STATISTICAL ANALYSIS PLAN

Protocol GWEP1447

EudraCT Number: 2015-002939-18

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHARMACOKINETIC TRIAL IN TWO PARALLEL GROUPS TO INVESTIGATE POSSIBLE DRUG-DRUG INTERACTIONS BETWEEN STIRIPENTOL OR VALPROATE AND GWP42003-P IN PATIENTS WITH EPILEPSY

|  |  |
| --- | --- |
| **Protocol Number: (Version Date)** | GWEP1447  Version 4 (26-Jul-2016)  Version 3 (25-Jul-2016) (Sweden only)  Version 5 (28-Jul-2016) (France only) |
| **Name of Test Drug:** | Cannabidiol (GWP42003-P) |
| **Phase:** | 2 |
| **Methodology:** | Double-Blind, Randomized, Placebo-Controlled |
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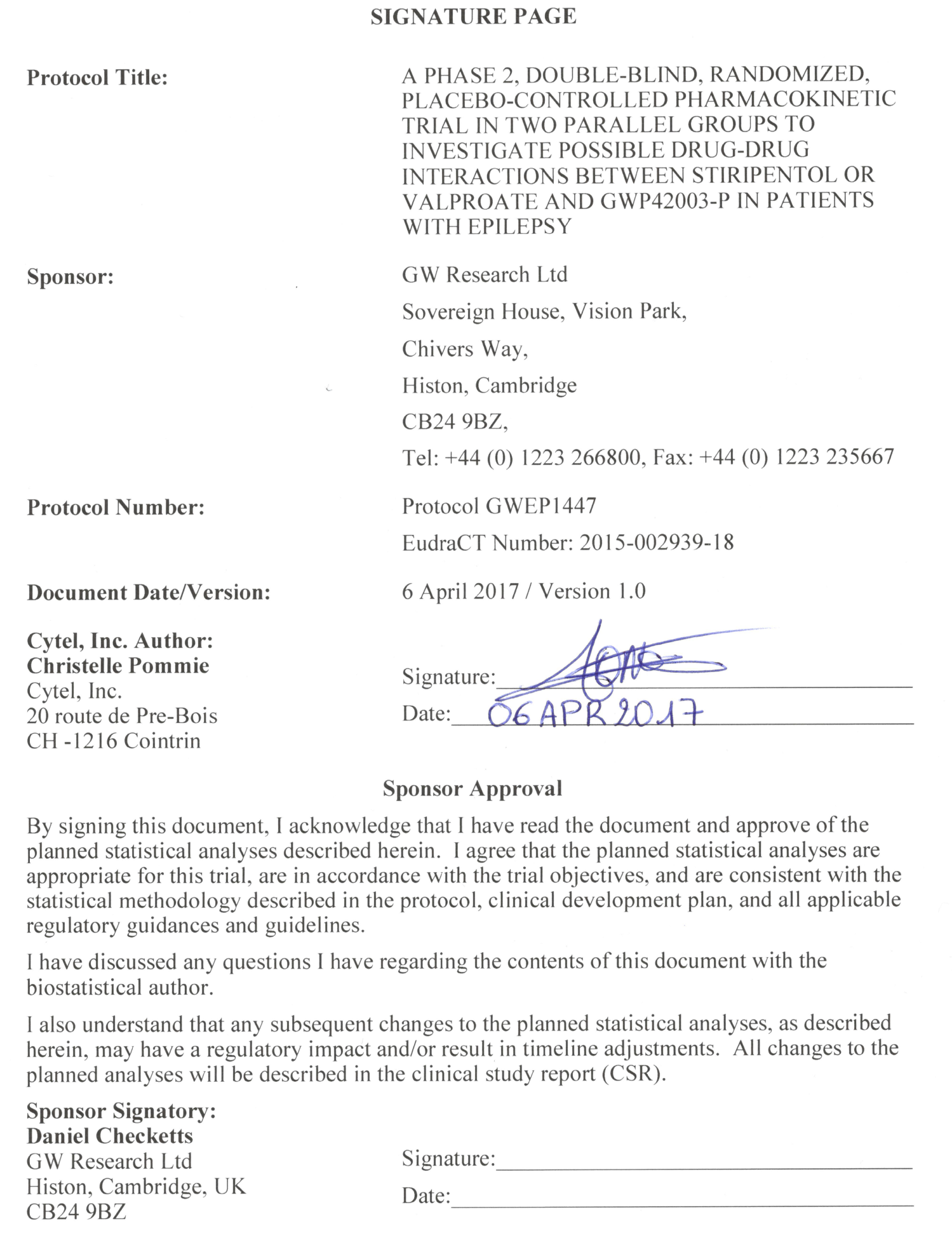


