

**TITLE: A PHASE II, SINGLE-BLIND, PLACEBO-CONTROLLED STUDY
TO INVESTIGATE POSSIBLE DRUG-DRUG INTERACTIONS BETWEEN
CLOBAZAM AND CANNABIDIOL (GWP42003-P)**

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Investigator Agreement

I have read the attached protocol entitled "A phase II, single-blind, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)", dated 26 January 2015 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s) the FDA regulations relating to good clinical practice and clinical trials and the European Union (EU) Clinical Trials Directive (2001/20/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (ICH GCP) where the EU Directive does not apply and to complete a Form 1572 if required.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Centre No: _____

Print Name: _____

Date: _____

Principal Investigator

(DD Month YYYY)

Signature: _____

GW Authorization

Print Name:  _____

Date: 27 JAN 2015

Clinical Manager  _____

(DD Month YYYY)

Signature:  _____

1. PROTOCOL SYNOPSIS

Study Title	A phase 2, single-blind, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)
Clinical Study Type	Phase 2
Indication	Epilepsy
Primary Objective	To determine whether cannabidiol (CBD) affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyloclobazam (N-CLB).
Secondary Objective(s)	To assess the safety and tolerability of CBD in the presence of CLB.
Study Design	<p>This is a phase 2, single-blind, placebo-controlled study in 20 patients.</p> <ul style="list-style-type: none"> • All patients will be given placebo first followed by CBD during the course of the study. Patients will receive placebo in the first part of the single-blind phase (Days 2 to 26) and CBD during the second part of the single-blind phase (Day 27 onwards). • 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 CBD. 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 CBD over a 10 day period and will have a telephone follow-up visit four weeks after the end of taper day on Day 89. • Day 1 (Visit 2), patients will not be dosed with investigational medicinal product (IMP) but will continue to take CLB at a stable dose. • Day 2 (Visit 2), patients will begin the up-titration with placebo to an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • After up-titration with placebo, the patients will remain on the maintenance dose for 14 days (Days 12 to 25). • On Day 27 (Visit 3), patients will begin the up-titration with CBD to the maintenance dose of 20 mg/kg/day over a period of 10 days (Days 27 to 36). • After up-titration with CBD, the patients will remain on the maintenance dose for a further 14 days (Day 37 to 51). • On Day 52 (Visit 4), patients will be invited to receive CBD in the

	<p>OLE period. If the patient enters the OLE period of the study, the patient will continue to take CBD as advised by the investigator.</p> <ul style="list-style-type: none"> • If the patient does not enter the OLE period of the study, the patient will taper off of CBD by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with end of taper on Day 61 (Visit 5). <p>PK samples will be taken on the day of enrollment (Visit 2, Day 1), after completing 14 days treatment on placebo (Visit 3, Day 26) and prior to starting on CBD, and after the completing 14 days treatment on CBD (Visit 4, Day 451). The PK assessments will therefore capture the following combinations of CLB and IMP:</p> <ul style="list-style-type: none"> • First PK Assessment: CLB only. • Second PK Assessment: CLB and placebo. • Third PK Assessment: CLB and CBD. <p>Each PK assessment should be performed at time points in respect to a morning dose of CLB. The time points are as follows: Pre-dose, 15 min, 30 min, 1h, 1.5h, 2h, 4h, 6h, 12h and 24h. It is expected that the patient will continue to take their CLB as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The IMP should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD and CBD major metabolites.</p> <p>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 adverse events (AEs) that may occur whilst receiving IMP and any other medications. Patients will also be requested to record the number and type of seizures for each day whilst on the study.</p>
Primary Endpoint	<p>The primary endpoints of the study are the PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</p> <ul style="list-style-type: none"> • CLB • N-desmethyleclobazam (N-CLB) • CBD • CBD major metabolites
Secondary Endpoint(s)	<p>To assess the safety and tolerability of CBD compared with placebo when taken in combination with CLB. Safety and tolerability will be assessed using the following parameters:</p> <ul style="list-style-type: none"> • AEs • 12-lead Electrocardiogram (ECG) • Clinical laboratory parameters (clinical chemistry, hematology and urinalysis) • Vital signs • Columbia-Suicide Severity Rating Scale (C-SSRS) • Seizure Frequency

Sample Size	A total of 20 patients will be enrolled in this study. Recruitment for the study will be competitive between participating sites. There is no formal sample size: Calculation and analysis is descriptive only.
Summary of Participant Eligibility Criteria	<p>For inclusion in the study patients must fulfil ALL of the following criteria:</p> <ul style="list-style-type: none"> • Male or female patients aged 18 to 55 years inclusive. • Patient must have epilepsy as determined by the investigator and be taking CLB. • Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition. • Patient must have experienced at least one seizure of any type (i.e., tonic-clonic, tonic, clonic, atonic seizures) within the two months prior to randomization. • Patients must be taking CLB and no more than two other anti-epileptic drugs (AEDs) during the course of the study. • AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study. • Intervention with vagus nerve stimulation and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must be willing to maintain a stable regimen throughout the duration of the study. • Patients must abstain from alcohol during the single-blind phase of the study. • Patient and/or legal representative is available to attend all PK visits within the required visit window. • Patient and/or legal representative must be willing and able to give informed consent for participation in the study • Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements. • Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable. • Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study. <p>Exclusion: The patient may not enter the study if ANY of the following apply:</p> <ul style="list-style-type: none"> • Patient has clinically significant unstable medical conditions other than epilepsy.

	<ul style="list-style-type: none"> • Patients on CLB at doses above 20 mg per day. • Patients taking CLB intermittently as rescue medication. • Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes. • Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening. • Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy. • Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain for the duration of the study. • Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry. • Patient has any known or suspected history of any drug abuse or addiction. • Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration for the study. • Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil • Female patients must have a negative pregnancy test and be willing and able to use a reliable method of contraception throughout the trial and for three months after last dose. In the context of this trial, an effective method is defined as those which result in low failure rate (i.e., less than 1% per year) when used consistently and correctly such as: combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence. • Female patient who is pregnant, lactating or planning pregnancy during the course of the study and for three months thereafter. • Patients who have received an IMP within the 12 weeks prior to the screening visit. • Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study. • Following a physical examination, the patient has any abnormalities
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	<p>that, in the opinion of the investigator would prevent the participant from safe participation in the study.</p> <ul style="list-style-type: none"> • Patient has significantly impaired hepatic function, as determined at screening or enrollment (Alanine aminotransferase [ALT] $>5 \times$ upper limit of normal [ULN] or total bilirubin [TBL] $>2 \times$ ULN) OR the ALT or Aspartate aminotransferase (AST) $>3 \times$ ULN and (TBL $>2 \times$ ULN or international normalized ratio [INR] >1.5). <p><i>This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion must be withdrawn from the study.</i></p> <ul style="list-style-type: none"> • Unwilling to abstain from donation of blood during the study. • Travel outside the country of residence planned during the study. • Patients previously enrolled into this study.
Criteria for Withdrawal	<p>Patients must be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Administrative decision by the investigator or GW Research Ltd or Regulatory Authority. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient. • Withdrawal of patient consent. • Withdrawal of legal representative consent. • Lost to follow up. • ALT $>3 \times$ ULN or AST $>3 \times$ ULN and (TBL $>2 \times$ ULN or INR >1.5). • ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$). • ALT or AST $>8 \times$ ULN. • ALT or AST $>5 \times$ ULN for more than two weeks. <p>Patients may also be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Patient non-compliance. • AE, which in the investigator's opinion, would compromise the continued safe participation of the patient in the study. • Any evidence of drug abuse or diversion. • Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.
Investigational Medicinal Product:	GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry

<p>Dosage, Regimen, Formulation and Mode of Administration</p>	<p>flavoring).</p> <p>Placebo oral solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring.</p> <p>The IMP should be taken orally as per intended commercial therapeutic use.</p> <p>IMP will be taken twice daily (morning and evening) following the dose schedule below:</p> <ul style="list-style-type: none"> • Day 2 (Visit 2), patients will begin the up-titration with placebo to an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • After up-titration with placebo, the patients will remain on the maintenance dose for 14 days (Days 12 to 25). • On Day 27 (Visit 3), patients will begin the up-titration with CBD to the maintenance dose of 20 mg/kg/day over a period of 10 days (Days 27 to 36). • After up-titration with CBD, the patients will remain on the maintenance dose for a further 14 days (Day 37 to 50). <p>Please refer to Table 8.1-1 for details of the up-titration doses for CBD and placebo for each of the ten days.</p> <p>On Day 52 (Visit 4), patients will be invited to receive CBD in the open label extension (OLE) period. If the patient enters the OLE period of the study, the patient will continue to take CBD as advised by the investigator.</p>
<p>Control Group</p>	<p>All patients will receive placebo in the first part of the single-blind phase (Days 2 to 26) and CBD during the second part of the single-blind phase (Day 27 onwards). There is no separate control group.</p>
<p>Procedures</p>	<p>VISIT 1 - Screening (Day -7)</p> <p>The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG and vital signs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.</p> <p>Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will be assigned a unique patient number and then begin the seven day baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be instructed on how</p>

	<p>to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.</p> <p>VISIT 2 - Enrollment (Day 1) +3 days window</p> <p>This visit will occur 7 days after Visit 1.</p> <p>The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.</p> <p>Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic on Day 2 ahead of additional sample collection.</p> <p>VISIT 2 - Enrollment (Day 2)</p> <p>This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.</p> <p>IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1. Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.</p> <p>VISIT 3 - Day 26 ±3 days window</p> <p>This visit will occur 25 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP. The following observations will be made at Visit 3 (Day 26): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.</p> <p>Blood samples will be taken for analysis of plasma concentrations of</p>
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	<p>CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of IMP. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients are expected to remain in clinic throughout this PK sampling process.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 3 - Day 27</p> <p>This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 25 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 27: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.</p> <p>IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1. Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period.</p> <p>VISIT 4 - Day 51 \pm3 days window</p> <p>This visit will occur 50 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP. The following observations will be made at Visit 4 (Day 51): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of IMP. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients are expected to remain in clinic throughout this PK sampling.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 4 - Day 52</p> <p>This is the second part of the two day visit. The final PK sample will be</p>
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	<p>collected 24 hours after the Day 51 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 52: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.</p> <p>At the end of the blinded phase of the study on Day 52, providing the investigator and patient both agree, patients will be invited to continue taking IMP and to enter the OLE.</p> <p>Patients who enter the OLE will be dispensed CBD on Day 52. The dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day in the blinded phase to a maximum of 30 mg/kg/day in the OLE. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1.</p> <p>Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of IMP. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 60.</p> <p>Patients Not Entering OLE</p> <p>VISIT 5 – Day 61 (End of Taper) +3 days window</p> <p>This visit will occur 60 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.</p> <p>All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including height and body weight) and vital signs will be assessed and the C-SSRS will be administered.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.</p> <p>SAFETY FOLLOW-UP CALL - Day 89 ±3 days</p> <p>This visit is required for patients who do not enter the OLE study on Day 52, or who withdraw from the study early. This visit should occur four weeks (±3 days) after Visit 5, or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 89: concomitant medications (including AEDs) and AEs.</p> <p>Patients Entering OLE</p> <p>Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 52) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 52).</p>
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	<p>VISIT 5 (OLE) – Two Weeks ± 3 days</p> <p>This visit will occur two weeks after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 6 (OLE) – One Month ± 3 days</p> <p>This visit will occur one month after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 7 (OLE) – Two Months ± 3 days</p> <p>This visit will occur two months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 8 (OLE) - Three Months ± 7 days</p> <p>This visit will occur three months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p>
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	<p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 9 (OLE) - Six Months ± 7 days</p> <p>This visit will occur six months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 10 (OLE) - Nine Months ± 7 days</p> <p>This visit will occur nine months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 11 – Twelve Months (OLE End of Treatment) ± 7 days</p> <p>This visit will occur twelve months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>Starting at Visit 11, patients will begin to taper down their IMP dose.</p>
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	<p>The dose will be reduced by 10% of their OLE maintenance dose per day.</p> <p>VISIT 12 - OLE End of taper +3 days</p> <p>This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including height and body weight), ECG and vital signs will be assessed and the C-SSRS will be administered.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.</p> <p>SAFETY FOLLOW-UP CALL (OLE)</p> <p>This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.</p>
Statistical Considerations	<p>Plasma concentration data will be analyzed to estimate pharmacokinetic endpoints C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ of the following analytes CLB, N-CLB, CBD and major metabolites.</p> <p>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 group ratios of geometric means of C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will be done on logarithm scale using a linear mixed effect model with treatment (CBD or placebo) as fix 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.</p> <p>Descriptive summaries (means and standard deviations or counts [%] as appropriate) will be presented for all secondary endpoints (adverse events, laboratory data, vital signs, physical examination, C-SSRS and seizure frequency) for each phase of the study.</p>
Sponsor	<p>Sovereign House Vision Park Histon Cambridge CB24 9BZ United Kingdom</p>

Figure 1-1 Study Design and Treatment Schema

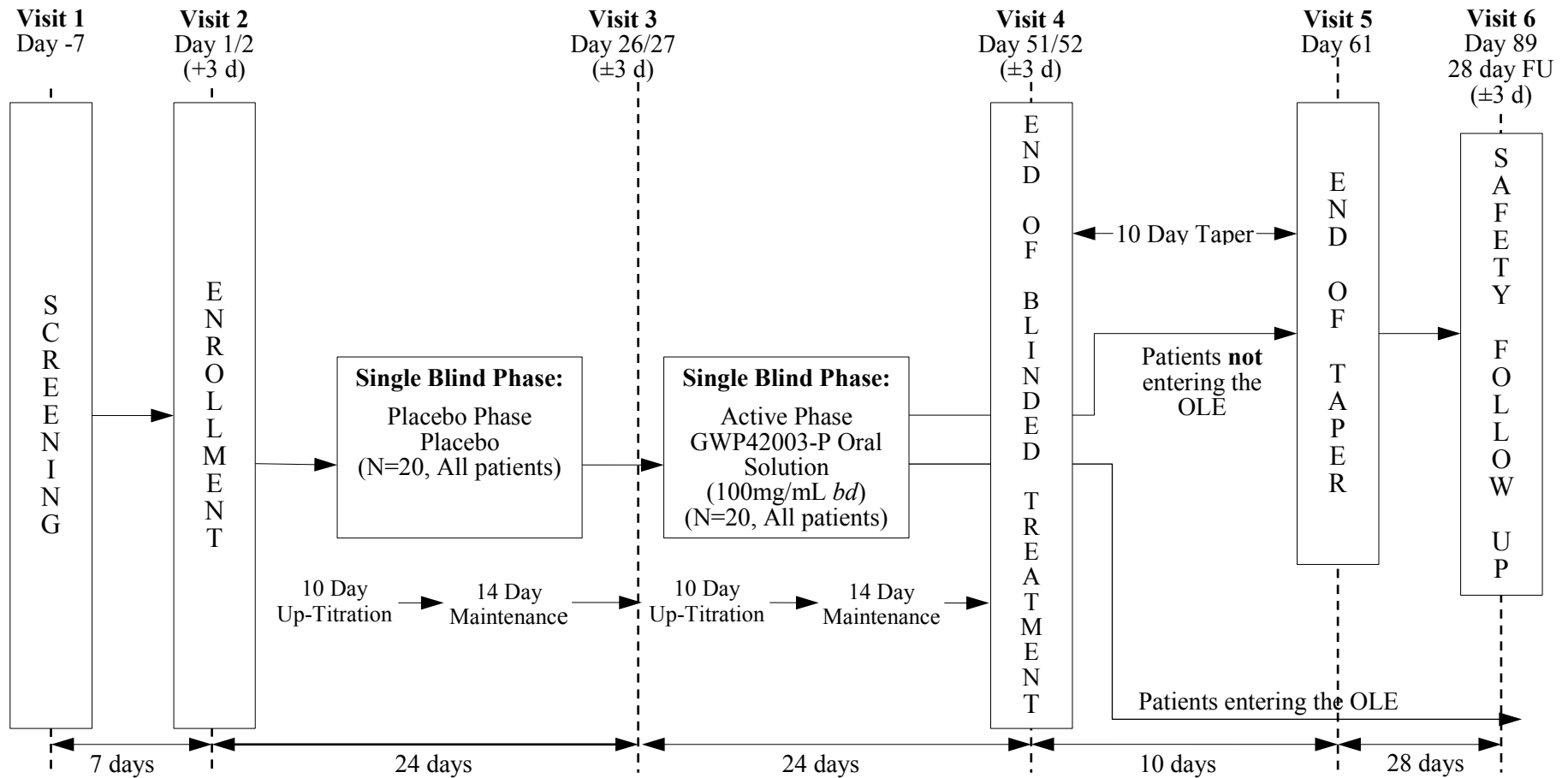


Figure 1-2 Study Design and Treatment Schema

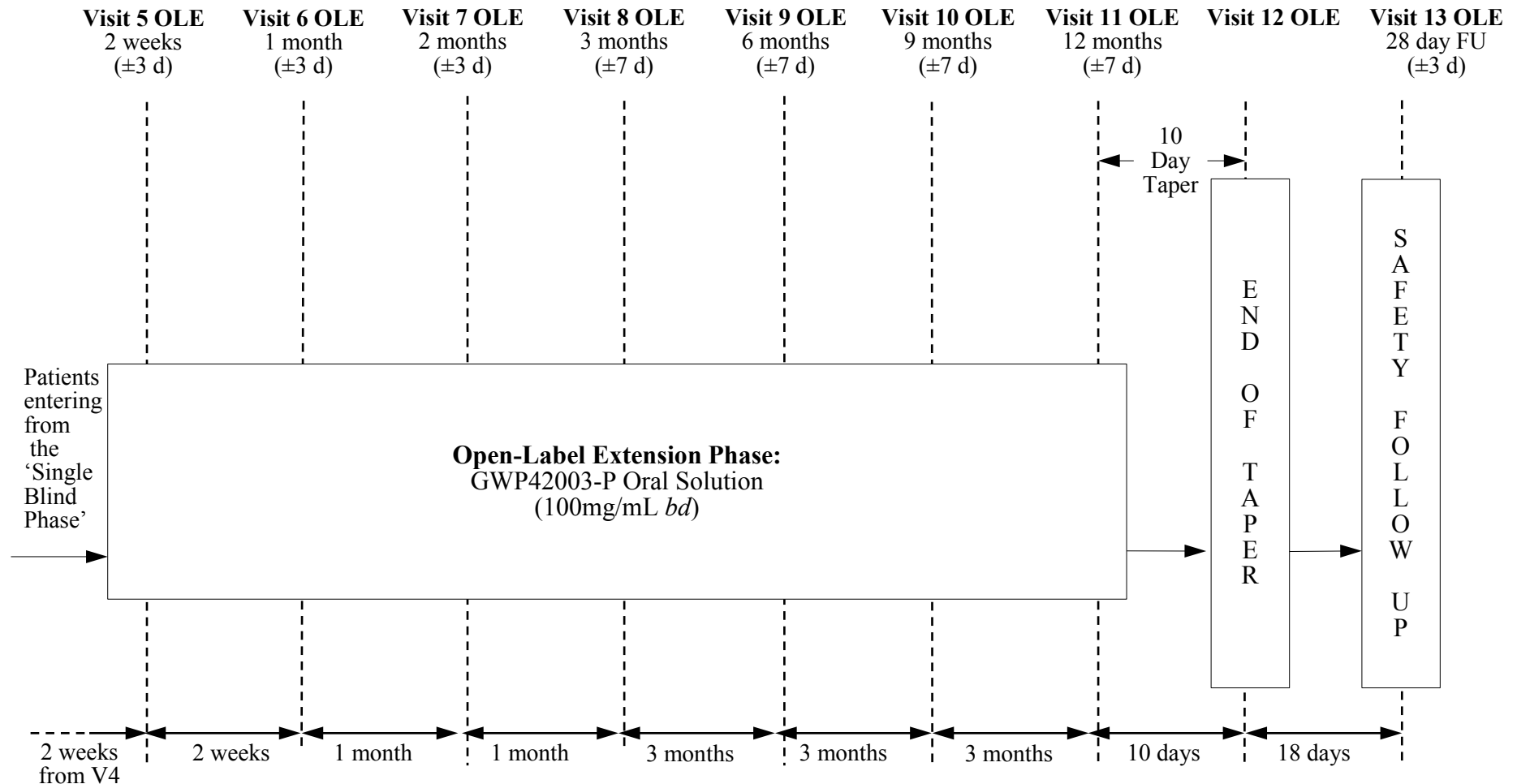


Table of Contents

Title Page	1
1. PROTOCOL SYNOPSIS.....	3
Table of Contents	17
Table of Appendices	22
List of In-text Tables	23
List of In-text Figures.....	24
List of Abbreviations	25
Definition of Terms.....	27
2. OBJECTIVES.....	28
2.1 Primary	28
2.2 Secondary	28
3. BACKGROUND AND RATIONALE	28
3.1 Disease.....	28
3.2 GWP42003-P Background.....	28
3.3 Rationale.....	29
3.3.1 Selection of Study Doses	30
3.4 Clinical Hypothesis	31
4. EXPERIMENTAL PLAN.....	31
4.1 Study Design	31
4.1.1 Primary Endpoint.....	33
4.1.2 Secondary Endpoint(s).....	33
4.2 Number of Centers	33
4.3 Number of Patients.....	33
5. INVESTIGATIONAL MEDICINAL PRODUCT	33
5.1 GWP42003-P Oral Solution.....	34
5.2 Placebo Oral Solution.....	34
5.3 Packaging, Storage and Drug Accountability	34
5.3.1 Packaging and Labelling.....	34
5.3.2 Storage	35
5.3.3 Supply and Return of Investigational Medicinal Product.....	35
5.3.4 Investigational Medicinal Product Accountability	35

6.	PARTICIPANT ELIGIBILITY	36
6.1	Inclusion Criteria	36
6.2	Exclusion Criteria	37
7.	PATIENT ENROLLMENT	39
7.1	Treatment Assignment	39
7.2	Randomization	39
8.	TREATMENT PROCEDURES	40
8.1	Investigational Medicinal Product Dosage, Administration and Schedule	40
8.1.1	Dose Administration	40
8.1.2	Dose Escalation and Dose Adjustments	40
8.2	Concomitant Therapy	41
8.3	Prohibited Therapy During Study Period	41
8.4	Compliance in Investigational Medicinal Product Administration	42
8.5	Access to Blinded Treatment Assignment	42
9.	STUDY PROCEDURES	43
9.1	Study Procedure Listing	43
9.1.1	Contraception	43
9.1.2	Informed Consent	43
9.1.3	Demographics	43
9.1.4	Medical History	44
9.1.5	Concomitant Medication	44
9.1.6	Physical Examination	44
9.1.7	Vital Signs	44
9.1.8	12-Lead Electrocardiogram	44
9.1.9	Clinical Laboratory Sampling	44
9.1.10	Pharmacokinetic Analyses	46
9.1.11	Columbia Suicide Severity Rating Scale	46
9.1.12	Patient Diary	47
9.1.13	Investigational Medicinal Product Accountability	47
9.1.14	Adverse Events	47
9.2	Study Procedures by Visit	48
9.2.1	Single Blind Phase	48

