDY OUTCOME (Page B57, O52)

Date of last taper dose	DSTP	DSLSTDT	DSLSTDT
Was the taper period completed?	DSTP	TAPYN	TAPPYN
Specify the treatment option the patient will receive	DSTP	TRTOPT	TRTOPT
Other, specify	DSTP	TRTSPC	TRTSPC
Primary Reason for not completing the taper period	DSTP	DSTERM	DSTERM
Adverse event number(s)	DSTP	OCAEITX	OCAEITX
Patient withdrew consent to participate Specify	DSTP	OCCOSTX	OCCOSTX
Patient met (protocol specified) withdrawal criteria Specify criteria	DSTP	OCPROTX	OCPROTX
Patient was withdrawn from participation by the Investigator Specify	DSTP	OCINVTX	OCINVTX
Other, Specify	DSTR	DSSPEC	DSSPC

5.2 Random Selection QC

A random selection of the subjects in the project database will have the non-critical CRF data (and related documents such as Data Clarification Forms, Self Evident Corrections, Data Entry Guidelines) checked against the database. Data received as electronic copies from third-party providers/vendors will not be QC'd.

Non Critical CRF datasets:

Datasets	Description
MHEE	Electroencephalography (EEG) History
MHNR	Neuroimaging History
CMAE & CMAECM	History of Anti-Epileptic Medications (AEDs) And Therapies
MHSZ(1) & MHSZMH	History of Seizures no longer occurring
MHSZ(2) & MHSZMH	History of Current Seizures
MH &MHMH	Non-Epilepsy Medical History
CANN	Previous Use Of Cannabis
DIYN	Patient Diary
CSSR	Columbia-Suicide Severity Rating Scale (C-SSRS)
SV	Visit dates
INV	Investigator signature and date
FUP & FUPFUP	Telephone Follow-up, Safety Telephone Follow-up
CO & COCO	General Comments
DIDI	Epilepsy Daily Diary Record
CHK	Has the patient had a change in any medication or therapies/AE since the previous visit?
SF	Screen Failure
SMUB & SMUBQS	Study Medication Use & Behaviour Survey
DASP	Supplemental Drug Accountability Form
AESP	Supplemental Adverse Event Form
DASC & DASCDASC	Site Classification Form

The number of subjects selected is determined by the total number of subjects in the project:

- For 100 subjects or less: 10% of the number of subjects (n) in the project, with a minimum of 3 subjects.
- For over 100 subjects: square root of the number of subjects, plus one. i.e. (√n)+1.

Subjects will be selected using the RANUNI random function within SAS. 20 subjects are planned for this project; therefore a planned 3 subjects will be selected randomly for the QC process. The subject numbers of the selected subjects will be recorded in the 'Final Data Quality Control Report' (CDM-ATT-021).

All findings will be documented on the 'Final Data Quality Control Form' (CDM-ATT-022) and corrected. All updates will be checked by an appropriately qualified member of Quanticate Clinical Data Management independent of the person who performed the update to assess if the finding is an error.

In order for the database to be released for analysis, an error rate of the Quanticate standard of less than or equal to 0.05% must be obtained calculated as:

$$\frac{\text{Total Number of Errors (N)}}{\text{Total Number of Data Points reviewed}} * 100$$

The number of errors will be totalled and expressed as a percentage of the total (non-critical) variables audited. This error rate will then be applied to the database as a whole.

If the Final Data QC fails, i.e. the error rate is greater than the Quanticate standard of less than or equal to 0.05% the customer will be informed and a further random sample of subject CRFs will be QC'd. The error rate is re-calculated and re-assessed on the new random sample.

5.3 Definition of an Error

An error is:

- Any discrepancy between the CRF data and the data in the database where there is no documentation (e.g. DCF, Data Entry Guidelines, SEC) to support the discrepancy, except, spelling and/or punctuation mistakes which do not affect the meaning of the text.
- Incorrect updating of a DCF or incorrect implementation of a global ruling or incorrect application of a Self Evident Correction.