TABLE OF CONTENTS

| **Section Page** |
| --- |
| [1. INTRODUCTION AND OBJECTIVES OF ANALYSIS 8](#_Toc479252944)  [1.1. Introduction 8](#_Toc479252945)  [1.2. Objectives of Statistical Analysis 8](#_Toc479252946)  [Objectives of the trial 8](#_Toc479252947)  [Objectives of the statistical analysis plan 8](#_Toc479252948)  [2. TRIAL DESIGN 9](#_Toc479252949)  [2.1. Synopsis of Trial Design 9](#_Toc479252950)  [2.2. Randomization Methodology 10](#_Toc479252951)  [2.3. Stopping Rules and Unblinding 10](#_Toc479252952)  [2.4. Trial Procedures 10](#_Toc479252953)  [2.5. Efficacy, Pharmacokinetic and Safety Variables 14](#_Toc479252954)  [Primary Endpoint(s) 14](#_Toc479252955)  [Secondary Endpoint(s) 14](#_Toc479252956)  [3. PATIENT POPULATIONS 16](#_Toc479252957)  [3.1. Population Definitions 16](#_Toc479252958)  [Screened Population 16](#_Toc479252959)  [Safety Population 16](#_Toc479252960)  [Pharmacokinetic Population 16](#_Toc479252961)  [Open Label Extension Population 16](#_Toc479252962)  [3.2. Protocol Deviations/Violations 17](#_Toc479252963)  [4. STATISTICAL METHODS 18](#_Toc479252964)  [4.1. Sample Size Justification 18](#_Toc479252965)  [4.2. General Statistical Methods and Data Handling 18](#_Toc479252966)  [General Methods 18](#_Toc479252967)  [Computing Environment 18](#_Toc479252968)  [Methods of Pooling Data 18](#_Toc479252969)  [Adjustments for Covariates 18](#_Toc479252970)  [Multiple Comparisons/Multiplicity 18](#_Toc479252971)  [Withdrawals, Dropouts, Loss to Follow-up 18](#_Toc479252972)  [Missing, Unused, and Spurious Data 18](#_Toc479252973)  [Visit Windows 19](#_Toc479252974)  [Handling of Partially Missing Dates 19](#_Toc479252975)  [4.3. Interim Analyses 19](#_Toc479252976)  [4.4. Patient Disposition 20](#_Toc479252977)  [4.5. Demographic and Baseline Characteristics 21](#_Toc479252978)  [Demographics 21](#_Toc479252979)  [Medical History 21](#_Toc479252980)  [Prior Medications 22](#_Toc479252981)  [Other Baseline Characteristics 22](#_Toc479252982)  [4.6. Efficacy Evaluation 23](#_Toc479252983)  [4.7. Pharmacokinetic Evaluations 23](#_Toc479252984)  [Reporting of Pharmacokinetic Parameters 23](#_Toc479252985)  [4.8. Safety Analyses 25](#_Toc479252986)  [Treatment Compliance and Extent of Treatment Exposure 25](#_Toc479252987)  [Adverse Events 25](#_Toc479252988)  [Laboratory Data 27](#_Toc479252989)  [Vital Signs, Physical Examinations and Blood Pressure 28](#_Toc479252990)  [12-lead Electrocardiogram 29](#_Toc479252991)  [Concomitant Medications 29](#_Toc479252992)  [C-SSRS 29](#_Toc479252993)  [Abuse liability 30](#_Toc479252994)  [Patient Diary 30](#_Toc479252995)  [Seizure Frequency 30](#_Toc479252996)  [5. CHANGES TO PLANNED ANALYSES 31](#_Toc479252997)  [6. REFERENCES 32](#_Toc479252998)  [7. APPENDICES 33](#_Toc479252999)  [7.1. Statistical Tables to be Generated, CRF data 33](#_Toc479253000)  [7.2. Toxicity criteria for laboratory parameters 34](#_Toc479253001)  [7.3. Trial Design 36](#_Toc479253002) |