9.2.1.1	Visit 1 (Day -7, Screening)	48
9.2.1.2	Visit 2	49
9.2.1.2.1	Visit 2 (Day 1) – Enrollment (+3 days).....	49
9.2.1.2.2	Visit 2 (Day 2) - Enrollment.....	49
9.2.1.3	Visit 3	49
9.2.1.3.1	Visit 3 (Day 25) (± 3 days).....	49
9.2.1.3.2	Visit 3 (Day 26)	50
9.2.1.4	Visit 4	50
9.2.1.4.1	Visit 4 (Day 50) (± 3 days).....	50
9.2.1.4.2	Visit 4 (Day 50)	51
9.2.1.5	Visit 5 (Patients not entering OLE) (+3 days)	51
9.2.1.6	Safety Follow up Call (Day 87) (± 3 days)	52
9.2.2	Open Label Extension.....	52
9.2.2.1	Visit 5 (Open Label Extension) - Two Weeks (± 3 days).....	52
9.2.2.2	Visit 6 (Open Label Extension) - One Month (± 3 days).....	52
9.2.2.3	Visit 7 (Open Label Extension) - Two Months (± 3 days)	52
9.2.2.4	Visit 8 (Open Label Extension) - Three Months (± 7 days)	53
9.2.2.5	Visit 9 (Open Label Extension) - Six Months (± 7 days)	53
9.2.2.6	Visit 10 (Open Label Extension) - Nine Months (± 7 days)	53
9.2.2.7	Visit 11 (Open Label Extension End of Treatment) - Twelve Months (± 7 days)	54
9.2.2.8	Visit 12 (Open Label Extension End of Taper)	54
9.2.2.9	Safety Follow Up Call (± 3 days)	54
10.	WITHDRAWAL.....	54
11.	URGENT SAFETY MEASURES	56
12.	ADVERSE EVENT REPORTING.....	56
12.1	Definitions	56
12.1.1	Adverse Event.....	56
12.1.2	Investigator	56
12.2	Serious Adverse Events.....	56
12.3	Reporting Procedures for Serious Adverse Events	57
12.4	Pregnancy	58
12.5	Causality Assessment.....	58

12.6	Reporting Procedures for All Adverse Events	59
12.7	Follow up Procedures for Adverse Events	61
12.8	Reporting Clinically Significant Laboratory Results	61
12.9	Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees.....	62
13.	STATISTICAL CONSIDERATIONS.....	64
13.1	Sample Size, Power and Significance Levels	64
13.2	Interim Analysis	64
13.3	Analysis Sets	64
13.3.1	Safety Set.....	64
13.3.2	Pharmacokinetic Analysis Set	64
13.3.3	Protocol Deviations	64
13.4	General Considerations	64
13.5	Accountability and Background Characteristics	65
13.5.1	Enrolment and Disposition	65
13.5.2	Baseline and Demographic Characteristics	65
13.5.3	Medical History	65
13.5.4	Concomitant Medication	65
13.6	Endpoints and Statistical Methods	65
13.6.1	Primary Endpoint(s).....	65
13.6.2	Secondary Endpoint(s).....	65
13.6.3	Pharmacokinetics	65
13.6.4	Safety	67
13.6.4.1	Treatment Compliance and Extent of Treatment Exposure	67
13.6.4.2	Adverse Events.....	67
13.6.4.3	Clinical Laboratory Data.....	67
13.6.4.4	Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data	67
13.6.4.5	Seizure Data	68
14.	DATA SAFETY MONITORING COMMITTEE	68
15.	REGULATORY AND ETHICAL OBLIGATIONS.....	69
15.1	Declaration of Helsinki	69
15.2	Informed Consent	69
15.3	Institutional Review Board/Ethics Committee.....	69

15.4	Pre-Study Documentation Requirements	70
15.5	Participant Confidentiality	70
16.	ADMINISTRATIVE AND LEGAL OBLIGATIONS.....	72
16.1	Protocol Amendments and End of Study or Termination	72
16.2	Study Documentation and Storage	72
16.3	Study Monitoring and Data Collection	73
16.4	Quality Assurance	75
16.5	Compensation.....	75
16.6	Publication Policy.....	75
16.7	Intellectual Property Rights.....	76
16.8	Confidential Information.....	76
17.	REFERENCES	77

Table of Appendices

APPENDIX 1.	Schedule of Assessments	80
APPENDIX 2.	Study Personnel	83
Appendix 3.1	Investigator Details	83
Appendix 3.2	Sponsor Contact Details	83

List of In-text Tables

Table 3.3.1-1	Epidiolex Adverse Events.....	31
Table 5.1-1	Formulation of GWP42003-P Oral Solution	34
Table 5.2-1	Formulation of Placebo Oral Solution	34
Table 8.1-1	Dose Titration Regimen*	41
Table 9.1-1	Hematology, Biochemistry, Urinalysis and THC Screen	45

List of In-text Figures

Figure 1-1	Study Design and Treatment Schema	15
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List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic Drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC _(0-∞)	The area under the plasma concentration versus time curve from zero to 't' calculated as AUC _(0-t) plus the extrapolated amount from time 't' to infinity
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
BP	Blood Pressure
CLB	Clobazam
CBD	Cannabidiol
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLB	Clobazam
C _{max}	Maximum measured plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	Drug-Induced Liver Injury
EC	Ethics Committee
ECG	12-lead Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GW	GW Research Ltd
GWP	GW Pharma Ltd
IB	Investigator Brochure
ICH GCP	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio

IRB	Institutional Review Board
ITT	Intention to Treat
IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward
MMRM	Mixed-effects Model Repeated Measures
N-CLB	N-desmethyleclobazam
OLE	Open label extension
PBPK	Physiologically-based pharmacokinetic interactions
PI	Principal Investigator
PP	Per Protocol
PVD	Pharmacovigilance Department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
TBL	Total bilirubin
THC	Δ^9 -tetrahydrocannabinol
t_{max}	Time to the maximum measured plasma concentration
ULN	Upper Limit of Normal
USA	United States of America
VNS	Vagus Nerve Stimulation

Definition of Terms

Term	Definition
Baseline period	The seven-day period from screening (Visit 1) to enrollment (Visit 2).
Convulsive seizures	Tonic-clonic, tonic, clonic or atonic seizures.
Countable partial seizures	Partial/focal seizures with a motor or behavioral component that allow such seizures to be easily identified and hence counted.
Day 1	The day a patient is enrolled and begins PK sampling.
End of treatment	Completion of the treatment period (Visit 5 or Visit 11) or withdrawal.
End of study	Last patient's last visit / last contact.
IMP	Investigational Medicinal Product (Study Medication). Used to describe both investigational active product and reference therapy (placebo).
INR	International Normalized Ratio (INR) is a calculation made to standardize prothrombin time.
Investigator	Study Principal Investigator or a formally delegated study physician.
Non-convulsive seizures	Myoclonic, partial or absence seizures.
Partial seizures	Partial (focal) seizures occur when the electrical activity remains in a limited area of the brain.
Status epilepticus	Seizures lasting for 30 minutes or longer.
Sub-types of seizures	Seizure sub-types can be tonic, clonic, tonic-clonic, atonic, myoclonic, absence (typical and atypical), countable partial and other partial.

2. OBJECTIVES

2.1 Primary

To determine whether cannabidiol (CBD) affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyloclobazam (N-CLB).

2.2 Secondary

To assess the safety and tolerability of CBD in the presence of CLB.

3. BACKGROUND AND RATIONALE

3.1 Disease

Epilepsy is a common disorder¹. Approximately 1% of the world's population is chronically affected by epilepsy². It shows no particular geographic distribution and the gender distribution is more or less equal. The incidence of epilepsy is greater in childhood and in elderly people^{2,3,4,5}. Focal seizures represent the most frequent seizure type (around 60% of all cases of epilepsy, and a substantial percentage of them are not well controlled)⁶.

Overall, and despite the introduction of a substantial number of new antiepileptic drugs (AEDs) in the last two decades, around 30% of patients remain refractory to currently available treatment^{7,8,9}. In addition, most currently approved AEDs are associated with significant motor and cognitive adverse reactions^{10,11}.

Currently available AEDs each belong to one of a large number of different classes. The principal targets for existing AEDs tend to be either modulators of voltage-dependent ion channels, enhancers of inhibitory neurotransmission, and attenuators of excitatory neurotransmission, with the aim being to reduce neuronal excitotoxicity^{12,13}.

3.2 GWP42003-P Background

The cannabis plant (*Cannabis sativa* L.) produce trichomes that synthesize a large number of pharmacologically active compounds called phytocannabinoids. The most abundant of these are Δ^9 -tetrahydrocannabinol (THC) and CBD, although the amounts and proportions of the various phytocannabinoids in each plant vary by strain and can be adjusted by breeding.

The Investigational Medicinal Product (IMP), GWP42003-P, is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from

these plants are processed to yield pure (>98%) CBD that typically contains less than 0.5% (w/w) THC. The pure CBD is subsequently dissolved in excipients with added sweetener and flavoring.

The pharmacological effects of phytocannabinoids are thought to be mediated primarily via their interaction with the endocannabinoid system, which consists of cannabinoid receptors, endogenous ligands (endocannabinoids) and enzymes for endocannabinoid synthesis and degradation. Two G-protein-coupled receptors for cannabinoids have so far been identified, designated cannabinoid CB₁ and CB₂ receptors. CBD does not bind to either of these receptors with any great affinity but does modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects ion channel conductance and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1¹⁴ and the orphan receptor GPR55¹⁵. Importantly, in contrast to THC, CBD lacks detectable psychoactivity. CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity¹⁶. Very little data concerning AEs of CBD in humans exists to date. However, doses of up to 1500 mg CBD per day are reported to be well tolerated in humans¹⁷.

3.3 Rationale

CBD has shown therapeutic potential as an AED, with preclinical studies demonstrating anticonvulsant effects in a number of animal models of seizure^{16,18,19}. Although no placebo-controlled trials have been completed to date, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures while taking CBD-enriched cannabis, with over half of those reporting either >80% reduction in seizure frequency or complete seizure freedom²⁰. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness and better mood. There has been a program of expanded access by GW Pharma Ltd (GWP) in the USA, primarily in children with severe epilepsy, that has shown encouraging reports of reductions in multiple seizure types with good tolerability in 151 exposures²¹.

Population-based studies of drug utilization demonstrate that 19-24% of patients with epilepsy use polytherapy with AEDs^{22,23,24}. In recent studies of children and adults with refractory epilepsy, 64 % used polytherapy with two or more AEDs, resulting in a considerable risk of interactions^{25,26}. CLB is a widely used 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). The pharmacological action of CLB is to decrease abnormal electrical activity in the brain via allosteric activation of the ligand-gated γ -aminobutyric acid (A) receptor.

CLB is in a class of medications called benzodiazepines. Similar to other benzodiazepine medications, clobazam is metabolized by cytochrome P450 (CYP450) enzymes (mainly in the liver). This metabolism results in the formation of an active metabolite N-desmethyclobazam (N-CLB), amongst others.

Cytochrome P450 enzymes are a family of heme-containing enzymes responsible for the metabolism of over half of all prescribed medications and interactions with these enzymes are the major source of physiologically-based pharmacokinetic (PBPK) interactions between drugs. It is anticipated that patients taking CBD may also be taking clobazam and as CBD has been shown to both inhibit CYP450 enzymes in vitro (K_i CYP3A4 = 1.5 μ M) and induce CYP450 enzymes in vitro (EC_{50} CYP3A4 = 1.2 μ g/mL) a possibility of a pharmacokinetic (PK) interaction between CBD and clobazam exists. Furthermore, CLB has been shown to undergo PBPK interactions with other AED medications via both CYP induction (such as with felbamate where the formation of the active metabolite of clobazam, N-CLB was increased several-fold²⁷) and also CYP inhibition (such as with stiripentol where serum concentrations of CLB were increased and metabolites decreased^{28,29,30}). Given the high likelihood that patients prescribed CBD will also be using clobazam, it is the aim and purpose of this study to determine whether a PK interaction between CBD and CLB exists.

3.3.1 Selection of Study Doses

Doses up to 800 mg CBD per day for up to eight weeks have been well tolerated in adults in GW Research Ltd (GW) clinical study GWMD09112, which, assuming an average weight of 70 kg, equates to a daily dose of 11.4 mg/kg. In the literature, doses of CBD have been given up to 1500 mg CBD per day for four weeks in adults, which, in a 70 kg human equates to a daily dose of 21.4 mg/kg CBD.

Data on the safety of CBD is emerging from the physician-initiated Epidiolex[®] Expanded Access Program being conducted in the USA. This program has been running since January 2014 and at the time of writing had data on 63 patients. The mean maximum exposure achieved in this patient population of refractory epilepsies was a daily dose of 24.4 mg/kg (n=59 patients) with a maximum dose of 51 mg/kg in one patient. Please see below for a break-down of the groups:

- ≤ 20 mg/kg CBD n=13 (21%)
- >20 mg/kg ≤ 30 mg/kg CBD n=40 (64%)
- >30 mg/kg ≤ 40 mg/kg CBD n=4 (6%)

- >40 mg/kg CBD n=2 (3%)
- Dose not reported n=4(6%)

11 patients had a daily CBD dose of >25 mg/kg, of which five did not report any adverse events (AEs). Of note, the patient who received 51 mg/kg did not have any AEs at this dose. The remaining six patients experienced AEs as documented in the [Table 3.3.1-1](#) below:

Table 3.3.1-1 Epidiolex Adverse Events	
Adverse Event Term	Number of Events
Loose stools / urgent bowel movements	2
Increase in seizures	2
Drowsiness	1
Aspiration pneumonia	1
Lethargy	1
Decreased appetite	1
Dyskinesia	1
Urinary tract infection	1

Based on the above, a daily dose up to 20 mg/kg/day (given as two divided doses) has been selected for the CBD dose in the current study, including a titration period with daily increments of 2.5 mg/kg and 5 mg/kg. 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 interest. During the OLE doses may be adjusted up or down, dependent on investigator opinion, to a maximum daily dose of 30 mg/kg CBD.

3.4 Clinical Hypothesis

CBD can act as both a CYP inhibitor and inducer in human hepatocytes in vitro. Therefore, the potential for PK interactions with other drugs that are metabolized by CYP450 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 CBD.

4. EXPERIMENTAL PLAN

4.1 Study Design

This phase 2, placebo-controlled study consists of a 52 day, single-blind phase followed by an optional maximum one year OLE. Patients will continue to take CLB as advised by their physician for the duration of the study. The IMP will be taken twice daily immediately after their CLB dose.

Patients will enter the study and begin a 10 day placebo titration phase. During this period patients will be up-titrated to an equivalent maintenance dose of 20 mg/kg/day. Patients will continue to take this maintenance dose of placebo for 14 days (Days 12 to 26).

On Day 27 patients will begin a 10 day CBD titration phase. During this period patients will be up-titrated to a maintenance dose of 20 mg/kg/day CBD. Patients will continue to take this maintenance dose for 14 days (Days 37 to 50).

Upon completion of the single blind phase of the study (Day 52) patients will be invited to receive CBD during the OLE phase. If a patient enters the OLE they will continue to take CBD 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 CBD 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 60 and they will receive a telephone follow-up visit four weeks after the end of IMP dosing (Day 89).

PK samples will be taken on three occasions during the single blind phase of the study:

- Day 1 (Visit 2) before beginning treatment (patients will be taking CLB only).
- Day 26 (Visit 3) following 14 days of placebo maintenance (patients will be taking CLB and placebo).
- Day 51 (Visit 4) following 14 days of CBD maintenance (patients will be taking CLB and CBD).

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 (primary metabolite of CLB), CBD and CBD major metabolites.

Patients should try to be consistent in the timing of their food intake in relation to dosing throughout the single blind phase of the study.

Upon entry into the OLE the dose of CBD 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.

A study schema ([Figure 1-1](#)), presented at the end of [Section 1](#), depicts the overall study design. More detailed information on treatment and study procedures are provided in [Section 7](#) and [Section 9](#) respectively.

4.1.1 Primary Endpoint

The primary endpoints of the study are the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- CLB
- N-desmethyleclobazam (N-CLB)
- CBD
- CBD major metabolites

4.1.2 Secondary Endpoint(s)

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

- AEs
- 12-lead Electrocardiogram (ECG)
- Clinical laboratory parameters (clinical chemistry, hematology and urinalysis)
- Vital signs
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Seizure Frequency

4.2 Number of Centers

An estimated number of two centers is expected to participate in this study.

4.3 Number of Patients

A total of 20 patients will be enrolled into the study. Recruitment for the study will be competitive between participating sites.

The sample size calculation is explained fully in [Section 13.1](#).

5. INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.1 GWP42003-P Oral Solution

GWP42003-P oral solution is presented as an oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.1-1](#).

Table 5.1-1 Formulation of GWP42003-P Oral Solution	
Material	Quantity
CBD	100 mg/mL
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.2 Placebo Oral Solution

Placebo oral solution contains the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.2-1](#).

Table 5.2-1 Formulation of Placebo Oral Solution	
Material	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.3 Packaging, Storage and Drug Accountability

5.3.1 Packaging and Labelling

The IMP will be manufactured and packaged by GWP. It will be distributed by GWP or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each visit considering the weight of each patient. A unique pack identification number will be used to identify each box and the medication it contains. The pack numbers will cross check with the batch numbers held at GWP. GWP will ensure that all IMP provided is fully labelled and packaged. Label text will comply with European Union (EU) guidance on Good Manufacturing Practice, Annex 13 Labelling and will be fully described in the separate Pharmacy Manual. In addition, any local country requirements in accordance with local drug law or regulatory requirement will be included in the final label text.

Directions of use, name, address and telephone number of investigator, or main contact for information about the product or the clinical trial, will be provided separately to the patient.

5.3.2 Storage

The IMP must be stored upright at room temperature (<30°C) and must not be refrigerated or frozen. It must also be kept away from heat and direct sunlight.

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities.

Should storage conditions deviate from these specified requirements, the GW study monitor should be contacted immediately to confirm if the IMP remains suitable for use. IMP should be placed under quarantine until confirmation is received that IMP is suitable for use.

Temperature records of the storage location must be maintained on a daily basis (a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each site. These records must contain at least the minimum and maximum daily temperatures and should be made available to the appropriate GW personnel for review throughout the study.

5.3.3 Supply and Return of Investigational Medicinal Product

Once a site has been activated at study initiation, IMP will be shipped to a responsible person, such as the pharmacist, at the investigator's center, who will check the amount received and the condition of the drug. Details of the IMP received will be recorded in the IMP accountability record. The site will acknowledge IMP receipt and will complete any receipt forms required. IMP will be dispensed and returned as detailed in [Section 5.3.4](#) with further IMP shipments to be requested as necessary. As directed, all supplies, including unused, partially used, or empty containers, will be returned to GWP or destroyed at the center if agreed in writing by the study monitor.

5.3.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMPs must be kept current and should contain:

- The dates and quantities of IMP received from GWP.
- Patient's identification.
- Date and quantity of IMP dispensed.
- The initials of the dispenser.
- Date and quantity of IMP returned to the investigator/pharmacy.

A record of returned IMP must be completed and included in the shipment of used and unused IMP to GWP. At the end of the study a record/statement of reconciliation must be completed and provided to GWP.

These inventories must be made available for inspection by authorized GW or GWP representatives and local officials or regulatory agency inspectors.

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

6. PARTICIPANT ELIGIBILITY

Investigators will be required to maintain a log that includes limited information about all screened patients (initials, age, and gender; as allowed per local regulations) and outcome of screening.

6.1 Inclusion Criteria

For inclusion in the study patients must fulfil ALL of the following criteria:

- 6.1.1 Male or female patients aged 18 to 55 years inclusive.
- 6.1.2 Patient must have epilepsy as determined by the investigator and be taking CLB.
- 6.1.3 Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition.
- 6.1.4 Patient must have experienced at least one seizure of any type (i.e., tonic-clonic, tonic, clonic, atonic seizures) within the two months prior to randomization.
- 6.1.5 Patients must be taking CLB and no more than two other AEDs during the course of the study.
- 6.1.6 AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study.
- 6.1.7 Intervention with vagus nerve stimulation (VNS) and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must be willing to maintain a stable regimen throughout the duration of the study.
- 6.1.8 Patients must abstain from alcohol during the single-blind phase of the study.
- 6.1.9 Patient and/or legal representative is available to attend all PK visits within the required visit window.
- 6.1.10 Patient and/or legal representative must be willing and able to give informed consent for participation in the study
- 6.1.11 Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements.

- 6.1.12 Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable.
- 6.1.13 Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study.

6.2 Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

- 6.2.1 Patient has clinically significant unstable medical conditions other than epilepsy.
- 6.2.2 Patients on CLB at doses above 20 mg per day.
- 6.2.3 Patients taking CLB intermittently as rescue medication.
- 6.2.4 Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes.
- 6.2.5 Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening.
- 6.2.6 Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy.
- 6.2.7 Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain for the duration of the study.
- 6.2.8 Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry.
- 6.2.9 Patient has any known or suspected history of any drug abuse or addiction.
- 6.2.10 Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration for the study.
- 6.2.11 Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits.
- 6.2.12 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil.
- 6.2.13 Female patients must have a negative pregnancy test and be willing and able to use a reliable method of contraception throughout the trial and for three months after last dose. In the context of this trial, an effective method is defined as those which result in low failure rate (i.e., less than 1% per year) when used consistently and correctly such as: combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence. The use of hormonal contraception must be supplemented with a barrier method (preferably male condom).

- 6.2.14 Female patient who is pregnant, lactating or planning pregnancy during the course of the study and for three months thereafter.
- 6.2.15 Patients who have received an IMP within the 12 weeks prior to the screening visit.
- 6.2.16 Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study.
- 6.2.17 Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator would prevent the patient from safe participation in the study.
- 6.2.18 Patient has significantly impaired hepatic function, as determined at screening or enrollment (Alanine aminotransferase [ALT] $>5 \times$ upper limit of normal [ULN] or total bilirubin [TBL] $>2 \times$ ULN) OR the ALT or Aspartate aminotransferase (AST) $>3 \times$ ULN **and** (TBL $>2 \times$ ULN **or** international normalized ratio [INR] >1.5). *This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion **must** be withdrawn from the study.*
- 6.2.19 Unwilling to abstain from donation of blood during the study.
- 6.2.20 Travel outside the country of residence planned during the study.
- 6.2.21 Patients previously enrolled into this study.

7. PATIENT ENROLLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center's Ethics Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent forms and other patient information material. Patients will be considered enrolled in the study from the time of providing written informed consent. All patients, or legal representatives, where appropriate, must personally sign and date the consent form prior to any procedures being performed (refer to [Section 9.1.2](#) and [Section 15.2](#)).

7.1 Treatment Assignment

At the start of Visit 1, patients will be allocated a unique patient number, consisting of a four digit GW center number and a three digit patient identification number. The three digit patient number will be assigned in ascendant numerical order at each site. The unique patient number will be preceded by a unique letter. For example, P1234001, denoting patient 001 at site 1234. GWP will provide all IMP packed and labelled. Following enrollment at Visit 2, patients will be allocated a pre-packed numbered IMP.

7.2 Randomization

This is a single-blind study with all patients following the same treatment regimen.

8. TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The IMP will be presented as an oral solution containing either the active pharmaceutical ingredient and excipients (in the case of GWP42003-P) or only excipients (in the case of placebo). For details regarding IMP formulations, see [Section 5](#).

The IMP will consist of two types of medication:

- GWP42003-P Oral Solution containing 100 mg/mL CBD.
- Placebo Oral Solution containing excipients.

All patients will be weighed during Visit 2 and the daily volumes of IMP solution to be taken during the titration period, and for the remainder of the study, will be calculated and provided to the patient and/or caregiver. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Each patient will take their first dose of IMP at Visit 2, Day 2 in the clinic. Patients not entering the OLE will take their final maintenance dose of IMP at Visit 4 (Day 51) in the clinic. Patients entering the OLE will take their final dose of IMP at Visit 11 (one year after the end of the blinded phase of the study) or sooner (if marketing authorization is granted within one year).

8.1.1 Dose Administration

The IMP will be administered orally by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided. The IMP should be taken immediately after the patient's usual CLB administration. The IMP should be swallowed, as per the intended commercial therapeutic route, and may be taken with other concomitant medications, as directed by the investigator.

8.1.2 Dose Escalation and Dose Adjustments

Patients will enter the single blind phase of the study and will be up-titrated over ten days (Day 2 to Day 11) to an equivalent maintenance dose of placebo of 20 mg/kg/day. From Day 27 to Day 36 patients will be up-titrated to a maintenance dose of 20 mg/kg/day CBD. The titration regimen is described in [Table 8.1-1](#).

For those patients who do not enter the OLE the dose of CBD will taper off over 10 days beginning on Day 52. The patient will reduce the dose by 10% of the maintenance dose each day and treatment will end on Day 60.

For patients who enter the OLE the maintenance dose of CBD may be adjusted up or down, depending on investigator opinion, to a maximum of 30 mg/kg/day.