LIST OF IN-TEXT TABLES

| **Table Page** |
| --- |
| [Table 1 Schedule of Assessments 11](#_Toc479253003)  [Table 2 Pharmacokinetic parameters 14](#_Toc479253004)  [Table 3 Hematology, Biochemistry, Urinalysis and THC Screen 27](#_Toc479253005)  [Table 4 Toxicity Criteria for Biochemistry Parameters 34](#_Toc479253006)  [Table 5 Toxicity Criteria for Hematology Parameters 35](#_Toc479253007) |

ABBREVIATIONS

| **Abbreviation** | **Definition** |
| --- | --- |
| 4-ene-VPA | 2-propyl-4-pentenoic acid |
| AE | Adverse Event |
| AEDs | Antiepileptic Drugs |
| ATC | Anatomic Therapeutic Class |
| AUCtau | Area under the plasma concentration‑time curve over a dosing interval, where tau is the dosing interval |
| BMI | Body Mass Index |
| BUN | Urea |
| CBD | Cannabidiol |
| CI | Confidence Interval |
| CL | Total Clearance |
| CLB | Clobazam |
| Clast | Last measured plasma concentration |
| Cmax | Maximum measured plasma concentration |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| DB | Double-Blind |
| DDI | Drug-drug interaction |
| ECG | 12-Lead Electrocardiogram |
| EEG | Electroencephalography |
| GW | GW Research Ltd |
| GWP | GW Pharma Ltd |
| ICH | International Conference of Harmonisation |
| 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 |
| 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 | Δ9-tetrahydrocannabinol |
| Tlast | Time to last measured plasma concentration |
| Tmax | Time to maximum measured plasma concentration |
| TPM | Topiramate |
| VPA | Valproate |
| WHO | World Health Organization |

# INTRODUCTION AND OBJECTIVES OF ANALYSIS

## Introduction

GWP42003-P (cannabidiol [CBD]‑oral solution) 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. Stiripentol (STP) and valproate (VPA) are widely used antiepileptic drugs (AEDs), prescribed with other medication(s) to control seizures in adults and children. VPA is in a class of medications called fatty acyls. The mechanisms of VPA therapeutic actions are not well understood. It may act by increasing gamma-aminobutyric acid levels in the brain or by altering the properties of voltage‑dependent sodium channels. STP belongs to the aromatic allylic alcohols and is an adjunctive AED that is often given along with VPA and clobazam (CLB).

CBD can act as both a cytochrome P450 (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 STP and VPA may be altered (increased or decreased) by the chronic administration of GWP42003-P.

GWEP1447 is a phase 2, double-blind (DB), randomized, placebo-controlled trial to investigate possible drug-drug interactions (DDI) between STP or VPA and GWP42003-P in patients with epilepsy.

## Objectives of Statistical Analysis

### Objectives of the trial

Primary

To determine whether GWP42003-P affects the PK profile of STP or VPA.

Secondary

To assess the safety and tolerability of GWP42003-P in the presence of STP or VPA.

### Objectives of the statistical analysis plan

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of trial data in order to answer the trial 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 reports (CSR) for this trial.

This SAP covers the 2 analyses planned, at the end of the DB period and the end of the trial (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 trial protocol.