Table 8.1-1 Dose Titration Regimen*		
Day - Placebo	Day - CBD	Dose Level (CBD or equivalent placebo)
2	26	2.5 mg/kg
3	27	2.5 mg/kg
4	28	5.0 mg/kg
5	29	5.0 mg/kg
6	30	7.5 mg/kg
7	31	7.5 mg/kg
8	32	10.0 mg/kg
9	33	10.0 mg/kg
10	34	15.0 mg/kg
11	35	15.0 mg/kg
12 onwards	36 onwards	20.0 mg/kg

*IMP is to be taken twice daily. Total daily doses are shown.

8.2 Concomitant Therapy

Doses of any concomitant AEDs, including CLB, must have been stable for at least four weeks prior to screening and must remain stable throughout the study period.

The use of rescue medication is allowed if necessary. The use of oxygen may be considered as rescue medication if used as required. Any medication, other than the IMP, taken during the study must be recorded on the Case Report Form (CRF).

Any non-pharmacological therapies (e.g., ketogenic diet, VNS) must also be stable up to four weeks prior to baseline and throughout the duration of the study.

8.3 Prohibited Therapy During Study Period

The following medications are prohibited for the duration of the study starting from acquisition of patient consent. However, any patients taking these medications after screening should not be withdrawn from the study unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered.

- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.
- Patients should not take any more than three AEDs inclusive of CLB.
- Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.
- Any other IMP taken as part of a clinical trial within six months or during the study.

8.4 Compliance in Investigational Medicinal Product Administration

Patients or their caregivers will record the total volume of IMP, administered on each treatment day, using the paper diary and will be asked to return all IMP (used and unused) at each subsequent visit. The site will check the returned IMP against the usage recorded in the diary and the projected usage. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

The investigator must inform GW promptly of all missing or unaccountable IMP.

Records of IMP accountability will be maintained according to [Section 5.3.4](#).

8.5 Access to Blinded Treatment Assignment

This is a single blind study. The identity of IMP assigned to patients will be known to the PI and the GWEP1428 study team at each site but will not be known by the patients.

9. STUDY PROCEDURES

A list of the required study procedures is provided in the subsections that follow, refer also to the Schedule of Assessments [APPENDIX 1](#). Assessments or tests that are not done and examinations that are not conducted must be reported as such on the CRFs.

The location of the source data for the following procedures will be documented, per center, in a signed ‘Source Data Verification plan’, for further details see [Section 16.2](#).

9.1 Study Procedure Listing

9.1.1 Contraception

To be eligible for the study, the patient must have agreed that if they or their partner are of child-bearing potential they are willing to use effective contraception for the duration of the study and for three months thereafter. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence⁶. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. The use of hormonal contraception must be supplemented with a barrier method (preferably male condom).

9.1.2 Informed Consent

Adult patients with an adequate level of understanding must personally sign and date the IRB/EC approved informed consent form before any study specific procedures are performed or any patient related data is recorded for the study. For adult patients with an insufficient level of understanding of what is proposed, only personal legal representative consent will be sought. The informed consent process should be documented within the patient notes.

GW requires a physician to be present for consent and to also sign the consent forms.

9.1.3 Demographics

Patient demographics will be recorded at Visit 1. The following information will be obtained for each patient: date of birth, gender and ethnic origin (if allowed per local regulations).

9.1.4 Medical History

Relevant, significant medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken) will be obtained during Visit 1 and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the study.

9.1.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 28 days) including AEDs will be recorded at the screening visit (Visit 1) and reviewed at each subsequent visit. AEDs used during the study should be maintained at a stable dose. Any changes in concomitant medication during the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to the screening visit, as defined in [Section 8.3](#).

9.1.6 Physical Examination

A physical examination will be performed at the screening visit (Visit 1) to ensure that the patient is eligible to enter the study. To ensure patient safety, further physical examinations will be performed at every hospital visit. Physical examinations will include height and body weight measurements.

9.1.7 Vital Signs

Vital sign measurements, taken after five minutes rest in a sitting position, will be completed alongside the physical examination at all visits. Postural BP will be assessed after five minutes in supine position and, if possible, two minutes in standing position. The pulse rate must also be measured as part of the vital sign assessments. BP and pulse rate must be recorded using the same arm throughout the study.

9.1.8 12-Lead Electrocardiogram

An ECG will be performed, after five minutes in supine position, at all hospital visits. A physician must review the ECG and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately in the CRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

9.1.9 Clinical Laboratory Sampling

Laboratory tests will be undertaken at all hospital visits and will include hematology, biochemistry, and urinalysis (provided urine can be obtained, with the exception of

screening where a urine sample for THC screen must be obtained). A serum pregnancy test (if appropriate) will also be performed at Visit 1.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further laboratory based urinalysis (urinalysis, microscopy, culture and sensitivity, as applicable).

The investigator and study monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in [Table 9.1-1](#).

Table 9.1-1 Hematology, Biochemistry, Urinalysis and THC Screen				
Biochemistry (serum)	Hematology (whole blood)	Urinalysis (urine)	Pregnancy Test	THC screen (urine)
Alanine aminotransferase (ALT)	Hematocrit	Bilirubin	Serum	THC
Albumin	Hemoglobin	Blood		
Alkaline phosphatase	Mean cell volume	Glucose		
Aspartate aminotransferase (AST)	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				

All laboratory results will be reviewed and the reports signed by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. See [Section 12.8](#) for guidance on evaluation of potential drug-induced liver injury (DILI). All laboratory results considered by the investigator to represent an AE must be documented on the CRF.

Repeat samples will be taken, if required, for clinical follow up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an

investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation.

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss in the four weeks prior to screening.

9.1.10 Pharmacokinetic Analyses

The plasma concentration/time curves of CLB, N-CLB, CBD and CBD major metabolites will be assessed at Visit 2 (Day 1 and Day 2), Visit 3 (Day 26 and Day 27) and Visit 4 (Day 51 and Day 52). Patients will be given their daily dose of clobazam at a scheduled time during Visit 2, Visit 3 and Visit 4 and the IMP immediately afterwards (Visit 3 and Visit 4 only) to facilitate the accurate timing of blood samples required for PK analysis. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted into a forearm vein 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.

The pre-dose blood sample will be taken within 30 minutes prior to dosing. The allowable window for post-dose blood sample collection is ± 2 minutes up to and including 1 hour post-dose, ± 5 minutes from 1.5 hours up to and including 6 hours post-dose and ± 1 hour at 12 hours and 24 hours post-dose.

In the event of an AE that, in the opinion of the investigator, is related to a concomitant AED, additional blood samples may be collected.

Analysis of all PK samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

9.1.11 Columbia Suicide Severity Rating Scale

The C-SSRS is to be completed by the investigator or his/her qualified designee at all hospital visits. Qualified designee is defined as physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant who is licensed and has completed the C-SSRS training within the last two years. It is a brief standardized measure that uniquely assesses the essential information (behavior, ideation, lethality and severity) and distinguishes between suicidal occurrences and non-suicidal self-

injury. The survey should be completed by the same assessor, where possible, throughout the study.

If the investigator or his/her qualified designee feel that the patient is either unable to answer the questions presented in C-SSRS, or that the questions are causing undue stress to the patient, the questionnaire may be skipped and this must be documented in the patient notes.

9.1.12 Patient Diary

Patients or their caregivers will be instructed on how to complete a paper diary and will be asked to record information daily in it. The number and type of seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from screening (Visit 1) until completion of dosing or withdrawal. Information on IMP intake will also be recorded each day from enrollment (Visit 2) until completion of dosing or withdrawal.

9.1.13 Investigational Medicinal Product Accountability

IMP will be dispensed at each of the following visits during the single blind phase:

- Visit 2 (Day 2)
- Visit 3 (Day 26)
- Visit 4 (Day 51)

IMP will be dispensed at each of the following visits for patients entering the OLE:

- Visit 5 (Two weeks)
- Visit 6 (One month)
- Visit 7 (Two months)
- Visit 8 (Three months)
- Visit 9 (Six months)
- Visit 10 (Nine months)
- Visit 11 (12 months)

Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 2 to 12). The site will check the returned IMP against the usage recorded in the paper diary. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

9.1.14 Adverse Events

Any adverse changes in the patient's medical condition, following completion of the consent form by the patient, will be recorded on the CRF as AEs, questioning the

patient further if necessary. All AEs* occurring during the study, whether or not attributed to the IMP, observed by the investigator or reported by the patient will be recorded in the CRF.

*For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures, must be documented as an AE.

Serious Adverse Events (SAEs) must be reported to GW Pharmacovigilance Department (PVD) within 24 hours of discovery or notification of the event, and recorded in the CRF.

Refer to [Section 12](#) for definitions, procedures and further information.

Inpatient hospitalizations that are, in the investigator's opinion, due to epilepsy will be recorded in the patient's CRF and through the SAE reporting process.

9.2 Study Procedures by Visit

Patients and their caregivers will be invited to participate in the study and will be issued with the patient information and informed consent or the personal legal representative information and informed consent (refer to [Section 9.1.2](#) and [Section 15.2](#)). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/legal representatives who provide written informed consent at Visit 1 will be screened for entry into the study.

9.2.1 Single Blind Phase

9.2.1.1 Visit 1 (Day -7, Screening)

The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG and vital signs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.

Patients who satisfy all inclusion and none of the exclusion criteria specified in [Section 6](#) will be assigned a unique patient number and then begin the seven day baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be

instructed on how to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.

9.2.1.2 Visit 2

9.2.1.2.1 Visit 2 (Day 1) – Enrollment (+3 days)

This visit will occur 7 days after Visit 1.

The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs and review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.

Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic on Day 2 ahead of additional sample collection.

9.2.1.2.2 Visit 2 (Day 2) - Enrollment

This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.

IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as described in [Section 8.1.2](#). Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.

9.2.1.3 Visit 3

9.2.1.3.1 Visit 3 (Day 26) (±3 days)

This visit will occur 25 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP. The following observations will be made at Visit 3 (Day 26):

concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.

Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of IMP. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients are expected to remain in clinic throughout this PK sampling process.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.1.3.2 Visit 3 (Day 27)

This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 26 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 27: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.

IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as described in [Section 8.1.2](#). Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period. Patients or their caregivers will be instructed how to record the diary information.

9.2.1.4 Visit 4

9.2.1.4.1 Visit 4 (Day 51) (± 3 days)

This visit will occur 50 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP. The following observations will be made at Visit 4 (Day 51): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of IMP.

Further samples will then be taken at the following times relative to the CLB dose:
15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours.
Patients are expected to remain in clinic throughout this PK sampling.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.1.4.2 Visit 4 (Day 52)

This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 51 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 52: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.

At the end of the blinded phase of the study on Day 52, providing the investigator and patient both agree, patients will be invited to continue taking IMP and to enter the OLE.

Patients who enter the OLE will be dispensed CBD on Day 52. The dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day in the blinded phase to a maximum of 30 mg/kg/day in the OLE. Patients and/or their caregivers will be provided with individual dosing schedules as described in [Section 8.1.2](#). Patients, or their caregivers, will be instructed how to record the diary information.

Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of IMP. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 60.

9.2.1.5 Visit 5 (Patients not entering OLE) (+3 days)

This visit will occur 60 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.

All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including height and body weight) and vital signs will be assessed and the C-SSRS will be administered.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.

9.2.1.6 Safety Follow up Call (Day 89) (± 3 days)

This visit is required for patients who do not enter the OLE study on Day 50, or who withdraw from the study early. This visit should occur four weeks after Visit 5, (± 3 days) or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 89: concomitant medications (including AEDs) and AEs.

9.2.2 Open Label Extension

Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 52) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 51).

9.2.2.1 Visit 5 (Open Label Extension) - Two Weeks (± 3 days)

This visit will occur two weeks after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.2 Visit 6 (Open Label Extension) - One Month (± 3 days)

This visit will occur one month after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.3 Visit 7 (Open Label Extension) - Two Months (± 3 days)

This visit will occur two months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE):

concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.4 Visit 8 (Open Label Extension) - Three Months (± 7 days)

This visit will occur three months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE):

concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.5 Visit 9 (Open Label Extension) - Six Months (± 7 days)

This visit will occur six months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE):

concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.6 Visit 10 (Open Label Extension) - Nine Months (± 7 days)

This visit will occur nine months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE):

concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.7 Visit 11 (Open Label Extension End of Treatment) - Twelve Months (± 7 days)

This visit will occur twelve months after Visit 4 (Day 51). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

Starting at Visit 11, patients will begin to taper down their IMP dose. The dose will be reduced by 10% of their OLE maintenance dose per day.

9.2.2.8 Visit 12 (Open Label Extension End of Taper)

This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including height and body weight), ECG and vital signs will be assessed and the C-SSRS will be administered.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.

9.2.2.9 Safety Follow Up Call (± 3 days)

This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.

10. WITHDRAWAL

In accordance with the Declaration of Helsinki³¹, the FDA regulations relating to good clinical practice (GCP) and clinical trials^{32,33,34}, the EU Clinical Trials Directive

(2001/20/EC)³⁵ and/or other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

The patient must be withdrawn from the study if any of the following apply:

- Administrative decision by the investigator, GW, or a Regulatory Authority.
- Pregnancy.
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- Withdrawal of patient consent.
- Withdrawal of legal representative consent.
- Lost to follow up.
- ALT $>3 \times$ ULN or AST $>3 \times$ ULN **and** (TBL $>2 \times$ ULN **or** INR >1.5).
- ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- ALT or AST $>8 \times$ ULN.
- ALT or AST $>5 \times$ ULN for more than two weeks.

Patients may also be withdrawn from the study for any of the following:

- Patient non-compliance.
- AE, which in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Any evidence of drug abuse or diversion.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

Should a patient request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients who withdraw should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator's clinical judgment. All assessments required at Visit 4 (if the withdrawal is during the blinded phase) or Visit 11 (if the withdrawal is during the OLE) should be conducted if possible. If the tapered dose is administered, patients should return for Visit 5 (if withdrawal is during the blinded phase) or Visit 12 (if the withdrawal is during the OLE) if possible. Wherever possible, the safety follow-up visit should be conducted 28 days from the date of the last dose of IMP. Patients withdrawing due to an AE should be followed up according to [Section 12.7](#). All information should be reported on the applicable CRF pages

11. URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the investigator they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to Competent Authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the Competent Authorities and IRB/EC within three days.

12. ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this study an AE is defined as:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which is present following screening (Visit 1) throughout the study and up to the post treatment, safety follow-up visit (28 days after last dose of IMP), which may or may not be considered to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

Surgical/Investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-study existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization which prolongs their scheduled hospital stay in which case it would be considered a SAE (refer to [Section 12.2](#)).

If reporting a fatal event, the SAE term should be the underlying cause of the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

The term ‘investigator’ refers to the study PI or a formally delegated study physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported

promptly to Regulatory/Competent Authorities, applicable IRB/ECs and Investigators (expedited reporting) by GW.

An AE must only be classed as serious i.e., an SAE, when the event falls into one of the following criteria:

- Results in death.
- Is life-threatening.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Medically significant.**

* The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

** Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.3 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study must be reported to GW with any other supporting information and recorded in the AE section of the CRF. Any on-going SAEs should be followed up until resolution wherever possible. For all deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports and relevant medical reports should be sent to GW promptly.

All SAEs must be reported directly to GW PVD within 24 hours of discovery or notification of the event. All SAE information must be recorded on the SAE forms provided in the site files and faxed to GW PVD. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form, signed/dated and faxed to the GW PVD and the AE section of the CRF must be updated.

The investigator should continue to document all AEs which occur up to the last formal follow-up visit (Visit 13 for patients entering the OLE and Visit 6 for those

patients that are not entering the OLE). If the investigator subsequently becomes aware of any deaths or a new IMP-related SAE after the last formal follow-up period of the study, these should still be reported to the GW PVD.

Any other problem discovered outside these time limits which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have participated in the study, then these should be treated as an SAE and reported to GW PVD. Such post study SAEs do not need to be recorded on the patient's CRF if editing rights to the CRF have been removed.

Contact details for the GW PVD are provided at the front of the site files for all study centers, and upon the GW SAE Report form.

12.4 Pregnancy

Any patient, or patient's partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD within 24 hours of first awareness. Please use the GW Pregnancy Monitoring Forms provided. Where possible the investigator should provide the outcome of the pregnancy.

The investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the investigator becomes aware of a new pregnancy outside this time limit then they should report it as above. GW PVD will follow up for all pregnancy outcomes.

12.5 Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the study medication must be reported as such. The expression "*reasonable causal relationship*" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the investigator for all AEs is used to capture the reasonable causal relationship of an event to the study medication:

"In your opinion is there a plausible relationship to the study medication?" The answer is "yes" or "no".

Events that start before the first dose of study medication (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of study medication, a new event record should be entered into the CRF.

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the investigator assess not only the possible role of the study medication but also competing etiological factors as the underlying cause. Factors for consideration may include:

- Medical history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.
- Withdrawal of study medication.
- Protocol-related procedure.

12.6 Reporting Procedures for All Adverse Events

All AEs* (including SAEs) occurring during the study will be reported on the running logs in the AE section of the CRF. This includes all events from the time following screening (Visit 1) to post study follow-up (Visit 13 for patients entering the OLE and Visit 6 for those patients that are not entering the OLE), whether or not attributed to IMP and observed by the investigator or patient.

*For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures must be documented as an AE. Any AE which meets SAE criteria should still be reported as a SAE.

The following information will need to be provided for all AEs:

A) Adverse event (diagnosis or syndrome if known, or signs and symptoms)

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded on the AE section of the CRF. Once a diagnosis has been determined the AE section of CRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the CRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated e.g., fever and malaise due to a respiratory tract infection.

B) Adverse Event Start date and Stop date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given then record as much information as possible (i.e., month and year or in exceptional circumstances just year). When the actual start date becomes known the CRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one for the following categories:

- Recovered.
- Recovered with sequelae.
- Continuing.
- Patient died.

D) Severity

When describing the severity of an AE the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, for example, a headache or constipation, the change in severity should not be recorded each time, instead only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore it should not be classed as serious.

E) Causality

See [Section 12.5](#) above.

F) Action taken with Study Medication

This question refers to the action taken with the IMP due to an AE. The action with the IMP must be classed as:

- None.
- Dose reduced temporarily.
- Dose reduced.

- Study medication interrupted.
- Study medication stopped.

12.7 Follow up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the GW PVD for any AEs reported.

AEs considered related to the IMP by the investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE, further details of withdrawal are presented in [Section 10](#). If either of these occurs, the patient must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

12.8 Reporting Clinically Significant Laboratory Results

All investigational sites are required to submit to the GW PVD the laboratory results for any patient after randomization that meet the criteria for the selected laboratory parameters as follows:

- ALT or AST $>3 \times$ ULN **and** (TBL $>2 \times$ ULN **or** INR >1.5).
- ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- ALT or AST $>8 \times$ ULN.
- ALT or AST $>5 \times$ ULN for more than two weeks.

These reports must be sent to the GW PVD using the same fax number for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the patient's baseline laboratory results with all reports to GW PVD.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of DILI and will be considered as protocol defined criteria for withdrawal and important medical events. The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment, detailed history and physical examination. Patients should be followed until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees.

In accordance with the EU Clinical Trials Directive³⁵, relevant parts of the FDA Code of Federal Regulations and any national regulations, GW will inform investigators, regulatory authorities and relevant IRB/ECs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through three sources:

- Investigator Brochure³⁶: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study on the IMP in human participants. The IB is updated annually.
- Development Core Safety Information: this document actually forms the Safety Section of the IB³⁶, or is updated as an appendix of the IB³⁶. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).
- Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the regulatory authorities, the relevant central IRB/ECs which have approved the study and investigators. As required, the investigator should notify their regional IRB/EC of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the USA, investigators are normally required to promptly report to their IRBs all unanticipated problems involving risks to human patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance³² the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human patients, and reported to the IRB, *only* if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

The FDA guidance³⁷ states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a

multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW will inform investigators (regulatory authorities and applicable IRB/EC's) of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the study does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

As a minimum, the recipient will be sent all of the above and relevant updates between the period from ethics approval and final database lock.

13. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be produced prior to the database lock and analysis of the study. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

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

13.2 Interim Analysis

An interim analysis will be conducted at the end of the Single Blind phase of the study and may also be considered during the OLE phase, if long term data is required to support New Drug Application/Marketing Authorization Application submissions.

13.3 Analysis Sets

13.3.1 Safety Set

All subjects who are treated and receive at least one dose of IMP will be included. The Safety set is the primary analysis set for all safety endpoints.

13.3.2 Pharmacokinetic Analysis Set

All subjects who are treated and receive at least one dose of IMP and who provide some on-treatment data will be included.

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

13.3.3 Protocol Deviations

Any protocol deviations will be listed and reasons for exclusion from the analysis populations will be summarized

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (n), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category. Summaries will be presented for data recorded pre-treatment, during each 25 day dosing phase (placebo and CBD) and during the OLE phase separately.

13.5 Accountability and Background Characteristics

13.5.1 Enrolment and Disposition

All patients (screened, treated, completing the study and those prematurely terminated IMP) will be accounted for in the enrolment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Age, sex, race (as allowed per local regulations) and any other demographic or baseline characteristics will be summarized, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by system organ class, including details of the duration of epilepsy and the types of seizures currently experienced by the patients.

13.5.4 Concomitant Medication

Concomitant medications taken prior to and during the study will be summarized, by medication class and active ingredients. Summaries of medications taken during the IMP treatment phases and during OLE will be presented separately.

13.6 Endpoints and Statistical Methods

13.6.1 Primary Endpoint(s)

The primary endpoints of the study are the pharmacokinetic parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- CLB
- N-desmethyclobazam (N-CLB)
- CBD
- CBD major metabolites

13.6.2 Secondary Endpoint(s)

The secondary endpoints of the study are the safety parameters (see [Section 13.6.5](#)).

13.6.3 Pharmacokinetics

Calculation of PK parameters will be based on actual blood sampling times [h] (relative to the corresponding administration time) rounded to two decimal digits with negative pre-dose times set to zero. Plasma concentrations of CLB, N-CLB, CBD and

the major metabolites will be displayed graphically, summarized and listed. For descriptive statistics, values below the lower limit of quantification of the assay (LLOQ) will be excluded from any calculations. Descriptive statistics of concentrations will be calculated if at least half of the individual data points that have been measured are equal to or above the LLOQ.

For calculation of the PK parameters, the following rules will be applied:

At time zero and at time points in the lag-time between time zero and the first quantifiable concentration, concentrations below the LLOQ will be set to zero. All other concentrations below the LLOQ will not be used in calculations.

Variables derived from plasma concentrations:

- Concentration maximum (C_{max}): Highest observed plasma concentration of the measured concentration-time profile. Dimension: [amount / volume].
- Terminal half-life $t_{1/2} = \ln(2)/\lambda_z$.
- The rate constant of the terminal phase λ_z will be determined by linear regression of log-transformed concentration data after the time of maximum concentration. A sequence of terminal elimination rate constants will be created by linear regression. Linear regressions are repeated using the last three points with a quantifiable concentration, the last four points, the last five points etc. For each regression, an adjusted R^2 is computed. The regression with the largest adjusted R^2 is selected to estimate the terminal half-life. Dimension: [time].
- Area under the concentration-time curve from administration until the last sampling point (t) equal or above the LLOQ $AUC_{(0-t)}$ will be calculated by the linear trapezoidal formula. Dimension: [time • amount / volume].
- Area under the concentration-time curve extrapolated to infinity: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_{last}/\lambda_z$ and C_{last} is the concentration observed at the last time point with a quantifiable concentration, λ_z refers to the terminal elimination rate constant. Dimension: [time • amount / volume].
- Time of maximum concentrations: T_{max} will be taken as the time after administration at which C_{max} occurs. Dimension: [time].
- PK parameters for each analyte will be summarized for the two treatment phases of the study separately, as appropriate.
- 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 group ratios of geometric means of C_{max} , $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will be carried on logarithm scale using a linear mixed effect model with treatment (CBD or placebo) as fix 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.

13.6.4 Safety

13.6.4.1 Treatment Compliance and Extent of Treatment Exposure

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

13.6.4.2 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary.

A treatment emergent AE is one that started, or worsened in severity or seriousness, following the first dose of IMP.

Descriptive presentations of treatment emergent AEs will be given by preferred term and system organ class for the safety analysis set. The number of patients reporting at least one AE will be provided. Summaries will be provided for each phase of the study separately.

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.

13.6.4.3 Clinical Laboratory Data

Clinical laboratory data at screening and at the end of each 24 day treatment phase and the change from baseline to end of treatment (OLE) will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range.

13.6.4.4 Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data

The C-SSRS, vital signs, ECG and physical examination data will be summarized at screening, at the end of each 24 day treatment phase and during the OLE treatment period using appropriate summary statistics. Changes in the vital signs from baseline to end of each treatment phase will also be summarized.

13.6.4.5 Seizure Data

Seizure data collected during each 24 day treatment phase and during the OLE phase of the study will be summarized using appropriate summary statistics.

14. DATA SAFETY MONITORING COMMITTEE

GW does not plan to use an independent data safety monitoring committee as part of this study.

15. REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the^{31,35} and the clinical trial regulations adopting European Commission Directives into national legislation^{38,39,40}.

15.2 Informed Consent

Initial master informed consent forms will be provided to the investigator to prepare the informed consent documents to be used at his or her center. The GW Clinical Manager will communicate updates to the templates by letter. The written informed consent documents should be prepared in the language(s) of the potential patient population.

Before a patient's participation in the trial, the investigator is responsible for obtaining written informed consent from the patient or legal representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol specific screening procedures or any IMPs are administered. The patient, or their legal representative, should have ample time for review to consider the information provided before giving written consent; more specific definitions of ample time may be in force if required by IRB/ECs or local regulations.

The acquisition of informed consent should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient or legal representative (as applicable) and by the person who conducted the informed consent discussion. GW also requires a physician to be present for consent and to sign the consent forms as well. The original signed informed consent forms should be retained and a copy provided to the patient or legal representative.

15.3 Institutional Review Board/Ethics Committee

A copy of the protocol, proposed informed consent forms, other patient information material, any proposed advertising material and any further documentation requested, must be submitted to the IRB/EC for written approval. GW must receive a copy of the written approval of the protocol and informed consent forms before enrollment of patients into the study and shipment of IMP.

The investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent

documents. The investigator should notify the IRB/EC of deviations from the protocol or SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The investigator will be responsible for obtaining on-going IRB/EC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/EC continuance of approval must be sent to GW.

15.4 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent for entry into the study:

- Signed and dated protocol signature page.
- Copy of approved informed consent forms and other patient information material.
- Copy of the IRB/EC approval of the protocol, informed consent forms and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/EC composition and/or written statement of the IRB/EC in compliance with the FDA regulations relating to GCP and clinical trials^{32,33,34,41}, the EU Clinical Trials Directive³⁵, or International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GC⁴² where the EU Directive does not apply).
- Signed laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed clinical trial agreement (including patient/investigator indemnity insurance and financial agreement).
- FDA 1572 form.
- Completed financial disclosure statements for the PI and all sub-investigators if relevant.

15.5 Participant Confidentiality

The investigator must ensure that the patient's anonymity is maintained. On the CRFs and within the databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials and ethnic origin (if allowed per local regulations) and a patient study number only. Documents that are not for submission to GW, e.g., signed informed consent forms should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to good clinical practice and clinical trials^{32,33,34,41}, and the EU Clinical Trials Directive³⁵/ICH GCP Guidelines⁴², it is

required that the investigator and institution permit authorized representatives of the company, the regulatory agencies and the IRB/EC direct access to review the patient's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the patient that his/her study related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the company.

16. ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Study or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent documents. The IRB/EC and Competent Authorities must be informed of all amendments and give approval for any substantial amendments prior to implementation. The investigator must send a copy of the approval letter from the IRB/EC to GW. Amendments for administrative changes can be submitted to the IRB/EC for information only.

Both GW and the investigator reserve the right to terminate the study, according to the clinical trial agreement. The investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to GW.

16.2 Study Documentation and Storage

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the GW delegation of authority and signature form.

Source documents are original documents, data and records from which the patient's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, electronic data captured by IVRS, microfiches, radiographs and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording; that is, there is no other written or electronic record of data. In the rare situations of this happening, then the source data from the CRF should be transcribed in the patient's notes with appropriate signature and date to provide a full audit trail. A Source Data Verification Plan, identifying the source for each data point at each site, will be agreed with each site prior to patient recruitment.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related, essential documentation (as outlined in ICH E6 Section 8.2⁴²), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consent forms and supporting copies of source documentation.

- Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see [Section 15.4](#)) and all correspondence to and from the IRB/EC and GW.
- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug related correspondence.

In addition, all original source documents supporting entries on the CRFs, paper diary data and electronic data captured by IVRS must be maintained and be readily available.

Following completion or termination of a clinical study, GW will initiate proper archive of clinical study related documentation and electronic records generated by the investigator and/or GW. All clinical trial related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 20 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by GW (EU Directive 2005/28/EC Chapter 4 Trial Master File and Archiving Article 16⁴³).

GW will inform the investigators for each site in writing of the need for record retention. No study document should be destroyed without prior written agreement between GW and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify GW in writing of the new responsible person and/or the new location.

16.3 Study Monitoring and Data Collection

The GW representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study for example, CRFs and other pertinent data provided that patient confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting the CRFs and available diary data at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor should have access to patient medical records and other study related records needed to verify the entries on the CRFs.

The investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

The investigator is responsible for ensuring the data recorded in the CRFs are accurate and complete. The CRF should be completed within five working days after the patient's visit and before review by the study monitor. Queries generated by GW or its representative are to be answered within a similar period of time. Shorter periods of time may apply during specific situations such as interim analysis or final database cleaning.

All handwritten medical records should be filled out with a black or blue ball-point pen and must be legible. Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator. No correction fluid or tape may be used. The PI will sign and date the indicated places on the CRF. These signatures will indicate that the PI inspected or reviewed the data on the CRF, the data queries and the site notifications and agrees with the content.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations^{32,33,34,41}, the ICH GCP Guideline⁴², and all other applicable regulatory requirements^{35,42}, to resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

GW's or the CRO's Clinical Data Management Department will correct the following issues in CRFs without any notification to site staff:

- Misspellings that do not change the meaning of the word, excluding AEs and medications.
- Date errors that occur at the end of the year and into the New Year.
- Temperature unit errors (Fahrenheit vs Centigrade).
- Weight unit errors (pounds vs kilograms) if a baseline weight has been established.
- Administrative data for example, event names for unscheduled visits or retests.
- Clarifying "other, specify" if data are provided for example, race, physical exam.

- If a YES or NO question for example, ‘Were there any AEs?’ is left blank yet AEs are listed on the CRF, YES will be entered in the blank.
- Correct CRF page numbers.

16.4 Quality Assurance

In accordance with the FDA regulations, EU Clinical Trials Directive/ICH GCP and the sponsor’s audit plans, representatives from GW’s Clinical Quality Assurance Department may select this study for audit. Inspection of site facilities for example, pharmacy, drug storage areas, laboratories and review of study related records will occur to evaluate the study conduct and compliance with the protocol, as per the EU Clinical Trials Directive/ICH GCP and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the study site in the event of any claim in respect of personal injury arising due to a patient’s participation in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical study patient would not otherwise have been exposed providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will co-ordinate this dissemination and may solicit input and assistance from the chief/PIs. A summary of the results of this study will be made available on <http://www.ClinicalTrials.gov>, as required by U.S. Law.

The raw data from this study may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analysis and are permitted to present such information along with methods and results of the clinical study at symposia, national or regional professional meetings, and to publish it in theses or dissertations.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this study, must be submitted to GW Medical Writing Department and, as applicable, GW Publication Committee for review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for

publication, public dissemination, or review by a publication committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

GW also reserve the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.7 Intellectual Property Rights

All Intellectual Property Rights owned by or licensed to either GW or the PIs, other than those arising from the clinical study, will remain their property. All Intellectual Property Rights arising out of the clinical study will vest in or be exclusively licensed to GW and as such, the PI should promptly disclose all knowledge to GW and refrain from using such knowledge without the prior written consent of GW.

16.8 Confidential Information

GW and the PI should ensure that only personnel directly concerned with the study should be party to confidential information and that any information coming to either party about the other during the course of the study should be kept strictly confidential and should not be disclosed to any third party or made use of without the prior written consent of the other.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Visit Number Day (Visit Window)	Visit 1 Day -7	Visit 2 Day 1 (+ 3 days)	Visit 2 Day 2	Visit 3 Day 26 (± 3 days)	Visit 3 Day 27	Visit 4 Day 51 (± 3 days)	Visit 4 Day 52	Visit 5* End of Taper	Visit 6* 4wk SFU (± 3 days)
Informed consent	X								
Eligibility criteria	X	X							
Enrollment		X							
Demographics	X								
Medical history	X								
Paper diary training	X		X						
Concomitant medications (including AEDs)	X	X	X	X	X	X	X	X	X
Physical examination (including height and body weight)	X	X	X	X	X	X	X	X	
ECG	X	X		X		X			
Vital signs	X	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	
Alcohol/THC test	X								
Pregnancy test (if appropriate)	X								
Pharmacokinetic blood sampling**		X	X	X	X	X	X		
C-SSRS	X	X		X		X		X	
Patient diary review		X		X		X		X	

Visit Number Day (Visit Window)	Visit 1 Day -7	Visit 2 Day 1 (+ 3 days)	Visit 2 Day 2	Visit 3 Day 26 (± 3 days)	Visit 3 Day 27	Visit 4 Day 51 (± 3 days)	Visit 4 Day 52	Visit 5* End of Taper	Visit 6* 4wk SFU (± 3 days)
(seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)									
IMP dispensing			X		X		X		
Collection of IMP				X		X		X	
IMP compliance review				X		X		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 and third PK visits the patient should take the IMP immediately after their daily dose of CLB.

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 height and body 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	

APPENDIX 2. STUDY PERSONNEL

Appendix 3.1 Investigator Details

At the time of protocol production, the participating investigators had not been confirmed. A list of all investigators will be maintained within the GW Master Files (electronically and added to the Trial Master File at the end of the study).

Appendix 3.2 Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting:	Fax: PPD [REDACTED]
	USA Toll Free Fax:
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TITLE: A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)

STUDY CODE: GWEP1428

EudraCT NUMBER: 2014-002942-33

PROTOCOL AMENDMENT NUMBER: 1

**to be incorporated into the Protocol, creating
PROTOCOL VERSION 2, DATE 09 JUL 2015**

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Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board/Independent Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

1. PROTOCOL SYNOPSIS

Study Title	A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)
Indication	Epilepsy
Study Design	<p>This is a phase 2, double-blind, randomized, placebo-controlled study in 20 patients.</p> <ul style="list-style-type: none"> Patients will be randomized in a 4:1 ratio to receive 20 mg/kg cannabidiol (CBD) 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. Day 1 (Visit 2), patients will not be dosed with GWP42003-P/placebo but will continue to take CLB at a stable dose. Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). Day 12 (Visit 3), patients will attend the study site to check safety and compliance. After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the patient will continue to take GWP42003-P as advised by the investigator. If the patient does not enter the OLE period of the study, the patient will taper off of GWP42003-P by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with end of taper on Day 43 (Visit 5). <p>Pharmacokinetic (PK) samples will be taken on the day of enrollment (Visit 2, Day 1) and after completing 21 days treatment on GWP42003-P or placebo (Visit 4, Day 33). The PK assessments will therefore capture the following combinations of CLB and GWP42003-P:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and GWP42003-P or placebo. <p>Each PK assessment should be performed at time points in respect to a</p>

	<p>morning dose of CLB. The time points are as follows: Pre-dose, 15 min, 30 min, 1h, 1.5h, 2h, 4h, 6h, 12h and 24h. It is expected that the patient will continue to take their CLB as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The GWP42003-P/placebo should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD, CBD major metabolites, Δ^9-tetrahydrocannabinol (THC) and THC major metabolites. Patients will be required to keep a paper diary to note the time and dose of GWP42003-P and CLB administration each morning and evening and to record any adverse events (AEs) that may occur whilst receiving investigational medicinal product (IMP) and any other medications. Patients will also be requested to record the number and type of seizures for each day whilst on the study.</p>
Sponsor	<p>GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom</p>

2. TABLE OF CONTENTS

1.	PROTOCOL SYNOPSIS	2
2.	TABLE OF CONTENTS	4
2.1	Table of Appendices	4
3.	RATIONALE	4
3.1	Study Design	4
3.2	Procedures	5
3.3	Investigational Medicinal Product	5
3.3.1	Clobazam	5
3.3.2	Cannabidiol/Placebo	5
3.4	Secondary Endpoints	6
3.5	Inclusion/Exclusion/Withdrawal Criteria	6
3.6	Clarification of Liver Function Testing	6
3.7	Administrative Changes	6
4.	IMPLEMENTATION OF THE AMENDMENT	6
5.	PRESENTATION OF AMENDED TEXT	7

2.1 Table of Appendices

APPENDIX 1.1	49
APPENDIX 1.2	53
APPENDIX 1.3	54
APPENDIX 1.4	55

3. RATIONALE

This protocol amendment 1 will be incorporated into the Protocol creating Protocol

Version 2, date 09 Jul 15) addresses the following issue(s):

3.1 Study Design

The study design has been amended as follows:

- Changed from a single-blind to a double-blind randomized design. Participants will be randomized in a 4:1 ratio to receive either GWP42003-P or placebo. This allows for the removal of one of the pharmacokinetic (PK) time points, therefore being of less burden to participants whilst maintaining the same outcome of the study.
- Increased screening period from 7 to 14 days to provide more flexibility to sites and participants.
- Increased maintenance period of the double-blind phase of the study from 14 to 21 days. Clobazam takes up to 14 days to reach steady state; therefore, increasing the

maintenance period to 21 days will ensure steady state has been achieved following the introduction of GWP42003-P or placebo.

- Visit 3 will be a site visit 12 days in to the treatment period to ensure participants have titrated up to the required dose and to check if they have experienced any adverse events (AEs) following introduction of the GWP42003-P/placebo.
- Visit 6 (safety follow up phone call) has changed from day 89 to day 71 due to the study design changes discussed above.

3.2 Procedures

The following procedures have been added to the protocol:

- A serum alcohol test will be performed at Visits 1, 2 and 4 to capture alcohol levels at the time of the PK draws as well as at screening.
- An additional blood sample will be taken at Visit 2 for genetic testing subject to additional consent being obtained from the participant. Genetic testing will be conducted to look at the CYP450 genes, with particular focus on CYP2C19 and CYP3A4, involved in the metabolism of anti-epileptic drugs (AEDs) and GWP42003-P.
- Guidance on monitoring human abuse liability via AEs and drug accountability throughout the study. In addition to ongoing reporting of such events, a Study Medication Use and Behavior Survey will be completed at the final dosing visit (Visit 5 or 12).

The following procedure has been removed from the protocol:

- Measurement of height at Visits 2 to 12 inclusive. It is not envisaged that a patient's height will change significantly during their participation in the study; therefore, it is an unnecessary burden to the patient.

3.3 Investigational Medicinal Product

3.3.1 Clobazam

In order to comply with a request received from the Medicines & Healthcare products Regulatory Agency, for the purposes of this study, Clobazam is now described as an investigational medicinal product (IMP) for the blinded phase of the study. References to IMP have been amended to GWP42003-P/placebo throughout the protocol where needed.

3.3.2 Cannabidiol/Placebo

- Color of GWP42003-P has been included.
- Guidance has been provided on the reduction of the GWP42003-P/placebo dose if AEs, which are attributable to the IMP or concomitant AEDs, occur during titration.
- References to 'CBD' have been updated throughout the protocol, as required, to reflect the product code GWP42003-P instead. In the interests of brevity, these changes have not been captured within section 5 of this amendment.

3.4 Secondary Endpoints

The following secondary endpoints have been added:

- PK parameters of Δ 9-tetrahydrocannabinol (THC) and THC major metabolites.
- Safety assessment to assess drug abuse liability.

3.5 Inclusion/Exclusion/Withdrawal Criteria

The inclusion/exclusion/withdrawal criteria have been updated as follows:

- Inclusion criterion regarding seizure type has been updated to specify the type of seizure a patient must have experienced to allow their inclusion into the study.
- Inclusion criteria regarding intervention with vagus nerve stimulation and ketogenic diet and alcohol consumption have been clarified that these should be stable throughout the blinded section of the study.
- Exclusion criterion regarding contraception has been updated to factor in male patients.
- Exclusion criterion regarding pregnancy has been updated to clarify that this must be confirmed by a positive pregnancy test.
- Withdrawal criterion added to specify that if any other IMP is taken as part of any other clinical trial during the study, the patient must be withdrawn.

3.6 Clarification of Liver Function Testing

- Additional details have been included regarding follow-up of elevated liver enzyme levels that do not meet the criteria for drug-induced liver injury (DILI).
- Section 12.8 has been re-titled as the text within concerns potential cases of DILI only.
- The eligibility criterion regarding impaired hepatic function has been amended to bring into line with the criteria for DILI.

3.7 Administrative Changes

Minor spelling/formatting/consistency/administrative issues have been corrected. (NB. in the interest of brevity, minor changes to grammar and punctuation are not captured in this amendment document).

4. IMPLEMENTATION OF THE AMENDMENT

This amendment will be issued as Protocol Version 2, Date 09 Jul 2015. It will be kept in the study master file at GW and in each investigator and pharmacy site file, if applicable.

5. PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 1, Dated 26 Jan 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 1 (Protocol Version 2, Dated 09 Jul 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
Investigator Agreement, pg 2; Section 1, Protocol Synopsis, Study Title, pg 3	A phase 2, single -blind, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)	A phase 2, <u>double</u> -blind, <u>randomized</u> , placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)	See section 3.1
Title page, pg 1	A phase H , single -blind, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)	A phase <u>2</u> , <u>double</u> -blind, <u>randomized</u> , placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)	See section 3.7
Cover Page, pg 1	GW RESEARCH LTD SOVEREIGN HOUSE, VISION PARK, HISTON, CAMBRIDGE CAMBS , CB24 9BZ	GW RESEARCH LTD SOVEREIGN HOUSE, VISION PARK, <u>CHIVERS WAY</u> HISTON, CAMBRIDGE CB24 9BZ	See section 3.7
Cover Page, pg 1 Confidentiality Statement	This document contains confidential information of GW Research Ltd that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board.	This document contains confidential information of GW Research Ltd that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board/ <u>Independent Ethics Committee</u> .	See section 3.7
Section 1, Protocol Synopsis, Study	This is a phase 2, single -blind, placebo-controlled study in 20 patients. • All -patients will be given placebo first followed	This is a phase 2, <u>double</u> -blind, <u>randomized</u> , placebo-controlled study in 20 patients. • <u>Patients will be randomized in a 4:1 ratio to</u>	See section 3.1

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 1, Dated 26 Jan 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 1 (Protocol Version 2, Dated 09 Jul 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
Design, pg 3	<p>by CBD during the course of the study. Patients will receive placebo in the first part of the single-blind phase (Days 2 to 26) and CBD during the second part of the single-blind phase (Day 27 onwards).</p> <ul style="list-style-type: none"> (...) Patients that do not continue onto the OLE will taper off of CBD over a 10 day period and will have a telephone follow-up visit four weeks after the end of taper day on Day 89. <p>(...)</p>	<p><u>receive 20 mg/kg GWP42003-P or placebo from days 2 to 33.</u></p> <ul style="list-style-type: none"> (...) Patients that do not continue onto the OLE will taper off of <u>GWP42003-P</u> over a 10 day period and will have a telephone follow-up visit four weeks after the end of taper day on Day <u>71</u>. <p>(...)</p>	See section 3.3.2
Section 1, Protocol Synopsis, Study Design, pg 3	<p>(...)</p> <ul style="list-style-type: none"> Day 1 (Visit 2), patients will not be dosed with investigational medicinal product (IMP) but will continue to take CLB at a stable dose. <p>(...)</p>	<p>(...)</p> <ul style="list-style-type: none"> Day 1 (Visit 2), patients will not be dosed with <u>GWP42003-P/placebo</u> but will continue to take CLB at a stable dose. <p>(...)</p>	See section 3.3.1
Section 1, Protocol Synopsis, Study Design, pg 3	<p>(...)</p> <ul style="list-style-type: none"> Day 2 (Visit 2), patients will begin the up-titration with placebo to an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). After up-titration with placebo, the patients will remain on the maintenance dose for 14 days (Days 12 to 25). On Day 27 (Visit 3), patients will begin the up-titration with CBD to the maintenance dose of 20 mg/kg/day over a period of 10 days (Days 27 to 36). After up-titration with CBD, the patients will remain on the maintenance dose for a further 	<p>(...)</p> <ul style="list-style-type: none"> Day 2 (Visit 2), patients will begin the up-titration with <u>GWP42003-P or placebo</u> to <u>a maintenance dose</u> or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). <u>Day 12 (Visit 3), patients will attend the study site to check safety and compliance.</u> After up-titration with <u>GWP42003-P or placebo</u>, the patients will remain on the maintenance dose for <u>21</u> days (Days 12 to <u>32</u>). 	See section 3.1

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Section 1, Protocol Synopsis, Study Design, pg 3	<p>14 days (Day 37 to 51).</p> <ul style="list-style-type: none"> On Day 52 (Visit 4), patients will be invited to receive CBD in the OLE period. (...) If the patient does not enter the OLE period (...) with end of taper on Day 61 (Visit 5). <p>PK samples will be taken on the day of enrollment (Visit 2, Day 1), after completing 14 days treatment on placebo (Visit 3, Day 26) and prior to starting on CBD, and after the completing 14 days treatment on CBD (Visit 4, Day 451). The PK assessments will therefore capture the following combinations of CLB and IMP:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and placebo. Third PK Assessment: CLB and CBD. <p>(...)</p>	<ul style="list-style-type: none"> On Day 34 (Visit 4), patients will be invited to receive <u>GWP42003-P</u> in the OLE period. (...) If the patient does not enter the OLE period (...) with end of taper on Day 43 (Visit 5). <p>PK samples will be taken on the day of enrollment (Visit 2, Day 1) <u>and</u> after completing <u>21</u> days treatment on <u>GWP42003-P or</u> placebo (Visit 4, Day 33). The PK assessments will therefore capture the following combinations of CLB and <u>GWP42003-P</u>:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and <u>GWP42003-P or</u> placebo. <p>(...)</p>	See section 3.1
Section 1, Protocol Synopsis, Study Design, pg 3-4	<p>(...)</p> <p>The IMP should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze (...) CBD and CBD major metabolites. 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 adverse events (AEs) that may occur whilst receiving IMP (...)</p>	<p>(...)</p> <p>The <u>GWP42003-P/placebo</u> should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze (...) CBD, CBD major metabolites, <u>Δ9-tetrahydrocannabinol (THC) and THC major metabolites</u>. Patients will be required to keep a paper diary to note the time and dose of <u>GWP42003-P</u> and CLB administration each morning and evening and to record any adverse events (AEs) that may occur whilst receiving <u>investigational medicinal product (IMP)</u> (...)</p>	See section 3.3.1 and 3.4
Section 1, Protocol Synopsis, Secondary	(...)	<p>(...)</p> <ul style="list-style-type: none"> <u>Abuse liability</u> <p><u>PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$)</u></p>	See section 3.4