This SAP has been prepared in conjunction with the protocol version 4 (date: 26-July-2016), protocol version 3 (date: 25-Jul-2016) (Sweden only) and protocol version 5 (date: 28‑July‑2016) (France only).

# TRIAL DESIGN

## Synopsis of Trial Design

This phase 2, placebo-controlled trial consists of a 26-day, DB phase followed by an optional maximum 1 year open label extension (OLE). Patients will continue to take STP or VPA as advised by their physician for the duration of the trial. GWP42003-P/placebo will be taken twice daily immediately after the STP or VPA dose. STP and VPA are considered investigational medicinal products (IMPs) for the DB period of the trial only.

Patients will enter the trial and begin a 10-day GWP42003-P or placebo titration phase. During this period patients will be titrated up to a maintenance dose or equivalent maintenance dose of 20 mg/kg/day. Patients will continue to take this maintenance dose of GWP42003-P or placebo for 14 days (Days 12 to 25).

Upon completion of the treatment period (Day 27) 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 36 and they will receive a telephone follow-up visit 4 weeks after the end of GWP42003-P/placebo dosing (Day 64).

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

* Day 1/2 (Visit 2) before beginning of treatment (patients will be taking STP or VPA only).
* Day 26/27 (Visit 4) following 14 days of GWP42003-P or placebo maintenance (patients will be taking STP or VPA 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 STP or VPA. 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 STP, VPA, 2-propyl-4-pentenoic acid (4-ene-VPA), CLB, N-desmethylclobazam (N-CLB), Levetiracetam (LEV), Topiramate (TPM), CBD, CBD major metabolites, THC (Δ9-tetrahydrocannabinol) and THC major metabolites.

Upon entry into the OLE, following tapering from blinded GWP42003-P or placebo and titration to open label GWP42003-P, the dose of AEDs may be adjusted. GWP42003-P may be adjusted up to a maximum of 30 mg/kg/day (20 mg/kg/day in Sweden) or down. The OLE will last for a maximum of 1 year or until marketing authorization is granted; whichever is earlier.

Patients will be required to keep a paper diary to note dosing of IMP 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 trial.

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

## Randomization Methodology

During the DB phase of this trial, patients will be randomized in a 4:1 ratio to receive 20 mg/kg/day GWP42003-P or placebo.

A total of 40 patients will be enrolled into the trial (20 patients in the STP arm and 20 in the VPA arm).

## 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.

## Trial Procedures

The schedule of assessments, as outlined in the trial 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 26  (± 3 days) | **Visit 4**  Day 27 | **Visit 5\***  End of Taper | **Visit 6\***  4wk SFUa  (± 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 |
| 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 |  |  |  |
| 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 |  |
| 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 STP or VPA.

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

# Height only required at Visit 1.

a SFU = Safety follow-up

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Open Label Extension Schedule of Assessments** | | | | | | | | | |
| **Visit Number**  Day  (Visit Window) | **Visit 5**  2 Weeks  (± 3 days) | **Visit 6**  4 Weeks  (± 3 days) | **Visit 7**  8 Weeks  (± 3 days) | **Visit 8**  12 Weeks  (± 7 days) | **Visit 9**  24 Weeks  (± 7 days) | **Visit 10**  36 Weeks  (± 7 days) | **Visit 11**  48 Weeks  (± 7 days) | **Visit 12**  End of Taper  Visit 11 + 10 days | **Visit 13**  4wk SFU  (± 3 days) |
| 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 |  |

## Efficacy, Pharmacokinetic and Safety Variables

### Primary Endpoint(s)

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

* STP
* VPA
* 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** |
| Cmax | Maximum measured plasma concentration |
| tmax | Time to the maximum measured plasma concentration |
| CLss/F | Apparent total clearance at steady state |
| AUCtau | Area under the concentration time curve over the dosing interval |
| Vss/F | Volume of distribution at steady state |

### Secondary Endpoint(s)

To assess the safety and tolerability of GWP42003-P compared with placebo when taken in combination with STP or VPA. 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
* Physical examination
* Columbia-Suicide Severity Rating Scale (C-SSRS)
* Seizure frequency
* Abuse liability
* CYP2C19 and CYP3A4 patient genotype analysis

PK parameters (Table 2) of the following analytes:

* THC
* THC major metabolites
* 4-ene-VPA
* CLB
* N-CLB
* LEV
* TPM

# PATIENT POPULATIONS

## 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 trial (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 trial 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 trial. Within each arm (STP or VPA), analyses will be done using actual treatment received (placebo or GWP42003-P) and not randomized treatment.

### Pharmacokinetic Population

All patients enrolled in the trial who are treated and receive at least one dose of 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 26/27 (visit 4).

Furthermore, patients must have been taking a stable dose of STP/VPA for four weeks prior to screening and their STP/VPA regimen must remain stable throughout the duration of the blinded period of the trial. Any subject who deviates will be excluded.

Also, for PK reporting, this population is further split by STP/VPA regimen.

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 trial who took at least one dose of IMP from Visit 4 (Day 27) 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 OLE period. Listings will be produced according to the treatment received during the DB treatment period (placebo and GWP42003-P combined with STP or VPA).

The analysis sets to be used for analyses are described in the table below. All listings will be presented using the screened or the safety analysis population, except for the PK data which will be presented using the pharmacokinetic population.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 |  |  | ✓ | ✓ |
| Abuse liability |  |  | ✓ | ✓ |
| CYP2C19 and CYP3A4 patient genotype analysis |  |  | ✓ | ✓ |
| Seizure Frequency |  |  | ✓ | ✓ |

## 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.

# STATISTICAL METHODS

## Sample Size Justification

A total of 40 patients will be enrolled in this trial (20 patients in the STP arm and 20 in the VPA arm). There is no formal sample size calculation and analyses are descriptive only.

## General Statistical Methods and Data Handling

### General Methods

All outputs will be incorporated into Word files, sorted and labeled according to guideline number ST-001 (CSR Section 12 and Appendix 2), 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.

Listings will include all patients with flags for the populations and be sorted by actual treatment (normally randomized treatment), patient number, trial 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 17.1 or later. Medications will be coded using World Health Organization (WHO) Drug Dictionary Enhanced, 01 June 2015.

### Methods of Pooling Data

Not applicable to the present trial.

### 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 trial with a descriptive interpretation*.*

### Withdrawals, Dropouts, Loss to Follow-up

Patients who withdraw from the trial 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 CSR.

In tables and listings, missing data may be completed with NR (not recordable) or NC (not calculable) if applicable.

### 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 trial reporting, tapering period is considered as part of the safety follow-up.

**Treatment Groups**

All outputs (tables, listings and figures) will be produced for each cohort (VPA and STP) using the following three treatment groups:

* GWP42003-P
* Placebo
* Overall

## Interim Analyses

The first analysis will be conducted at the end of the DB phase of the trial. 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.

Each arm will be analyzed separately, so data will be locked on one of the arms if it completes substantially ahead of the other. Final analysis will occur at the end of the trial. Analysis may also be considered during the OLE phase, if long term data is required to support New Drug Application/Marketing Authorization Application submissions.

## Patient Disposition

The number of patients enrolled by country and site will be summarized for the screened population. Romanian site numbers are 1261 and 1289, Spanish site numbers are 1114, 1160 and 1238 and the Swedish site number is 1242.

Patient disposition will be summarized overall and by treatment groups, for the screened, the safety and the PK populations, 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 trial completion information, including the reason for premature trial withdrawal, if applicable, will be presented. Information on informed consent for the trial and genetic testing (which is optional) will also be included.

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

## Demographic and Baseline Characteristics

Demographic, prior medications, medical history and other baseline information will be summarized for the safety and the PK populations 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/m2) 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.