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Endpoint(s), pg 4-5		<u>t_{1/2}</u> of the following analytes: • <u>THC</u> • <u>THC major metabolites</u>	
Section 1, Protocol Synopsis, Summary of Participant Eligibility Criteria, pg 5-6	<p>(...)</p> <ul style="list-style-type: none"> • Patient must have experienced at least one seizure of any type (i.e., tonic-clonic, tonic, clonic, atonic seizures) within the two months prior to randomization. <p>(...)</p> <ul style="list-style-type: none"> • Intervention with vagus (...) throughout the duration of the study. • Patients must abstain from alcohol during the single-blind phase of the study. <p>(...)</p> <ul style="list-style-type: none"> • Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain for the duration of the study. <p>(...)</p> <ul style="list-style-type: none"> • Female patients must have a negative pregnancy test and be willing and able to use a reliable method of contraception throughout the trial and for three months after last dose. In the context of this trial, an effective method is defined as those which result in low failure rate (i.e., less than 1% per year) when used consistently and correctly such as: combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal 	<p>(...)</p> <ul style="list-style-type: none"> • Patient must have experienced at least one seizure of any type (i.e., <u>convulsive</u>; tonic-clonic, tonic, clonic, atonic; <u>focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness or focal seizures evolving to bilateral secondary generalization</u>) within the two months prior to randomization. <p>(...)</p> <ul style="list-style-type: none"> • Intervention with vagus (...) throughout the <u>blinded phase</u> of the study. • Patients must abstain from alcohol during the <u>blinded</u> phase of the study. <p>(...)</p> <ul style="list-style-type: none"> • Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain <u>during the blinded phase</u> of the study. <p>(...)</p> <ul style="list-style-type: none"> • Female patient <u>is of child bearing potential or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use highly effective</u> contraception <u>for the duration of the study</u> and for three months <u>thereafter. Highly effective methods of contraception are</u> defined as those, <u>alone or in combination, that</u> result in <u>a</u> low failure rate (i.e., 	<p>See section 3.5</p> <p>See section 3.5</p> <p>See section 3.5</p> <p>See section 3.5</p>

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Section 1, Protocol Synopsis, Summary of Participant Eligibility Criteria, pg 6-7	<p>occlusion, vasectomized partner or sexual abstinence.</p> <ul style="list-style-type: none"> Female patient who is pregnant, lactating (...) Patient has significantly impaired hepatic function, as determined at screening or enrollment (Alanine aminotransferase [ALT] >5 × upper limit of normal [ULN] or total bilirubin [TBL] >2 × ULN) OR the ALT or Aspartate aminotransferase (AST) >3 × ULN and (TBL >2 × ULN or international normalized ratio [INR] >1.5). <p>(...)</p>	<p>less than 1% per year) when used consistently and correctly. <u>Such methods include hormonal</u> contraceptives, intrauterine devices/ hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.</p> <ul style="list-style-type: none"> Female patient who is pregnant (<u>positive pregnancy test</u>), lactating (...) Patient has significantly impaired hepatic function at screening (<u>Visit 1</u>) or enrollment (<u>Visit 2</u>), <u>defined as any of the following:</u> <ul style="list-style-type: none"> Alanine aminotransferase (<u>ALT</u>) or <u>Aspartate aminotransferase (AST)</u> >5 × upper limit of normal (<u>ULN</u>). ALT or AST >3 × ULN and <u>total bilirubin</u> (TBL) >2 × ULN or international normalized ratio (<u>INR</u>) >1.5. <u>ALT or AST >3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).</u> <p>(...)</p>	<p>See section 3.5</p> <p>See section 3.6</p>
Section 1, Protocol Synopsis, Criteria for Withdrawal, pg 8	(...)	<p>(...)</p> <ul style="list-style-type: none"> <u>Any other IMP is taken as part of a clinical trial during the study.</u> 	See section 3.5
Section 1, Protocol	GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener	GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener	See section 3.3.2

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Synopsis, Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration, pg 8	(sucralose) and strawberry flavoring). (...)	(sucralose) and strawberry flavoring), <u>pale yellow in color.</u> (...)	
Section 1, Protocol Synopsis, Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration, pg 8	<p>(...)</p> <ul style="list-style-type: none"> Day 2 (Visit 2), patients will begin the up-titration with placebo to an equivalent maintenance dose of 20 mg/kg/day (...) After up-titration with placebo, the patients will remain on the maintenance dose for 14 days (Days 12 to 25). On Day 27 (Visit 3), patients will begin the up-titration with CBD to the maintenance dose of 20 mg/kg/day over a period of 10 days (Days 27 to 36). After up-titration with CBD, the patients will remain on the maintenance dose for a further 14 days (Day 37 to 50). <p>Please refer to Table 8.1-4 for details of the up-titration doses for CBD and placebo for each of the ten days. On Day 52 (Visit 4), patients will be invited to receive CBD in the open-label extension (OLE) period. (...)</p>	<p>(...)</p> <ul style="list-style-type: none"> Day 2 (Visit 2), patients will begin the up-titration with <u>GWP42003-P or placebo to a maintenance dose or</u> an equivalent maintenance dose of 20 mg/kg/day (...) After up-titration with <u>GWP42003-P or placebo</u>, the patients will remain on the maintenance dose for <u>21</u> days (Days 12 to <u>32</u>). <p>Please refer to Table 8.1.<u>2</u>-1 for details of the up-titration doses for <u>GWP42003-P</u> and placebo for the ten day <u>taper period</u>. On Day <u>34</u> (Visit <u>4</u>), patients will be invited to receive <u>GWP42003-P</u> in the OLE period. (...)</p>	<p>See section 3.1</p> <p>See section 3.7, 3.3.2 and section 3.1</p>
Section 1, Protocol	(...)	(...) <u>Clobazam will be an IMP for the blinded section of</u>	See section 3.3.1

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Synopsis, Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration, pg 8		<u>the study. The patients' own supply of Clobazam will be used.</u>	
Section 1, Protocol Synopsis, Control Group, pg 8	All patients will receive placebo in the first part of the single-blind phase (Days 2 to 26) and CBD during the second part of the single-blind phase (Day 27 onwards). There is no separate control group.	<u>The control group will receive an equal volume of matching placebo.</u>	See section 3.1
Section 1, Protocol Synopsis, Procedures, pg 8-9	VISIT 1 - Screening (Day -7) The following observations (...) ECG and vital signs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, urinalysis (...) (...) Patients who satisfy all inclusion (...) and then begin the seven-day baseline period. (...) This visit will occur 7 days after Visit 1.	VISIT 1 - Screening (Day -14 to -7) The following observations (...) ECG, vital signs <u>and AEs</u> . Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, <u>alcohol testing, THC testing</u> , urinalysis (...) (...) Patients who satisfy all inclusion (...) and then begin the baseline period. (...) This visit will occur 7- <u>14</u> days after Visit 1.	See section 3.1 See section 3.1 and 3.7 See section 3.1 See section 3.1
Section 1, Protocol Synopsis, Procedures, pg 9	VISIT 2 - Enrollment (Day 1) +3 days window (...) The following observations will be made at Visit 2: (...) physical examination (including height and body weight, review of seizure diary and AEs. Clinical laboratory samples (blood and urine) will be taken for	VISIT 2 - Enrollment (Day 1) +3 days window (...) The following observations will be made at Visit 2: (...) physical examination (including body weight), review of <u>patient</u> diary and AEs. Clinical laboratory samples (blood and urine) will be taken for	See section 3.7 and 3.2 'Seizure' diary replaced with 'patient' diary (throughout) as

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	hematology, biochemistry and urinalysis. (...)	hematology, biochemistry, <u>alcohol testing</u> and urinalysis. (...)	the diary includes multiple items, not just seizure information.
Section 1, Protocol Synopsis, Procedures, pg 9	(...) (...)	(...) <u>Blood samples will also be taken for genetic testing if additional consent has been obtained.</u> (...)	See section 3.2
Section 1, Protocol Synopsis, Procedures, pg 9	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. (...)	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD ₂ major metabolites, <u>THC and THC major metabolites.</u> (...)	See section 3.4
Section 1, Protocol Synopsis, Procedures, pg 9-10	VISIT 2 - Enrollment (Day 2) (...)Following completion of the PK sampling process (...), physical examination (including height and body weight), vital signs, and AEs. IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. (...) Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period. (...)	VISIT 2 - Enrollment (Day 2) (...)Following completion of the PK sampling process (...), physical examination (including body weight), vital signs and AEs. <u>GWP42003-P/placebo</u> will be dispensed and both the morning dose of CLB and <u>GWP42003-P/placebo</u> will be taken in clinic. (...) Each patient will then receive their <u>GWP42003-P/placebo</u> for the 10 day titration period followed by the <u>21</u> day maintenance period. (...)	See section 3.2 and section 3.7 See section 3.3.1 See section 3.1
Section 1, Protocol Synopsis, Procedures, pg 10	(...) (...)	(...) <u>VISIT 3 – Day 12 +3 day window</u> <u>This visit will occur 11 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following</u>	See section 3.1

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		<u>observations will be made at Visit 3: concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, AEs and review of patient diary completion. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.</u> (...)	
Section 1, Protocol Synopsis, Procedures, pg 10	(...) VISIT 3 - Day 26 ±3 days window This visit will occur 25 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP . The following observations will be made at Visit 3 (Day 26): (...) physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. (...)	(...) VISIT <u>4</u> - Day <u>33</u> ±3 days window This visit will occur 32 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused <u>GWP42003-P/placebo</u> . The following observations will be made at Visit <u>4</u> (Day <u>33</u>): (...) physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, <u>alcohol testing</u> and urinalysis. (...)	See section 3.1 See section 3.3.1 See section 3.1 See section 3.7 See section 3.2
Section 1, Protocol Synopsis, Procedures, pg 10	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of IMP . (...)	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, <u>THC and THC major metabolites</u> . A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of <u>GWP42003-P/placebo</u> . (...)	See section 3.4 See section 3.3.1
Section 1, Protocol Synopsis,	(...) VISIT 3 - Day 27 (...)	(...) VISIT <u>4</u> - Day <u>34</u> (...)	See section 3.1 and section 3.2

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Procedures, pg 10 Section 1, Protocol Synopsis, Procedures, pg 10	<p>The final PK sample will be collected 24 hours after the Day 25 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 27: (...)physical examination (including height and body weight), vital signs, and AEs.</p> <p>IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1. Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period.</p> <p>VISIT 4 – Day 51 ±3 days window This visit will occur 50 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP. The following observations will be made at Visit 4 (Day 51): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of</p>	<p>The final PK sample will be collected 24 hours after the Day <u>33</u> morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day <u>34</u>: (...) physical examination (including body weight), vital signs, and AEs.</p>	See section 3.1 and section 3.2

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Section 1, Protocol Synopsis, Procedures, pg 10	<p>IMP. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients are expected to remain in clinic throughout this PK sampling. The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 4 – Day 52</p> <p>This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 51 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 52: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.</p> <p>At the end of the blinded phase of the study on Day 52 providing the investigator and patient both agree, patients will be invited to continue taking IMP and to enter the OLE.</p> <p>Patients who enter the OLE will be dispensed CBD on Day 52.</p> <p>(...)</p>	<p><u>On Day 34</u>, providing the investigator and patient both agree, patients will be invited to continue taking <u>GWP42003-P</u> and to enter the OLE.</p> <p>Patients who enter the OLE will be dispensed <u>GWP42003-P</u> on Day 34.</p> <p>(...)</p>	<p>See section 3.1 and section 3.2</p> <p>See section 3.1 and 3.3.1</p>
Section 1, Protocol Synopsis, Procedures, pg 11	<p>(...)</p> <p>Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of IMP. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 60.</p> <p>(...)</p>	<p>(...)</p> <p>Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of <u>GWP42003-P</u>. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42.</p> <p>(...)</p>	<p>See section 3.3.1</p> <p>See section 3.1</p>

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Section 1, Protocol Synopsis, Procedures, pg 11	(...) VISIT 5 – Day 61 (End of Taper) +3 days window This visit will occur 60 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including height and body weight) and vital signs (...) (...)	(...) VISIT 5 – Day <u>43</u> (End of Taper) +3 days window This visit will occur <u>42</u> days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE. All <u>GWP42003-P/placebo</u> (used and unused) will be collected and a check of the returned <u>GWP42003-P/placebo</u> against usage must be made. A physical examination (including body weight), <u>ECG</u> and vital signs (...) <u>The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</u> (...)	See section 3.1 See section 3.3.1 See section 3.2 To be consistent with Visit 12 ECG See section 3.2
Section 1, Protocol Synopsis, Procedures, pg 11	(...) SAFETY FOLLOW-UP CALL - Day 89 ±3 days This visit is required for patients who do not enter the OLE study on Day 52 , or who withdraw from the study early. (...) The following observations will be made on Day 89 : (...)	(...) <u>VISIT 6 -</u> SAFETY FOLLOW-UP CALL - Day <u>71</u> ±3 days This visit is required for patients who do not enter the OLE study on Day <u>34</u> , or who withdraw from the study early. (...) The following observations will be made on Day <u>71</u> : (...)	See section 3.1
Section 1, Protocol Synopsis, Procedures, pg 11	(...)	(...) <u>At the point of entry to the OLE, patients will be transitioned to the OLE treatment over a 10 day period in order to maintain blinding.</u>	To provide clarity over how patients will transition from the blinded to

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	Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 52) (...). The visit schedule is calculated relative to Visit 4 (Day 52). (...)	Patients who enter the OLE will be dispensed IMP at Visit 4 (Day <u>34</u>) (...). The visit schedule is calculated relative to Visit 4 (Day <u>34</u>). (...)	OLE. See section 3.1
Section 1, Protocol Synopsis, Procedures, pg 11-13	<p>VISIT 5 (OLE) – Two Weeks ±3 days This visit will occur two weeks after Visit 4 (Day 51). (...). physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. (...)</p> <p>VISIT 6 (OLE) – One Month ±3 days This visit will occur one month after Visit 4 (Day 51). (...). physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. (...)</p> <p>VISIT 7 (OLE) – Two Months ±3 days This visit will occur two months after Visit 4 (Day 51). (...). physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. (...)</p> <p>VISIT 8 (OLE) - Three Months ±7 days This visit will occur three months after Visit 4 (Day 51). (...). physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. (...)</p> <p>VISIT 9 (OLE) - Six Months ±7 days This visit will occur six months after Visit 4 (Day 51). (...). physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. (...)</p> <p>VISIT 10 (OLE) - Nine Months ±7 days This visit will occur nine months after Visit 4 (Day</p>	<p>VISIT 5 (OLE) – Two Weeks ±3 days This visit will occur two weeks after Visit 4 (Day <u>34</u>). (...). physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. (...)</p> <p>VISIT 6 (OLE) – One Month ±3 days This visit will occur one month after Visit 4 (Day <u>34</u>). (...). physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. (...)</p> <p>VISIT 7 (OLE) – Two Months ±3 days This visit will occur two months after Visit 4 (Day <u>34</u>). (...). physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. (...)</p> <p>VISIT 8 (OLE) - Three Months ±7 days This visit will occur three months after Visit 4 (Day <u>34</u>). (...). physical examination (including height and body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. (...)</p> <p>VISIT 9 (OLE) - Six Months ±7 days This visit will occur six months after Visit 4 (Day <u>34</u>). (...). physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. (...)</p> <p>VISIT 10 (OLE) - Nine Months ±7 days This visit will occur nine months after Visit 4 (Day</p>	<p>See section 3.1, 3.2 and 3.7</p> <p>See section 3.1, 3.2 and 3.7</p>

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Section 1, Protocol Synopsis, Procedures, pg 11-13	51 . (...) physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. (...) VISIT 11 – Twelve Months (OLE End of Treatment) ±7 days This visit will occur twelve months after Visit 4 (Day 51). (...) physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. (...)	34 . (...) physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs.(...) VISIT 11 – Twelve Months (OLE End of Treatment) ±7 days This visit will occur twelve months after Visit 4 (Day 34). (...) physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. (...)	See section 3.1, 3.2 and 3.7
Section 1, Protocol Synopsis, Procedures, pg 13-14	(...) VISIT 12 - OLE End of taper +3 days (...) A physical examination (including height and body weight), (...) (...) SAFETY FOLLOW-UP CALL (OLE) (...)	(...) VISIT 12 - OLE End of taper +3 days (...) A physical examination (including body weight), (...) <u>The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</u> (...) <u>VISIT 13 - SAFETY FOLLOW-UP CALL (OLE)</u> (...)	See section 3.2 See section 3.2 See section 3.7
Section 1, Protocol Synopsis, Procedures, pg 14	(...)	(...) <u>Monitoring of Drug Abuse Liability</u> <u>During the routine collection of AEs in this study, if AEs are reported which can illuminate an abuse potential signal (specific AEs detailed in Section 9.1.16.1.1), then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussions of the event(s) with the patient/caregiver.</u>	See section 3.2

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Section 1, Protocol Synopsis, Procedures, pg 14		<u>The second trigger that will require the investigator or study coordinator to discuss abuse potential signals with the patient/caregiver is drug accountability issues regarding overuse of the IMP or missing IMP bottles.</u> <u>Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.</u> <u>A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.</u>	See section 3.2
Section 1, Protocol Synopsis, Statistical Considerations, pg 14	Plasma concentration data will be analyzed to estimate pharmacokinetic endpoints C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ of the following analytes CLB, N-CLB, CBD and major metabolites. (...) (...) In order to assess (...) linear mixed effect model with treatment (CBD or placebo) as fix effect (...) (...)	Plasma concentration data will be analyzed to estimate PK endpoints C_{max} , <u>t_{max}</u> , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and <u>$t_{1/2}$</u> of the following analytes: CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites . (...) (...) In order to assess (...) linear mixed effect model with treatment (CLB or CLB+CBD) as a fixed effect (...) (...) (...)	See section 3.7 See section 3.4 See section 3.1 and section 3.7
Section 1, Protocol Synopsis,	Sovereign House Vision Park Histon	GW Research Ltd Sovereign House Vision Park	Added sponsor name and corrected

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Sponsor, pg 14	Cambridge CB24 9BZ United Kingdom	Chivers Way Histon Cambridge CB24 9BZ United Kingdom	sponsor address.
Section 1, Figure 1-1, Figure 1-2, Study Design and Treatment Schema, pg 16-17	<< Note: See Appendix 1.1 for detailed changes >>	<< Note: See Appendix 1.1 for detailed changes >>	See section 3.1
Section 1, List of Abbreviations, pg 26-27	(...) AUC _(0-∞) (...) DILI EC (...) t _{1/2} (...) (...)	(...) AUC _(0-∞) (...) Area under the concentration time curve from zero to infinity with extrapolation of the terminal phase EC (...) t _{1/2} (...) (...) Terminal half-life	See section 3.7 See section 3.7
Section 1, Definition of Terms, pg 28	(...) Baseline period The seven-day period from screening (Visit 1) to enrollment (Visit 2). (...) End of treatment Completion of the treatment period (Visit 5 or Visit 14) or withdrawal. (...)	(...) Baseline period The period from screening (Visit 1) to enrollment (Visit 2). (...) End of treatment Completion of the treatment period (Visit 5 or Visit <u>12</u>) or withdrawal.(...)	See section 3.1

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Section 3.3, Rationale, pg 31	(...) (...) active metabolite N-desmethylelobazam (N-CLB), amongst others. (...)	(...) (...) active metabolite N-CLB, amongst others. (...)	See section 3.7
Section 3.3.1, Selection of Study Doses, pg 32	(...) • >20 mg/kg ≤ 30 mg/kg CBD n=40 (64%) • >30 mg/kg ≤ 40 mg/kg CBD n=4 (6%) (...) 11 patients had a daily CBD dose of (...).	(...) • >20 mg/kg ≤ <u>30</u> mg/kg <u>GWP42003-P</u> n=40 (64%) • >30 mg/kg ≤ <u>40</u> mg/kg <u>GWP42003-P</u> n=4 (6%) (...) <u>Eleven</u> patients had a daily <u>GWP42003-P</u> dose of (...).	See section 3.7
Section 4.1, Study Design, pg 32–33	This phase 2, placebo-controlled study consists of a 52 day, single -blind phase followed by an optional maximum one year OLE. (...) The IMP will be taken twice daily immediately after their CLB dose. (...) Patients will enter the study and begin a 10 day placebo titration phase. During this period patients will be up-titrated to an equivalent maintenance dose of 20 mg/kg/day. Patients will continue to take this maintenance dose of placebo for 14 -days (Days 12 to 26). On Day 27 patients will begin a 10 day CBD titration phase. During this period patients will be up-titrated to a maintenance dose of 20 mg/kg/day CBD. Patients will continue to take this maintenance dose for 14 days (Days 37 to 50). Upon completion of the single blind phase of the study (Day 52) patients will be invited to receive CBD during the OLE phase. (...)	This phase 2, placebo-controlled study consists of a <u>34</u> day, <u>double</u> -blind phase followed by an optional maximum one year OLE. (...) <u>GWP42003-P /placebo</u> will be taken twice daily immediately after their CLB dose. (...) Patients will enter the study and begin a 10 day <u>GWP42003-P or</u> placebo titration phase. During this period patients will be up-titrated to a maintenance dose <u>or equivalent</u> of 20 mg/kg/day. Patients will continue to take this maintenance dose of <u>GWP42003-P or</u> placebo for <u>21</u> days (Days 12 to <u>32</u>). Upon completion of the <u>treatment period</u> (Day <u>34</u>) patients will be invited to receive <u>GWP42003-P</u> during the OLE phase. (...)	See section 3.1 See section 3.3.1 See section 3.1 See section 3.1

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Section 4.1, Study Design, pg 32–33	<p>If a patient chooses not to enter the OLE, (...) they will taper off their CBD treatment (...). For those patients not entering the OLE, dosing will end on Day 60 and they will receive a telephone follow-up visit four weeks after the end of IMP dosing (Day 89). PK samples will be taken on three occasions during the single blind phase of the study: (...) <ul style="list-style-type: none"> Day 26 (Visit 3) following 14 days of placebo maintenance (patients will be taking CLB and placebo). Day 51 (Visit 4) following 14 days of CBD maintenance (patients will be taking CLB and CBD). (...) PK samples will be quantitatively analyzed for CLB, N-CLB (primary metabolite of CLB), CBD and CBD major metabolites. Patients should try to be consistent in the timing of their food intake in relation to dosing throughout the single blind phase of the study. Upon entry into the OLE the dose of CBD may be adjusted up or down to a maximum of 30 mg/kg/day. (...) More detailed information on treatment and study procedures are provided in Section 7 and Section 9 respectively.</p>	<p>If a patient chooses not to enter the OLE, (...) they will taper off their <u>GWP42003-P/placebo</u> treatment (...). 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 <u>GWP42003-P/placebo</u> dosing (Day <u>71</u>). PK samples will be taken on <u>two</u> occasions during the <u>blinded</u> phase of the study: (...) <ul style="list-style-type: none"> Day <u>33</u> (Visit <u>4</u>) following <u>21</u> days of <u>GWP42003-P or</u> placebo maintenance (patients will be taking CLB and <u>GWP42003-P or</u> placebo). (...) PK samples will be quantitatively analyzed for CLB, N-CLB, CBD, CBD major metabolites, <u>THC and THC major metabolites</u>. Patients should try to be consistent in the timing of their food intake in relation to dosing throughout the <u>blinded</u> phase of the study. Upon entry into the OLE the dose of <u>GWP42003-P and other AEDs</u> may be adjusted up or down to a maximum of 30 mg/kg/day. (...) More detailed information on treatment and study procedures are provided in Section <u>8</u> and Section 9 respectively.</p>	<p>See section 3.1</p> <p>See section 3.1 See section 3.3.1 See section 3.1</p> <p>See section 3.4</p> <p>See section 3.1 See section 3.7</p> <p>See section 3.7</p>
Section 4.1.1, Primary Endpoint, pg 34	<p>(...)</p> <ul style="list-style-type: none"> N-desmethylelobazam (N-CLB) <p>(...)</p>	<p>(...)</p> <ul style="list-style-type: none"> N-CLB <p>(...)</p>	See section 3.7