## Efficacy Evaluation

Not applicable

## 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 arm and treatment groups defined in section 4.2.

The plasma concentration/time curves of STP, VPA, 4-ene-VPA, CLB, N-CLB, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites will be assessed. Patients will be given their daily dose of STP or VPA 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 STP or VPA and GWP42003-P:

* First PK Assessment: STP or VPA only (*Visit 2: Days 1 and 2*)
* Second PK Assessment: STP or VPA and GWP42003-P/Placebo (*Visit 4: Days 26 and 27*)

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 STP or VPA.

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

### Reporting of Pharmacokinetic Parameters

#### Plasma Concentration

Plasma concentrations of STP, VPA, 4-ene-VPA, CBD, CBD major metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD), THC, THC major metabolites (11-OH-THC and 11-COOH-THC), CLB, CLB major metabolite (N-CLB), LEV and TPM will be displayed graphically, summarized and listed. Plasma concentrations will be summarized to 3 significant figures.

Plasma concentration will be summarized by visit, for STP, VPA, CBD, THC, CLB, LEV and TPM and their major metabolites. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point (predose to 12 hours postdose): n (number of non-missing observations), arithmetic mean, SD, median, Q1, Q3, minimum, maximum, geometric mean, geometric CV, where GCV%=SQRT(es²-1)\*100 and s is the standard deviation of the log-transformed values.

Geometric mean plasma concentration will be displayed graphically in linear and log scale. Nominal sampling times will be used in the table summaries and summary figures of plasma concentrations. On each AED plot, two timepoints will be plotted (Day 1 and Day 26) whereas for CBD, THC and metabolites plot, only Day 26 will be plotted. CBD and metabolites (THC and metabolites also) will be presented on the same plot only for GWP42003-P treatment. No line for Placebo will be plotted as all values will be LLOQ. So 4 lines will be plotted for CBD (CBD plus 3 metabolites) and 3 for THC (THC plus 2 metabolites).

Individual subject plasma concentration plots will be produced in linear and log scale. These patient profiles will be produced in 2 ways:

* Per trial day: so for each parameter, 2 plots will be produced (one for Visit 2 and one for Visit 4) with available individual subject plasma concentration
* Per subject: so for each parameter, a plot will be produced for each subject with available data, and on each we will have both timepoints (Visit 2 and Visit 4).

Actual sampling times will be used in the individual subject plasma concentration plots.

#### Handling of Values Below the LLOQ

For descriptive statistics, values below the lower limit of quantification of the assay (LLOQ) will be set to 0.

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.

All PK concentrations below the LLOQ will be excluded from plots on log scale.

#### PK parameters

All PK parameters will be listed by patient and summarized by treatment group and PK assessment period. The following descriptive statistics will be presented: n (number of non-missing observations), arithmetic mean, SD, median, Q1, Q3, minimum, maximum, geometric mean, geometric CV). PK parameters will be summarized to 3 significant figures, tmax to 2 decimal places and CV% to 1 decimal place.

#### 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 and geometric CV.

In order to assess whether the presence of CBD alters the PK profile of STP or VPA, a standard 90% confidence interval (CI) approach for the between time point ratios of geometric means of Cmax and AUC(0–tau) will be carried on logarithmic scale using a linear mixed effect model with treatment (STP or STP + CBD on a first model, VPA or VPA + CBD on a second model) as a fixed effect and subject as a random effect. 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\_arm;

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 STP and VPA, Cmax and AUCtau  will be dose normalized as Cmax divided by the dose (expressed in mg/kg) and AUC divided by the dose. Actual values will be also presented.

Plots of individual treatment ratios showing the patient on the x-axis and treatment ratio (Day 26 to Day 1, actual values) on y-axis with the 0.5 and 2.0 boundary lines; and a mean plot with the 90% confidence error bars will be produced on Cmax and AUCtau for STP, VPA and 4-ene-VPA.

## 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 trial 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 trial outcome) minus the date of first dose of trial medication (as reported in the trial 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: Trial Medication, IMP compliance review).

### Adverse Events

AEs will be coded using the MedDRA (Version 17.1 or later) 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 GWP42003‑P or placebo.