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Section 4.1.2, Secondary Endpoints, pg 34	(...)	(...) • <u>Abuse liability</u> <u>PK parameters (C_{max}, t_{max}, AUC_(0-∞), AUC_(0-t), t_{1/2}) of the following analytes:</u> • <u>THC</u> • <u>THC major metabolites</u>	See section 3.4
Section 4.2, Number of Centers, pg 34	An estimated number of two centers is expected to participate in this study.	An estimated number of <u>seven</u> centers <u>are</u> expected to participate in this study.	More centers required to conduct this study.
Section 5.1, GWP42003-P Oral Solution, pg 35	GWP42003-P oral solution is presented as an oily solution (...) (...)	GWP42003-P oral solution is presented as a <u>pale yellow</u> oily solution (...) (...)	See section 3.3.2
Section 5.3, Packaging, Storage and Drug Accountability (Cannabidiol/Placebo), pg 35	5.3 Packaging, Storage and Drug Accountability	5.3 Packaging, Storage and Drug Accountability <u>(Cannabidiol/Placebo)</u>	See section 3.3.1
Section 5.4, Clobazam, pg 37	N/A	<u>5.4 Clobazam</u> <u>Patients will use their own supply of Clobazam throughout the study. Clobazam usage will be recorded by the investigator. Clobazam is only an IMP for the blinded phase of the study.</u>	See section 3.3.1
Section 6.1, Inclusion Criteria, pg 37-38	(...) 6.1.4 Patient must have experienced at least one seizure of any type (i.e., tonic-clonic, tonic, clonic, atonic seizures) within the two months prior to	(...) 6.1.4 Patient must have experienced at least one seizure of any type (i.e., <u>convulsive</u> ; tonic-clonic, tonic, clonic, atonic; <u>focal; focal seizures with</u>	See section 3.5

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Section 6.1, Inclusion Criteria, pg 37-38	randomization. (...) 6.1.8 Patients must abstain from alcohol during the single -blind phase of the study. (...)	<u>retained consciousness and a motor component, focal seizures with impaired consciousness, focal seizures evolving to bilateral secondary generalization</u> within the two months prior to randomization. (...) 6.1.8 Patients must abstain from alcohol during the <u>blinded</u> phase of the study. (...)	See section 3.5 See section 3.1
Section 6.2, Exclusion Criteria, pg 38-39	(...) 6.2.7 Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain for the duration of the study. (...) 6.2.13 Female patients must have a negative pregnancy test and be willing and able to use a reliable method of contraception throughout the trial and for three months after last dose. In the context of this trial, an effective method is defined as those which result in low failure rate (i.e., less than 1% per year) when used consistently and correctly such as: combined or progesterone-only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence. 6.2.14 Female patient who is pregnant, lactating (...) (...) 6.2.18 Patient has significantly impaired hepatic function, as determined at screening or enrollment	(...) 6.2.7 Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain <u>during the blinded phase</u> of the study. (...) 6.2.13 Female patient <u>is of child bearing potential or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner</u> use <u>highly effective</u> contraception <u>for the duration of the study</u> and for three months <u>thereafter. Highly effective methods of contraception are</u> defined as those, <u>alone or in combination, that</u> result in <u>a</u> low failure rate (i.e., less than 1% per year) when used consistently and correctly. <u>Such methods include hormonal</u> contraceptives, intrauterine devices/ hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence. 6.2.14 Female patient who is pregnant (<u>positive pregnancy test</u>), lactating (...) (...) 6.2.18 Patient has significantly impaired hepatic	See section 3.5 See section 3.5 See section 3.5

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Section 6.2, Exclusion Criteria, pg 38-39	{Alanine aminotransferase {ALT} >5 × upper limit of normal {ULN} or total bilirubin {TBL} >2 × ULN OR the ALT or Aspartate aminotransferase (AST) >3 × ULN and (TBL >2 × ULN or international normalized ratio {INR} >1.5). (...) (...)	function at screening (<u>Visit 1</u>) or enrollment (<u>Visit 2</u>), <u>defined as any of the following:</u> <ul style="list-style-type: none"> - Alanine aminotransferase (<u>ALT</u>) or <u>Aspartate aminotransferase (AST)</u> >5 × upper limit of normal (<u>ULN</u>). - ALT or AST >3 × ULN and <u>total bilirubin (TBL)</u> >2 × ULN or international normalized ratio (<u>INR</u>) >1.5. - <u>ALT or AST >3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).</u> (...)	See section 3.6 See section 3.6 See section 3.6 See section 3.6
Section 7.1, Treatment Assignment, pg 40	(...) GWP will provide all IMP packed and labelled. (...)	(...) GWP will provide all <u>GWP42003-P/placebo</u> packed and labelled. (...)	See section 3.3.1
Section 7.2, Randomization, pg 40	This is a single-blind study with all patients following the same treatment regimen.	This is a <u>double-blind study. Patients will be randomised in a 4:1 ratio to receive 20 mg/kg GWP42003-P or placebo.</u>	See section 3.1
Section 8.1, Investigational Medicinal Product Dosage, Administration and Schedule, pg 41	The IMP will be presented as an oral solution containing either the active pharmaceutical ingredient and excipients (in the case of GWP42003-P) or only excipients (in the case of placebo). For details regarding IMP formulations, see Section 5. The IMP will consist of two types of medication: <ul style="list-style-type: none"> • GWP42003-P Oral Solution containing 100 mg/mL CBD. • Placebo Oral Solution containing excipients. 	The IMP will consist of <u>three</u> types of medication: <ul style="list-style-type: none"> • GWP42003-P Oral Solution containing 100 mg/mL CBD. • Placebo Oral Solution containing excipients. • <u>Clobazam (patient supplied).</u> 	See section 3.3.2 See section 3.3.1 See section 3.3.1

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	<p>All patients will be weighed during Visit 2 and the daily volumes of IMP solution to be taken (...) (...)</p> <p>Each patient will take their first dose of IMP at Visit 2, Day 2 in the clinic. Patients not entering the OLE will take their final maintenance dose of IMP at Visit 4 (Day 51) in the clinic. (...)</p>	<p><u>The GWP42003-P/placebo will be presented as an oral solution containing either the active pharmaceutical ingredient and excipients (in the case of GWP42003-P) or only excipients (in the case of placebo). For details regarding GWP42003-P/placebo formulations, see Section 5.</u></p> <p>All patients will be weighed during <u>the study visits</u> and the daily volumes of <u>GWP42003-P/placebo</u> solution to be taken (...) (...)</p> <p>Each patient will take their first dose of <u>GWP42003-P/placebo</u> at Visit 2, Day 2 in the clinic. Patients not entering the OLE will take their final maintenance dose of <u>GWP42003-P/placebo</u> at Visit 4 (Day <u>33</u>) in the clinic. (...)</p> <p><u>Patients will use their own supply of Clobazam throughout the study. Patients will continue on the dose that they were on at screening for the blinded phase of the study. Clobazam will only be an IMP for the blinded section of the study.</u></p>	<p>See section 3.3.2</p> <p>See section 3.7 See section 3.3.1</p> <p>See section 3.3.1</p> <p>See section 3.3.1 and 3.1</p> <p>See section 3.3.1</p>
Section 8.1.1, Dose Administration, pg 41	The IMP will be administered orally (...) The IMP should be taken immediately after the patient's usual CLB administration. The IMP should be swallowed, (...) (...)	<u>GWP42003-P/placebo</u> will be administered orally (...) <u>GWP42003-P/placebo</u> should be taken immediately after the patient's usual CLB administration. The <u>GWP42003-P/placebo</u> should be swallowed, (...) (...)	See section 3.3.1
Protocol Section 8.1.2, Dose Escalation and	Patients will enter the single blind phase of the study and will be up-titrated over ten days (Day 2 to Day 11) to an equivalent maintenance dose of placebo of	Patients will enter the blinded phase of the study and will be up-titrated over ten days (Day 2 to Day 11) to <u>a</u> maintenance dose <u>or equivalent</u> of	See section 3.3.1

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Dose Adjustments, pg 41-43	<p>20 mg/kg/day. From Day 27 to Day 36 patients will be up-titrated to a maintenance dose of 20 mg/kg/day CBD. (...)</p> <p>For those patients who do not enter the OLE the dose of CBD will taper off over 10 days beginning on Day 52. The patient will reduce the dose by 10% of the maintenance dose each day and treatment will end on Day 60.</p> <p>For patients who enter the OLE the maintenance dose of CBD may be adjusted up or down, depending on investigator opinion, to a maximum of 30 mg/kg/day.</p> <p><< Note: For changes to Table 8.1-4: See Appendix 1.2 >></p>	<p>GWP42003-P/placebo of 20 mg/kg/day. <u>If GWP42003-P is not tolerated then the dose can be reduced accordingly at the discretion of the investigator.</u> (...)</p> <p><<Note: For changes to Table 8.1.2-1: See Appendix 1.2 >></p> <p><u>The titration regimen defined above should be followed to the maximum dose (20 mg/kg/day). Should an AE occur during titration which is attributable to IMP or concomitant AED, then IMP dose should be reduced to the next lower dose. Any other changes in concomitant AED therapy should be reviewed with the medical monitor before being initiated.</u></p> <p><u>For those patients who do not enter the OLE the dose of GWP42003-P/placebo will taper off over 10 days beginning on Day 34. The patient will reduce the dose by 10% of the maintenance dose each day and treatment will end on Day 43. Patients who enter the OLE period will be transitioned to the OLE treatment over a 10-day period in order to maintain blinding, simultaneously down-titrating blinded GWP42003-P/placebo whilst up-titrating open-label GWP42003-P. As such, patients who were taking GWP42003-P during the blinded period will maintain their 20 mg/kg/day dose throughout the transition from the blinded period into the OLE</u></p>	See section 3.3.1

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Protocol Section 8.1.2, Dose Escalation and Dose Adjustments, pg 41-43		<u>period and patients who received placebo during the blinded period up-titrate slowly to the 20 mg/kg/day dose in the OLE period. After this has taken place, the maintenance dose of GWP42003-P may be adjusted up or down at the discretion of the investigator to a maximum of 30 mg/kg/day (no minimum).</u>	See section 3.3.1
Section 8.2, Concomitant Therapy, pg 43	Doses of any concomitant AEDs, (...) must remain stable throughout the study period . (...)	Doses of any concomitant AEDs, (...) must remain stable throughout the blinded phase of the study . If there are symptoms of toxicity suspected to be from a drug interaction, the investigator may adjust GWP42003-P/placebo or the CLB or other AEDs after discussion with the medical monitor. (...)	See section 3.3.2
Section 8.3, Prohibited Therapy During Study Period, pg 43	(...) Any other IMP taken as part of a clinical trial within six months or during the study.	(...) <u>If any other IMP is taken as part of a clinical trial within twelve weeks of the screening visit or during the study, the patient must be withdrawn from this study.</u>	See section 3.5
Section 8.5, Access to Blinded Treatment Assignment, pg 44	This is a single blind study. The identity of IMP assigned to patients will be known to the PI and the GWEP1428 study team at each site but will not be known by the patients.	<u>The identity of IMP assigned to patients will be held by the IVRS. The principal investigator (PI) at each center is responsible for all trial-related medical decisions and is responsible for ensuring that information on how to access the IVRS is available to the relevant staff in case of an emergency and unblinding is required. 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.</u>	See section 3.1

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Section 8.5, Access to Blinded Treatment Assignment, pg 44		<u>The investigator is encouraged to contact GW to discuss the rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of study medication will not be dependent upon the investigator receiving approval from GW (i.e., the investigator will be able to obtain the code break information independent of contacting GW).</u> <u>If the investigator does unblind they must contact GW within one working day of the event and must document the time, date and reasons for unblinding in the patient's CRF.</u>	See section 3.1
Section 9.1.1, Contraception, pg 45	(...) the patient must have agreed that if they or their partner are of child-bearing potential they are willing to use effective contraception (...) when used consistently and correctly such combined or progesterone (...)	(...) the patient must have agreed that if they or their partner are of child-bearing potential they are willing to use highly effective contraception (...) when used consistently and correctly such as combined or progesterone (...)	See section 3.5
Section 9.1.3, Demographics, pg 45 Section 15.5 Participant Confidentiality, pg 77	(...) ethnic origin (...)	(...) race (...)	See section 3.7
Section 9.1.6, Physical Examination, pg 46	(...) Physical examinations will include height and body weight measurements.	(...) Physical examinations will include height (at screening) and body weight measurements.	See section 3.7

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Section 9.1.9, Clinical Laboratory Sampling, pg 47	(...) (...) Table 9.1- 4 Hematology, Biochemistry, Urinalysis and THC Screen <table><tr><td>Biochemistry (serum)</td><td>(...)</td></tr><tr><td>(...)</td><td>(...)</td></tr><tr><td>Urea</td><td></td></tr></table>	Biochemistry (serum)	(...)	(...)	(...)	Urea		(...) <u>A serum alcohol test will be performed at Visits 1, 2 and 4.</u> (...) (...) Table 9.1. <u>9-1</u> Hematology, Biochemistry, Urinalysis and THC Screen <table><tr><td>Biochemistry (serum)</td><td>(...)</td></tr><tr><td>(...)</td><td>(...)</td></tr><tr><td>Urea <u>(BUN)</u></td><td></td></tr><tr><td><u>Triglycerides</u></td><td></td></tr></table>	Biochemistry (serum)	(...)	(...)	(...)	Urea <u>(BUN)</u>		<u>Triglycerides</u>		See section 3.2 See section 3.7 See section 3.7
Biochemistry (serum)	(...)																
(...)	(...)																
Urea																	
Biochemistry (serum)	(...)																
(...)	(...)																
Urea <u>(BUN)</u>																	
<u>Triglycerides</u>																	
Section 9.1.9, Clinical Laboratory Sampling, pg 47	(...) See Section 12.8 for guidance on evaluation of potential drug-induced liver injury (DILI). (...)	(...) See Section 12.8 for guidance on evaluation of potential drug-induced liver injury. (...)	See section 3.7														
Section 9.1.10, Pharmacokinetic Analyses, pg 48	The plasma concentration/time curves of CLB, N-CLB, CBD and CBD major metabolites will be assessed at Visit 2 (Day 1 and Day 2), Visit 3 (Day 26 and Day 27) and Visit 4 (Day 51 and Day 52) . Patients will be given their daily dose of clobazam at a scheduled time during Visit 2, Visit 3 and Visit 4 and the IMP immediately afterwards (Visit 3 and Visit 4 only) (...) (...) (...)	The plasma concentration/time curves of CLB, N-CLB, CBD, CBD major metabolites, <u>THC and THC major metabolites</u> will be assessed at Visit 2 (Day 1 and Day 2) <u>and</u> Visit <u>4</u> (Day <u>33</u> and Day <u>34</u>). Patients will be given their daily dose of clobazam at a scheduled time during Visit 2 and Visit 4 and the <u>GWP42003-P/placebo</u> immediately afterwards (Visit 4 only) (...) (...) (...)	See section 3.4 See section 3.1														
Section 9.1.11, Genetic Testing, pg 48	N/A	<u>9.1.11 Genetic Testing</u> <u>Genetic testing will only be conducted if specific consent is obtained from the participant. There is a separate informed consent form for this.</u> <u>Genetic testing will be conducted to look at the genes, CYP 2C19 and CYP 3A4, involved in the</u>	See section 3.2														

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		metabolization of AEDs and GWP42003-P.	
Section 9.1.14, Investigational Medicinal Product Accountability, pg 49	IMP will be dispensed at each of the following visits during the single blind phase: <ul style="list-style-type: none"> • Visit 2 (Day 2) • Visit 3 (Day 26) • Visit 4 (Day 51) (...)	GWP42003-P/placebo will be dispensed at each of the following visits during the blinded phase: <ul style="list-style-type: none"> • Visit 2 (Day 2) • Visit 4 (Day 34) (...)	See section 3.1
Section 9.1.15, Adverse Events, pg 50	(...)	(...) <u>Refer to Section 9.1.16.1.1 for the list of ‘Triggering AEs of Interest’ associated with monitoring of drug abuse liability.</u>	See section 3.4
Section 9.1.16, Monitoring of Drug Abuse Liability, pg 50	N/A	<u>9.1.16 Monitoring of Drug Abuse Liability</u> <u>There are two triggers that will require the investigator or study coordinator to discuss abuse potential signals with the patient or their caregiver. These are either AEs of interest that may be reported by the patient/caregiver, or drug accountability issues regarding overuse of the IMP or missing bottles. Different questionnaires will be completed by the site depending upon which trigger occurs (see Figure 9-1). Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (Visit 5 or Visit 12) or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator. Investigators and study coordinators will be provided with training on how to complete and perform the processes outlined in this section. This training must be completed and documented by the relevant site staff prior to implementation at site.</u>	See section 3.2

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Section 9.1.16.1, Monitoring of Adverse Events, pg 51 Section 9.1.16.1.1, List of ‘Triggering Adverse Events of Interest’ pg 51	N/A N/A	<p><u>9.1.16.1 Monitoring of Adverse Events</u> <u>AE information will be collected according to Section 9.1.15.</u></p> <p><u>9.1.16.1.1 List of ‘Triggering Adverse Events of Interest’</u> <u>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 Adverse Event Form and a Site Classification Form (investigator only) following further discussion of the event(s) with the patient or their caregiver. The categories are:</u></p> <ul style="list-style-type: none"> • <u>Euphoria or inappropriate elation.</u> • <u>Inappropriate laughter or exhilaration.</u> • <u>Mood changes.</u> • <u>Drunk, high or intoxicated.</u> • <u>Hallucinations (visual or auditory), dissociations, disorientation, agitation.</u> • <u>Disturbance in cognition, memory, or attention.</u> • <u>Drug abuse.</u> • <u>Drug withdrawal or drug withdrawal syndrome.</u> • <u>Addiction.</u> • <u>Overdose.</u> • <u>Misuse of IMP.</u> • <u>Thoughts of suicide, attempted suicide or suicide.</u> <p><u>An AE that is consistent with the above categories will be known as a ‘triggering AE of interest’ for</u></p>	<p>See section 3.2</p> <p>See section 3.2 See section 3.2</p>

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Section 9.1.16.1.2, Supplemental Adverse Event Form, pg 51	N/A	<p><u>the purposes of this study.</u></p> <p><u>9.1.16.1.2 Supplemental Adverse Event Form</u> <u>This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Adverse Event Form will then be transcribed into the patient's CRF for the study. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the site should contact the patient/caregiver to obtain the required answers as soon as possible.</u></p>	See section 3.2
Section 9.1.16.2, Monitoring Drug Accountability Discrepancies, pg 52	N/A	<p><u>9.1.16.2 Monitoring Drug Accountability Discrepancies</u> <u>Any time after enrollment until final collection of study data, drug accountability discrepancies are monitored as follows:</u></p> <ul style="list-style-type: none"> <u>At routine Drug Accountability collection times, the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the paper diary.</u> <u>At any time that the site is informed by the patient/caregiver about any overuse of IMP, suspected misuse, abuse, or diversion.</u> 	See section 3.2

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Section 9.1.16.2.1, List of 'Triggering Drug Accountability Discrepancies', pg 52	N/A	<p>9.1.16.2.1 List of 'Triggering Drug Accountability Discrepancies' <u>If there are any discrepancies in drug accountability as outlined by the criteria below, known as 'triggering drug accountability discrepancies', then the trained investigator or study coordinator will complete a Supplemental Drug Accountability Form and Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver. The triggering drug accountability discrepancies are as follows:</u></p> <ul style="list-style-type: none"> • <u>Missing bottle(s).</u> • <u>Compliance issues where one or more bottles are used compared to what was the expected use, according to the paper diary.</u> • <u>Returned IMP supply with evidence of tampering.</u> • <u>Greater than the target daily dose as recorded in the paper diary.</u> 	See section 3.2
Section 9.16.2.2, Supplemental Drug Accountability Form, pg 53	N/A	<p>9.1.16.2.2 Supplemental Drug Accountability Form <u>This form consists of eight questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the</u></p>	See section 3.2

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Section 9.16.2.2, Supplemental Drug Accountability Form, pg 53	N/A	<u>Supplemental Drug Accountability Form will then be transcribed into the patient's CRF for the study. The accountability reporting procedures will still occur. If the Supplemental Drug Accountability Form cannot be completed at the time the triggering drug accountability discrepancy is identified, then the site should contact the patient/caregiver by telephone to obtain the required answers as soon as possible (Note: IMP refers to GWP42003-P or placebo, not other concomitant medications).</u>	See section 3.2
Section 9.1.16.3, Site Classification Form, pg 53	N/A	<u>9.1.16.3 Site Classification Form</u> <u>The investigator should review the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then complete the Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.</u> <u>The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification. The answers from the Site Classification Form will then be transcribed into the patient's CRF for the study.</u>	
Section 9.16.4, Study	N/A	<u>9.1.16.4 Study Medication Use and</u>	

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Medication Use and Behavior Survey, pg 53	N/A	<p><u>Behavior Survey</u> <u>This form consists of 18 questions regarding the use of the IMP. The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit (Visit 5 or Visit 12) or withdrawal visit. The answers on the Study Medication Use and Behavior Survey will then be transcribed into the patient's CRF for the study.</u> <u>The Study Medication Use and Behavior Survey will be completed for all patients in the study and not only those that have reported a triggering AE or drug accountability discrepancy.</u></p>	See section 3.2
Section 9.16.5, Adjudication Committee – Assessment of Abuse Potential of GWP42003-P, pg 54		<p><u>9.1.16.5 Adjudication Committee – Assessment of Abuse Potential of GWP42003-P</u> <u>A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases. Only data from patients who have completed the study will be assessed.</u> <u>A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:</u></p> <ul style="list-style-type: none"> <u>All triggering AE information.</u> <u>Supplemental Adverse Event Form (if</u> 	See section 3.2

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Section 9.16.5, Adjudication Committee – Assessment of Abuse Potential of GWP42003-P, pg 54		<p><u>applicable).</u></p> <ul style="list-style-type: none"> • <u>All triggering drug accountability discrepancies.</u> • <u>Supplemental Drug Accountability Form (if applicable).</u> • <u>Site Classification Form.</u> • <u>Study Medication Use and Behavioral Survey.</u> • <u>Additional information from site(s) as requested by the Committee.</u> <p><u>The Adjudication Committee will assess all of the information. It will form a position on the classification of each event and will write a study-related report, detailing the conclusions and recommendations.</u></p> <p><u>The overall process is summarized in Figure 9-1.</u> << Note: For details of Figure 9-1 see Appendix 1.3 >></p>	<p>See section 3.2</p> <p>See section 3.2</p>
Section 9.2.1 Double Blind Phase, pg 56	9.2.1 Single Blind Phase	9.2.1 <u>Double</u> Blind Phase	See section 3.1
Section 9.2.1.1 Visit 1 (Day -14 to -7, Screening), pg 56	<p>9.2.1.1 Visit 1 (Day -7, Screening) The following observations (...) ECG and vital signs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, urinalysis (...) (...)</p> <p>Patients who satisfy all inclusion (...) and then begin the seven day-baseline period. (...)</p>	<p>9.2.1.1 Visit 1 (Day <u>-14</u> to -7, Screening) The following observations (...) ECG, vital signs <u>and AEs.</u></p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, <u>alcohol testing, THC testing,</u> urinalysis (...) (...)</p> <p>Patients who satisfy all inclusion (...) and then begin the baseline period. (...)</p>	<p>See section 3.1</p> <p>See section 3.2 and 3.7</p> <p>See section 3.1</p>

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Section 9.2.1.2.1 Visit 2 (Day 1) – Enrollment (+3 days), pg 56-57	This visit will occur 7 days after Visit 1. The following observations will be made at Visit 2: (...) physical examination (including height and body weight), ECG, vital signs and review of seizure diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. (...)	This visit will occur 7– 14 days after Visit 1. The following observations will be made at Visit 2: (...) physical examination (including body weight), ECG, vital signs and review of <u>patient</u> diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, <u>alcohol testing</u> and urinalysis. <u>Blood samples will also be taken for genetic testing if additional consent has been obtained.</u> (...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, <u>THC and THC major metabolites.</u> (...)	See section 3.1 See section 3.2 See section 3.7 See section 3.2 See section 3.4
Section 9.2.1.2.2 Visit 2 (Day 2) – Enrollment, pg 57	(...) (...) physical examination (including height and body weight), vital signs, and AEs. IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. (...) Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period. (...)	(...) (...) physical examination (including body weight), vital signs and AEs. <u>GWP42003-P/placebo</u> will be dispensed and both the morning dose of CLB and of <u>GWP42003-P/placebo</u> will be taken in clinic. (...) Each patient will then receive their <u>GWP42003-P/placebo</u> for the 10 day titration period followed by the <u>21</u> day maintenance period. (...)	See section 3.7 See section 3.3.1 See section 3.1
Section 9.2.1.3 Visit 3 (Day 12 +3 days), pg 57	9.2.1.3 Visit 3 9.2.1.3.1 Visit 3 (Day 26) (+3 days) This visit will occur 25 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP. The following observations will be made at Visit 3 (Day 26): concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, review of seizure	9.2.1.3 Visit 3 (Day 12 +3 days) This visit will occur <u>11</u> days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP. The following observations will be made at Visit 3 (Day <u>12</u>): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, <u>AEs and</u> review of <u>patient</u> diary <u>completion.</u>	See section 3.1 and section 3.2

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Section 9.2.1.3 Visit 3 (Day 12 +3 days), pg 57	<p>diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.</p> <p>Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of IMP. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients are expected to remain in clinic throughout this PK sampling process.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>9.2.1.3.2 Visit 3 (Day 27)</p> <p>This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 26 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 27: concomitant medications (including AEDs), physical examination (including height and body weight), vital signs, and AEs.</p> <p>IMP will be dispensed and both the morning dose of CLB and of IMP will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section</p>	<p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.</p>	See section 3.1

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	8.1.2. Each patient will then receive their IMP for the 10 day titration period followed by the 14 day maintenance period. Patients or their caregivers will be instructed how to record the diary information.		
Section 9.2.1.4.1 Visit 4 (Day 33 ±3 days), pg 57	9.2.1.4.1 Visit 4 (Day 51) (±3 days) This visit will occur 50 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused IMP . The following observations will be made at Visit 4 (Day 51): (...) physical examination (including height and body weight), ECG, vital signs, review of seizure diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. (...) The investigator must record the patient's attendance at the visit and the outcome. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD and CBD major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of IMP . (...)	9.2.1.4.1 Visit 4 (Day <u>33</u>) (±3 days) This visit will occur <u>32</u> days after Visit 2, Day 1 (enrollment). Patients will return all used and unused <u>GWP42003-P/placebo</u> . The following observations will be made at Visit 4 (Day <u>33</u>): (...) physical examination (including body weight), ECG, vital signs, review of <u>patient</u> diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, <u>alcohol testing</u> , and urinalysis. (...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, <u>THC and THC major metabolites</u> . A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of <u>GWP42003-P/placebo</u> . (...)	See section 3.1 See section 3.7 and section 3.2 See section 3.2 See section 3.4 See section 3.3.1
Section 9.2.1.4.2 Visit 4 (Day 34), pg 58	9.2.1.4.2 Visit 4 (Day 52) (...) The final PK sample will be collected 24 hours after the Day 51 morning CLB dose. Following completion of the PK sampling process the following observations will be made on Day 52 : (...) physical examination (including height and body weight), vital signs, and AEs. At the end of the blinded phase of the study on Day	9.2.1.4.2 Visit 4 (Day <u>34</u>) (...) The final PK sample will be collected 24 hours after the Day <u>33</u> morning CLB dose. Following completion of the PK sampling process the following observations will be made on Day <u>34</u> : (...) physical examination (including body weight), vital signs and AEs. At the end of the blinded phase of the study on Day	See section 3.1 See section 3.2

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Section 9.2.1.4.2 Visit 4 (Day 34), pg 58	52 , providing the investigator and patient both agree, patients will be invited to continue taking IMP and to enter the OLE. Patients who enter the OLE will be dispensed CBD on Day 52 . (...) (...) Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of IMP . The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 60 .	34 , providing the investigator and patient both agree, patients will be invited to continue taking <u>GWP42003-P</u> and to enter the OLE. Patients who enter the OLE will be dispensed <u>GWP42003-P</u> on Day 34 . <u>At the point of entry to the OLE, patients will be transitioned to the OLE treatment over a 10 day period in order to maintain blinding.</u> (...) (...) Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of <u>GWP42003-P/placebo</u> . The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42 .	To provide clarity over how patients will transition from the blinded to OLE. See section 3.3.1 See section 3.1
Section 9.2.1.5 Visit 5 (Patients not entering Open Label Extension) (Day 43 +3 days), pg 58-59	9.2.1.5 Visit 5 (Patients not entering OLE) (+3 days) This visit will occur 60 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including height and body weight) and vital signs (...) (...)	9.2.1.5 Visit 5 (Patients not entering <u>Open Label Extension</u>) (Day 43 +3 days) This visit will occur 42 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE. All <u>GWP42003-P/placebo</u> (used and unused) will be collected and a check of the returned <u>GWP42003-P/placebo</u> against usage must be made. A physical examination (including body weight), <u>ECG</u> and vital signs (...) <u>The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</u> (...) (...)	See section 3.1 See section 3.3.1 See section 3.2 To be consistent with visit 12 ECG See section 3.2
Section 9.2.1.6 Visit 6 - Safety Follow up Call	9.2.1.6 Safety Follow up Call (Day 89) (±3 days) This visit is required for patients who do not enter the OLE study on Day 50 , or who withdraw from the	9.2.1.6 <u>Visit 6</u> - Safety Follow up Call (Day 71) (±3 days) This visit is required for patients who do not enter the	See section 3.1

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(Day 71) (±3 days), pg 59	study early. (...) The following observations will be made on Day 89 : (...)	OLE study on Day <u>34</u> , or who withdraw from the study early. (...) The following observations will be made on Day <u>71</u> : (...)	
Section 9.2.2 Open Label Extension, pg 59	Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 52) (...). The visit schedule is calculated relative to Visit 4 (Day 51).	Patients who enter the OLE will be dispensed IMP at Visit 4 (Day <u>34</u>) (...). The visit schedule is calculated relative to Visit 4 (Day <u>34</u>).	See section 3.1
Section 9.2.2.1 Visit 5 (Open Label Extension) - Two Weeks (±3 days), pg 59	This visit will occur two weeks after Visit 4 (Day 51). (...) The following observations will be made at Visit 5 (OLE): (...), physical examination (including height and body weight) (...)	This visit will occur two weeks after Visit 4 (Day <u>34</u>). (...) The following observations will be made at Visit 5 (OLE): (...), physical examination (including body weight) (...)	See section 3.1 and section 3.2
Section 9.2.2.2 Visit 6 (Open Label Extension) – One Month (±3 days), pg 59	This visit will occur one month after Visit 4 (Day 51). (...) The following observations will be made at Visit 6 (OLE): (...), physical examination (including height and body weight) (...)	This visit will occur one month after Visit 4 (Day <u>34</u>). (...) The following observations will be made at Visit 6 (OLE): (...), physical examination (including body weight) (...)	See section 3.1 and section 3.2
Section 9.2.2.3 Visit 7 (Open Label Extension) – Two Months (±3 days), pg 60	This visit will occur two months after Visit 4 (Day 51). (...) The following observations will be made at Visit 7 (OLE): (...), physical examination (including height and body weight) (...)	This visit will occur two months after Visit 4 (Day <u>34</u>). (...) The following observations will be made at Visit 7 (OLE): (...), physical examination (including body weight) (...)	See section 3.1 and section 3.2
Section 9.2.2.4 Visit 8 (Open Label Extension) – Three Months (±3 days), pg 60	This visit will occur three months after Visit 4 (Day 51). (...) The following observations will be made at Visit 8 (OLE): (...), physical examination (including height and body weight) (...)	This visit will occur three months after Visit 4 (Day <u>34</u>). (...) The following observations will be made at Visit 8 (OLE): (...), physical examination (including body weight) (...)	See section 3.1 and section 3.2
Section 9.2.2.5 Visit 9 (Open Label Extension)	This visit will occur six months after Visit 4 (Day 51). (...) The following observations will be made at Visit 9 (OLE): (...), physical examination (including height	This visit will occur six months after Visit 4 (Day <u>34</u>). (...) The following observations will be made at Visit 9 (OLE): (...), physical examination (including body	See section 3.1 and section 3.2

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 1, Dated 26 Jan 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 1 (Protocol Version 2, Dated 09 Jul 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
– Six Months (±3 days), pg 60	and body weight) (...)	weight) (...)	
Section 9.2.2.6 Visit 10 (Open Label Extension) – Nine Months (±3 days), pg 61	This visit will occur nine months after Visit 4 (Day 54)(...) The following observations will be made at Visit 10 (OLE): (...), physical examination (including height and body weight) (...)	This visit will occur nine months after Visit 4 (Day <u>34</u>)(...) The following observations will be made at Visit 10 (OLE): (...), physical examination (including body weight) (...)	See section 3.1 and section 3.2
Section 9.2.2.7 Visit 11 (Open Label Extension) – Twelve Months (±3 days), pg 61	This visit will occur twelve months after Visit 4 (Day 54)(...) The following observations will be made at Visit 11 (OLE): (...), physical examination (including height and body weight) (...)	This visit will occur twelve months after Visit 4 (Day <u>34</u>)(...) The following observations will be made at Visit 11 (OLE): (...), physical examination (including body weight) (...)	See section 3.1 and section 3.2
Section 9.2.2.8 Visit 12 (Open Label Extension End of Taper), pg 61	(...) A physical examination (including height and body weight) (...) (...)	(...) A physical examination (including body weight) (...) <u>The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</u> (...)	See section 3.2 See section 3.2
Section 10 WITHDRAWAL, pg 62	(...) (...)	(...) • <u>Any other IMP is taken as part of a clinical trial during the study.</u> (...)	See section 3.5
Section 12.8, Potential Cases of Drug Induced Liver Injury, pg 68-69	12.8 Reporting Clinically Significant Laboratory Results (...) DILI (...) for repeat assessment, detailed history (...)	12.8 <u>Potential Cases of Drug Induced Liver Injury</u> (...) <u>drug-induced liver injury</u> (...) for repeat assessment <u>of ALT, AST, TBL and alkaline phosphatase levels</u> , detailed history (...) <u>Elevations in ALT or AST >3 × ULN or TBL >2 × ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as</u>	See section 3.6 See section 3.6

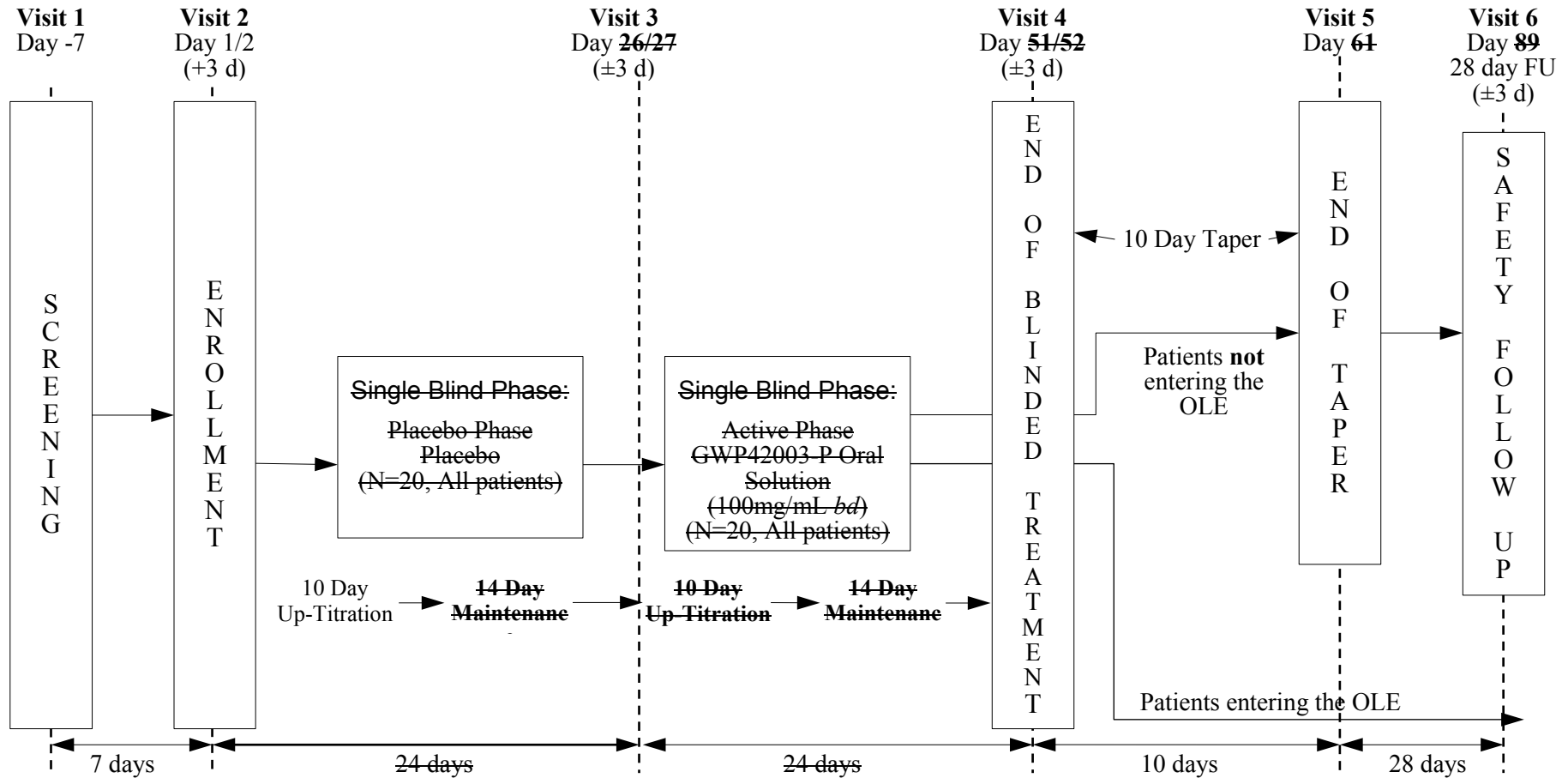
Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 1, Dated 26 Jan 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 1 (Protocol Version 2, Dated 09 Jul 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
		<u>detailed above, within 72 hours' notice of abnormal results. If the participant cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.</u>	
Section 13.2 Interim Analysis, pg 71	An interim analysis will be conducted at the end of the Single Blind phase (...)	An interim analysis will be conducted at the end of the <u>Double</u> Blind phase (...)	See section 3.1
Section 13.6.1 Primary Endpoint(s), pg 72	(...) The primary endpoints of the study are the pharmacokinetic parameters (...) • N-desmethylelobazam (N-CLB) (...)	(...) The primary endpoints of the study are the <u>PK</u> parameters (...) • N-CLB (...)	See section 3.7
Section 13.6.2 Secondary Endpoint(s), pg 72	The secondary endpoints of the study are the safety parameters (see Section 13.6.5).	The secondary endpoints of the study are the safety parameters (see Section 13.6.4) <u>and the PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</u> • <u>THC</u> • <u>THC major metabolites</u>	See section 3.7 See section 3.4
Section 13.6.3 Pharmacokinetics pg 73-74	(...)Plasma concentrations of CLB, N-CLB, CBD and the major metabolites will be (...) (...) • In order to assess (...) mixed effect model with treatment (CBD or placebo) as fix effect (...)	(...)Plasma concentrations of CLB, N-CLB, CBD, <u>CBD</u> major metabolites, <u>THC and THC major metabolites</u> will be (...) (...) • In order to assess (...) mixed effect model with treatment (<u>CLB or CLB+CBD</u>) as <u>a fixed</u> effect (...)	See section 3.4 and 3.1 See Section 3.7
Section 13.6.4.3 Clinical Laboratory Data pg 74	Clinical laboratory data at screening and at the end of each 24 day treatment phase (...)	Clinical laboratory data at screening and at the end of <u>the 31</u> day treatment phase (...)	See section 3.1

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 1, Dated 26 Jan 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 1 (Protocol Version 2, Dated 09 Jul 15) (Revised wording is underscored and in bold)	Rationale for the amendment.														
Section 13.6.4.4 Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data pg 75	(...) at the end of each 24 day treatment phase (...)	(...) at the end of <u>the 31</u> day treatment phase (...)	See section 3.1														
Section 13.6.4.5 Seizure Data pg 75	(...) collected during each 24 day treatment phase (...)	(...) collected during <u>the 31</u> day treatment phase (...)	See section 3.1														
APPENDIX 1, Schedule of Assessments, pg 86	<< Note: See Appendix 1.4 for detailed changes >>	<< Note: See Appendix 1.4 for detailed changes >>	See section 3.1 and 3.2														
Appendix 3.2, Sponsor Contact Details, pg 90-91	<table><tr><td>(...)</td><td>(...)</td></tr><tr><td>Sponsor:</td><td>GW Research Ltd Sovereign House Vision Park Histon Cambridge CB24 9BZ United Kingdom</td></tr><tr><td>Medical Monitor</td><td>(...)</td></tr><tr><td>Clinical Project</td><td>GW Research Ltd</td></tr></table>	(...)	(...)	Sponsor:	GW Research Ltd Sovereign House Vision Park Histon Cambridge CB24 9BZ United Kingdom	Medical Monitor	(...)	Clinical Project	GW Research Ltd	<table><tr><td>(...)</td><td>(...)</td></tr><tr><td>Sponsor:</td><td>GW Research Ltd Sovereign House Vision Park <u>Chivers Way</u> Histon Cambridge CB24 9BZ United Kingdom</td></tr><tr><td>Medical Monitor</td><td>(...)</td></tr></table>	(...)	(...)	Sponsor:	GW Research Ltd Sovereign House Vision Park <u>Chivers Way</u> Histon Cambridge CB24 9BZ United Kingdom	Medical Monitor	(...)	<div>See section 3.7</div> <div>Back up USA</div>
(...)	(...)																
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Medical Monitor	(...)																
Clinical Project	GW Research Ltd																
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Sponsor:	GW Research Ltd Sovereign House Vision Park <u>Chivers Way</u> Histon Cambridge CB24 9BZ United Kingdom																
Medical Monitor	(...)																

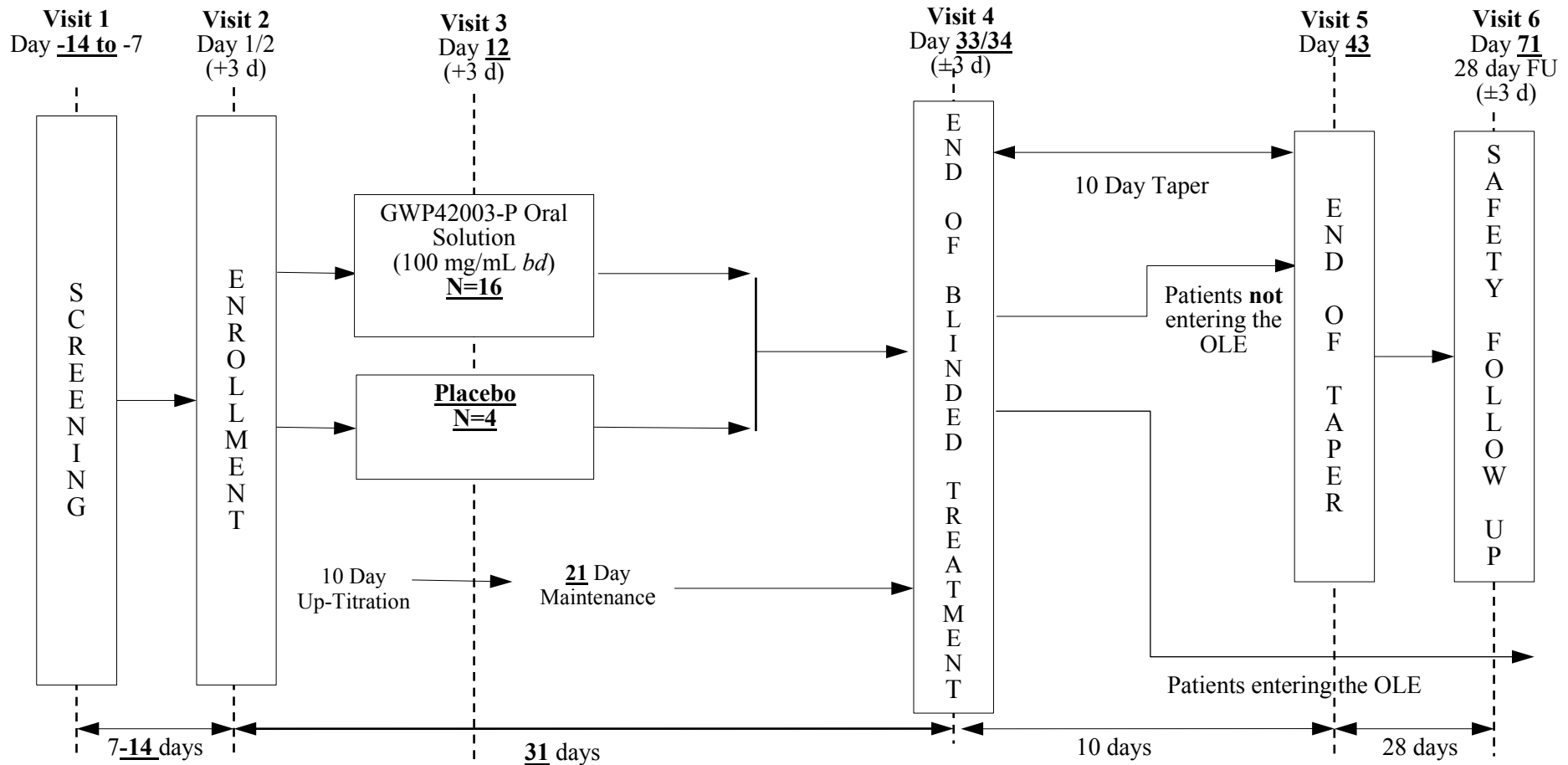
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APPENDIX 1.1

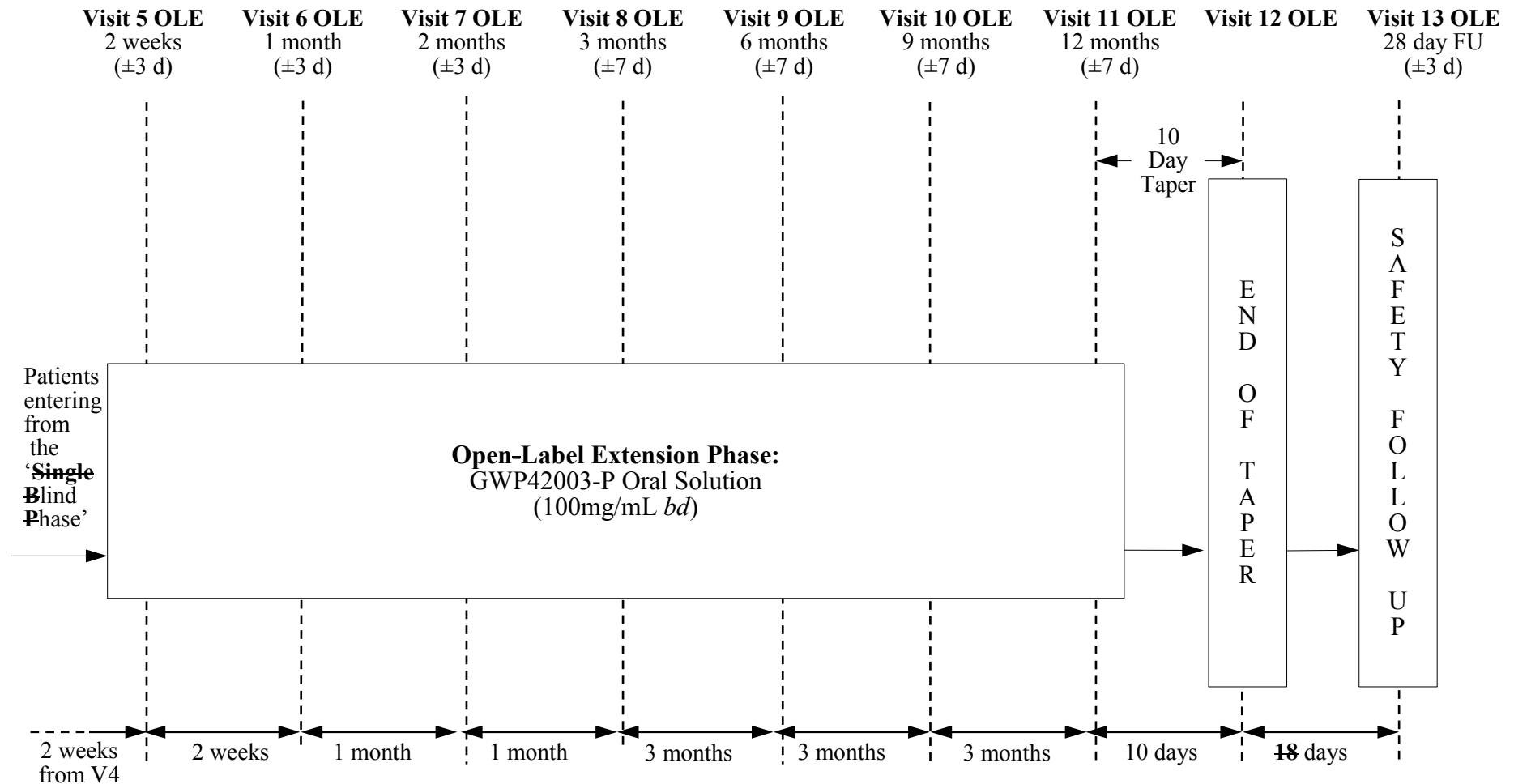
Study Design and Treatment Schema (Protocol V1 / Figure 1-1)