AE classification

AEs which occurred during the trial will be classified into three periods: pre-trial, 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-trial:** AE with onset prior to the first dose of the trial, 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-trial 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 trial separately on the safety population and the OLE population respectively.

For Pre-trial AEs, all AEs will be reported. For subsequent periods, the following summaries will be produced:

* All-causality AEs.
* Treatment related AEs.
* All-causality AEs by severity.
* All-causality serious AEs.
* Treatment related SAEs.
* AEs reported as leading to permanent cessation of trial treatment.
* AEs reported as leading to reduction of trial 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 trial including the ones in pre-trial 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 trial 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 |  |  |
| 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 mean value and mean change from baseline to each on trial 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 trial 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 trial 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 trial 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. Data related to meal time will be listed.

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 trial will be classified according to the start/end dates. Concomitant medications that were administered on or after the first trial dose date or that were administered before the first trial 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 trial dose date.
* **DB Treatment Period:** A concomitant medication with a start/end date on or after the date of the first trial dose date and with a start/end date before the start of OLE or with a start date before the date of the first trial 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.

### Abuse liability

The following listings will be provided:

* Study Medication Use and Behavior Survey
* Study Medication Dose Adjustment
* IMP Missed doses
* 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.

# CHANGES TO PLANNED ANALYSES

As of this date, there have been few changes between the protocol-defined statistical analyses and those presented in this statistical plan listed below:

* On the PK parameters: all the calculations will be based on the first dosing period (tau)

# REFERENCES

Not Applicable

# APPENDICES

## Statistical Tables to be Generated, CRF data

List of outputs and corresponding mock shells (tables, listings and figures) will be provided in a separate document.

## 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

## Trial Design

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

S

C

R

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G

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A

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D

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M

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E

N

D

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F

B

L

I

N

D

E

D

T

R

E

A

T

M

E

N

T

**Visit 1**

Day -14 to -7

**Visit 2**

Day 1/2

(+3 d)

**Visit 4**

Day 26/27

(±3 d)

E

N

D

O

F

T

A

P

E

R

10-day Taper

Patients **not**

entering the OLE period

Patients entering the OLE period

S

A

F

E

T

Y

F

O

L

L

O

W

-

U

P

10-day

Up-titration

14-day

Maintenance

**Visit 5**

Day 36

**Visit 6**

Day 64

28 day follow-up

(±3 d)

7-14 days

25 days

10 days

28 days

GWP42003-P Oral Solution

(20 mg/kg/day)

N=16

**or**

Placebo N=4

**Visit 3**

Day 12

(+3 d)

STP arm

N=20

GWP42003-P Oral Solution

(20 mg/kg/day)

N=16

**or**

Placebo N=4

VPA arm

N=20

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

Patients   
entering

from  
 the double  
blind period

**Visit 5 OLE**

2 weeks from Visit 4

(±3 d)

**Visit 7 OLE**

2 months from Visit 4

(±3 d)

**Visit 6 OLE**

1 month from Visit 4

(±3 d)

**Visit 8 OLE †**

3 months from Visit 4

(±7 d) †

**Visit 9 OLE †**

6 months from Visit 4

(±7 d) †

**Visit 11 OLE**

12 months from Visit 4

(±7 d) †

**Visit 10 OLE †**

9 months from Visit 4

(±7 d) †

**Visit 12 OLE**

E

N

D

O

F

T

A

P

E

R

**Visit 13 OLE**

28 day follow-up

(±3 d)

S

A

F

E

T

Y

F

O

L

L

O

W

-

U

P

**Open-Label Extension Period:**

GWP42003-P Oral Solution

Up to 30 mg/kg/day (20 mg/kg/day in Sweden)

10-day Taper

2 weeks from V4

2 weeks

1 month

1 month

3 months

3 months

3 months

10 days

28 days

† scheduling of extra dispensing visits/review of visit windows are required in order to comply with countries where controlled drugs can only be dispensed for a maximum of 28 days. Arrangements must be made with patients to come in every 4 weeks to be dispensed further IMP and used/unused IMP returned.