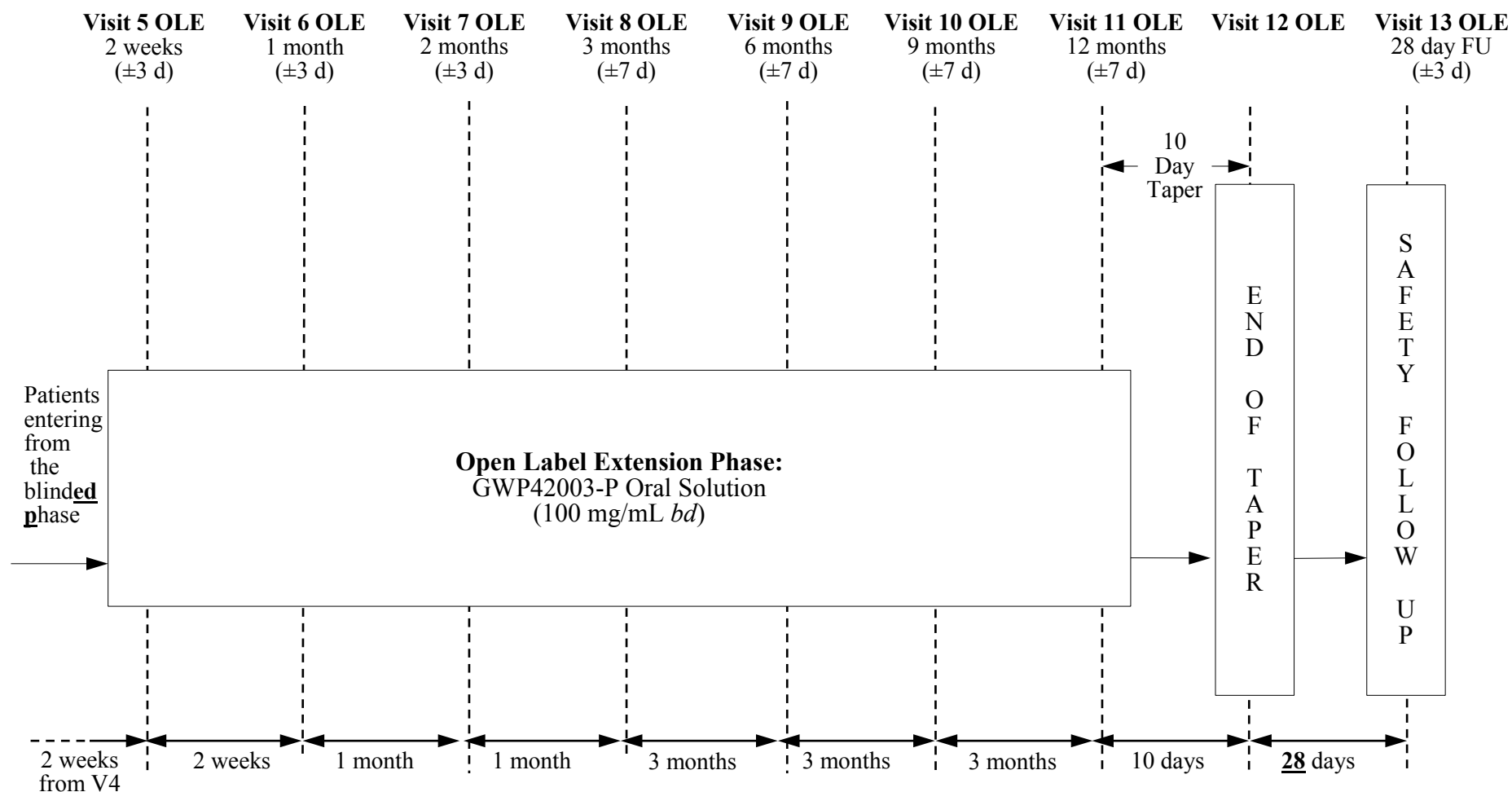
Study Design and Treatment Schema (Protocol V2 / Figure 1-1)



Study Design and Treatment Schema (Protocol V1 / Figure 1-2)



Study Design and Treatment Schema (Protocol V2 / Figure 1-2)



APPENDIX 1.2

Dose Titration Regimen (Protocol V1 / Table 8.1-4)

Table 8.1-4 Dose Titration Regimen*		
Day - Placebo	Day - CBD	Dose Level (CBD or equivalent placebo)
2	26	2.5 mg/kg
3	27	2.5 mg/kg
4	28	5.0 mg/kg
5	29	5.0 mg/kg
6	30	7.5 mg/kg
7	31	7.5 mg/kg
8	32	10.0 mg/kg
9	33	10.0 mg/kg
10	34	15.0 mg/kg
11	35	15.0 mg/kg
12 onwards	36 onwards	20.0 mg/kg

***IMP** is to be taken twice daily. Total daily doses are shown.

Dose Titration Regimen (Protocol V2 / Table 8.1.2-1)

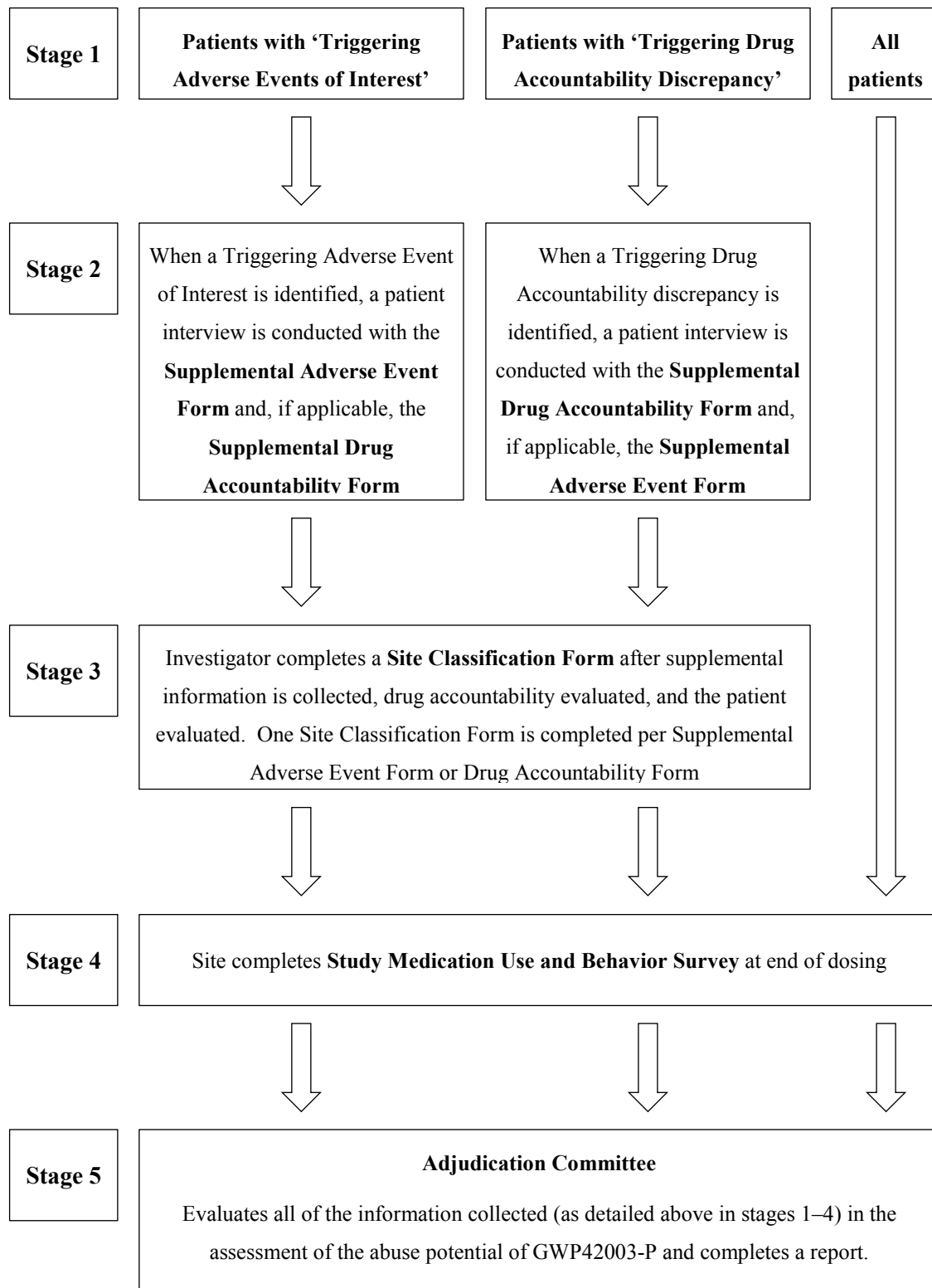
Table 8.1.2-1 Dose <u>Up</u>-Titration Regimen*		
Day - <u>GWP42003-P/Placebo</u> (Blinded Period)	Day - <u>GWP42003-P only</u> (OLE**)	Dose Level (GWP42003-P or equivalent placebo)
2	<u>34</u>	2.5 mg/kg
3	<u>35</u>	2.5 mg/kg
4	<u>36</u>	5.0 mg/kg
5	<u>37</u>	5.0 mg/kg
6	<u>38</u>	7.5 mg/kg
7	<u>39</u>	7.5 mg/kg
8	<u>40</u>	10.0 mg/kg
9	<u>41</u>	10.0 mg/kg
10	<u>42</u>	15.0 mg/kg
11	<u>43</u>	15.0 mg/kg
12 onwards	<u>44 onwards</u>	20.0 mg/kg

* **GWP42003-P /placebo** is to be taken twice daily. Total daily doses are shown.

**** Only patients who were taking placebo during the double-blind period will up-titrate according to this schedule during the OLE period. Those taking GWP42003-P during the double-blind period will down-titrate their blinded IMP whilst simultaneously up-titrating with GWP42003-P, thus maintaining a daily dose of 20 mg/kg/day GWP42003-P throughout.**

APPENDIX 1.3

Figure 9-1 Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization Tabulation and Analysis which can Illuminate an Abuse Potential Signal



APPENDIX 1.4

Schedule of Assessments Blinded Phase (Protocol V1 / Appendix 1)

Visit Number Day (Visit Window)	Visit 1 Day -7	Visit 2 Day 1 (+ 3 days)	Visit 2 Day 2	Visit 3 Day 26 (± 3 days)	Visit 3 Day 27	Visit 4 Day 51 (± 3 days)	Visit 4 Day 52	Visit 5* End of Taper	Visit 6* 4wk SFU (± 3 days)
Informed consent	X								
Eligibility criteria	X	X							
Enrollment		X							
Demographics	X								
Medical history	X								
Paper diary training	X		X						
Concomitant medications (including AEDs)	X	X	X	X	X	X	X	X	X
Physical examination (including height and body weight)	X	X	X	X	X	X	X	X	
ECG	X	X		X		X			
Vital signs	X	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	
Alcohol /THC test	X								
Pregnancy test (if appropriate)	X								
Pharmacokinetic blood sampling**		X	X	X	X	X	X		
C-SSRS	X	X		X		X		X	
Patient diary review		X		X		X		X	

Visit Number Day (Visit Window)	Visit 1 Day -7	Visit 2 Day 1 (+ 3 days)	Visit 2 Day 2	Visit 3 Day 26 (± 3 days)	Visit 3 Day 27	Visit 4 Day 51 (± 3 days)	Visit 4 Day 52	Visit 5* End of Taper	Visit 6* 4wk SFU (± 3 days)
(seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)									
IMP dispensing			X		X		X		
Collection of IMP				X		X		X	
IMP compliance review				X		X		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 and third PK visits the patient should take the ~~IMP~~ immediately after their daily dose of CLB.

Schedule of Assessments Blinded Phase (Protocol V2 / Appendix 1)

Visit Number Day (Visit Window)	Visit 1 Day <u>-14 to</u> -7	Visit 2 Day 1 (+ 3 days)	Visit 2 Day 2	Visit 3 Day <u>12</u> (+ 3 days)	Visit 4 Day <u>33</u> (± 3 days)	Visit 4 Day <u>34</u>	Visit 5* End of Taper	Visit 6* 4wk SFU (± 3 days)
Informed consent	X							
Eligibility criteria	X	X						
Enrollment		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		<u>X</u>	
Vital signs	X	X	X	X	X	X	X	
AEs	<u>X</u>	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							
<u>Alcohol Test</u>	<u>X</u>	<u>X</u>			<u>X</u>			
Pregnancy test (if appropriate)	X							
Pharmacokinetic blood sampling**		X	X		X	X		
<u>Sample for Genetic Testing***</u>		<u>X</u>						

Visit Number Day (Visit Window)	Visit 1 Day <u>-14 to</u> -7	Visit 2 Day 1 (+ 3 days)	Visit 2 Day 2	Visit 3 Day <u>12</u> (+ 3 days)	Visit 4 Day <u>33</u> (± 3 days)	Visit 4 Day <u>34</u>	Visit 5* End of Taper	Visit 6* 4wk SFU (± 3 days)
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	
<u>Study Medication Use and Behavior Survey</u>							<u>X</u>	

* 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 (Protocol V1 / Appendix1)

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 height and body 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	

Open Label Extension Schedule of Assessments (Protocol V2/ Appendix1)

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	
<u>Study Medication Use and Behavior Survey</u>								<u>X</u>	

**TITLE: A PHASE2, DOUBLE-BLIND, RANDOMIZED,
PLACEBO-CONTROLLED STUDY TO INVESTIGATE POSSIBLE
DRUG-DRUG INTERACTIONS BETWEEN CLOBAZAM AND
CANNABIDIOL (GWP42003-P)**

STUDY CODE: GWEP1428

EudraCT NUMBER: 2014-002942-33

**GW RESEARCH LTD
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Confidentiality Statement

This document contains confidential information of GW Research Ltd that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board/Independent Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Investigator Agreement

I have read the attached protocol entitled "A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)", dated version 2 date 09 Jul 15 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s) the FDA regulations relating to good clinical practice and clinical trials and the European Union (EU) Clinical Trials Directive (2001/20/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (ICH GCP) where the EU Directive does not apply and to complete a Form 1572 if required.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Center No: _____

Print Name: _____

Principal Investigator

Date: _____

(DD Month YYYY)

Signature: _____

GW Authorization

Print Name: _____

Clinical Manager _____

Signature: _____

Date: 17th July 2015

(DD Month YYYY)

1. PROTOCOL SYNOPSIS

Study Title	A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)
Clinical Study Type	Phase 2
Indication	Epilepsy
Primary Objective	To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyclobazam (N-CLB).
Secondary Objective(s)	To assess the safety and tolerability of GWP42003-P in the presence of CLB.
Study Design	<p>This is a phase 2, double-blind, randomized, placebo-controlled study in 20 patients.</p> <ul style="list-style-type: none"> • 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. • Day 1 (Visit 2), patients will not be dosed with GWP42003-P/placebo but will continue to take CLB at a stable dose. • Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • Day 12 (Visit 3), patients will attend the study site to check safety and compliance. • After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). • On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the patient will continue to take GWP42003-P

	<p>as advised by the investigator.</p> <ul style="list-style-type: none"> If the patient does not enter the OLE period of the study, the patient will taper off of GWP42003-P by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with end of taper on Day 43 (Visit 5). <p>PK samples will be taken on the day of enrollment (Visit 2, Day 1) and after completing 21 days treatment on GWP42003-P or placebo (Visit 4, Day 33). The PK assessments will therefore capture the following combinations of CLB and GWP42003-P:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and GWP42003-P or placebo. <p>Each PK assessment should be performed at time points in respect to a morning dose of CLB. The time points are as follows: Pre-dose, 15 min, 30 min, 1h, 1.5h, 2h, 4h, 6h, 12h and 24h. It is expected that the patient will continue to take their CLB as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The GWP42003-P/placebo should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD, CBD major metabolites, Δ^9-tetrahydrocannabinol (THC) and THC major metabolites. Patients will be required to keep a paper diary to note the time and dose of GWP42003-P and CLB administration each morning and evening and to record any adverse events (AEs) that may occur whilst receiving investigational medicinal product (IMP) and any other medications. Patients will also be requested to record the number and type of seizures for each day whilst on the study.</p>
Primary Endpoint	<p>The primary endpoints of the study are the PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$ $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</p> <ul style="list-style-type: none"> CLB N-desmethyleclobazam (N-CLB) CBD CBD major metabolites
Secondary Endpoint(s)	<p>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:</p> <ul style="list-style-type: none"> 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

	<p>PK parameters (C_{\max}, t_{\max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</p> <ul style="list-style-type: none"> • THC • THC major metabolites
Sample Size	<p>A total of 20 patients will be enrolled in this study. Recruitment for the study will be competitive between participating sites. There is no formal sample size: Calculation and analysis is descriptive only.</p>
Summary of Participant Eligibility Criteria	<p>For inclusion in the study patients must fulfil ALL of the following criteria:</p> <ul style="list-style-type: none"> • Male or female patients aged 18 to 55 years inclusive. • Patient must have epilepsy as determined by the investigator and be taking CLB. • Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition. • Patient must have experienced at least one seizure of any type (i.e., convulsive: tonic-clonic, tonic, clonic, atonic; focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness focal seizures evolving to bilateral secondary generalization) within the two months prior to randomization. • Patients must be taking CLB and no more than two other anti-epileptic drugs (AEDs) during the course of the study. • AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study. • Intervention with vagus nerve stimulation and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must be willing to maintain a stable regimen throughout the blinded phase of the study. • Patients must abstain from alcohol during the blinded phase of the study. • Patient and/or legal representative is available to attend all PK visits within the required visit window. • Patient and/or legal representative must be willing and able to give informed consent for participation in the study • Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements. • Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable. • Patient is willing to allow his or her primary care practitioner and

	<p>consultant, if appropriate, to be notified of participation in the study.</p> <p>Exclusion: The patient may not enter the study if ANY of the following apply:</p> <ul style="list-style-type: none"> • Patient has clinically significant unstable medical conditions other than epilepsy. • Patients on CLB at doses above 20 mg per day. • Patients taking CLB intermittently as rescue medication. • Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes. • Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening. • Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy. • Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain during the blinded phase of the study. • Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry. • Patient has any known or suspected history of any drug abuse or addiction. • Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration for the study. • Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil • Female patient is of child bearing potential or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/ hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence. • Female patient who is pregnant (positive pregnancy test), lactating
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	<p>or planning pregnancy during the course of the study and for three months thereafter.</p> <ul style="list-style-type: none"> • Patients who have received an IMP within the 12 weeks prior to the screening visit. • Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study. • Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator would prevent the participant from safe participation in the study. • Patient has significantly impaired hepatic function at screening (Visit 1) or enrollment (Visit 2), defined as any of the following: <ul style="list-style-type: none"> - Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $>5 \times$ upper limit of normal (ULN). - ALT or AST $>3 \times$ ULN and total bilirubin (TBL) $>2 \times$ ULN or international normalized ratio (INR) >1.5. - ALT or AST $>3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$). <p><i>This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion must be withdrawn from the study.</i></p> • Unwilling to abstain from donation of blood during the study. • Travel outside the country of residence planned during the study. • Patients previously enrolled into this study.
Criteria for Withdrawal	<p>Patients must be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Administrative decision by the investigator or GW Research Ltd or Regulatory Authority. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient. • Withdrawal of patient consent. • Withdrawal of legal representative consent. • Lost to follow up. • ALT $>3 \times$ ULN or AST $>3 \times$ ULN and (TBL $>2 \times$ ULN or INR >1.5). • ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).

	<ul style="list-style-type: none"> • ALT or AST $>8 \times$ ULN. • ALT or AST $>5 \times$ ULN for more than two weeks. • Any other IMP is taken as part of a clinical trial during the study. <p>Patients may also be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Patient non-compliance. • AE, which in the investigator's opinion, would compromise the continued safe participation of the patient in the study. • Any evidence of drug abuse or diversion. • Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.
Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration	<p>GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring), pale yellow in color.</p> <p>Placebo oral solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring.</p> <p>The IMP should be taken orally as per intended commercial therapeutic use.</p> <p>IMP will be taken twice daily (morning and evening) following the dose schedule below:</p> <ul style="list-style-type: none"> • Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). <p>Please refer to Table 8.1.2-1 for details of the up-titration doses for GWP42003-P and placebo for the ten day taper period.</p> <p>On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the patient will continue to take GWP42003-P as advised by the investigator.</p> <p>Clobazam will be an IMP for the blinded section of the study. The patients' own supply of Clobazam will be used.</p>
Control Group	The control group will receive an equal volume of matching placebo.
Procedures	<p>VISIT 1 - Screening (Day -14 to -7)</p> <p>The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination</p>

	<p>(including height and body weight), ECG, vital signs and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, THC testing, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.</p> <p>Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will be assigned a unique patient number and then begin the baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be instructed on how to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.</p> <p>VISIT 2 - Enrollment (Day 1) +3 days window</p> <p>This visit will occur 7-14 days after Visit 1.</p> <p>The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. Blood samples will also be taken for genetic testing if additional consent has been obtained. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.</p> <p>Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic on Day 2 ahead of additional sample collection.</p> <p>VISIT 2 - Enrollment (Day 2)</p> <p>This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.</p> <p>GWP42003-P/placebo will be dispensed and both the morning dose of CLB and GWP42003-P/placebo will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as</p>
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	<p>described in Section 8.1. Each patient will then receive their GWP42003-P/placebo for the 10 day titration period followed by the 21 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.</p> <p>VISIT 3 – Day 12 +3 day window</p> <p>This visit will occur 11 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 3: concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, AEs and review of patient diary completion.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.</p> <p>VISIT 4 - Day 33 ±3 days window</p> <p>This visit will occur 32 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 4 (Day 33): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. The C-SSRS will be administered.</p> <p>Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of GWP42003-P/placebo. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients are expected to remain in clinic throughout this PK sampling process.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 4 - Day 34</p> <p>This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 33 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 34: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.</p> <p>On Day 34, providing the investigator and patient both agree, patients will be invited to continue taking GWP42003-P and to enter the OLE. Patients who enter the OLE will be dispensed GWP42003-P on Day 34. The dose may be adjusted up or down by the investigator from the</p>
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	<p>maintenance dose of 20 mg/kg/day in the blinded phase to a maximum of 30 mg/kg/day in the OLE. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1. Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of GWP42003-P. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42.</p> <p>Patients Not Entering OLE</p> <p>VISIT 5 – Day 43 (End of Taper) +3 days window</p> <p>This visit will occur 42 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.</p> <p>All GWP42003-P/placebo (used and unused) will be collected and a check of the returned GWP42003-P/placebo against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.</p> <p>VISIT 6 - SAFETY FOLLOW-UP CALL - Day 71 ±3 days</p> <p>This visit is required for patients who do not enter the OLE study on Day 34, or who withdraw from the study early. This visit should occur four weeks (±3 days) after Visit 5, or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 71: concomitant medications (including AEDs) and AEs.</p> <p>Patients Entering OLE</p> <p>At the point of entry to the OLE, patients will be transitioned to the OLE treatment over a 10 day period in order to maintain blinding. Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 34) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 34).</p> <p>VISIT 5 (OLE) – Two Weeks ±3 days</p> <p>This visit will occur two weeks after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p>
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	<p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 6 (OLE) – One Month \pm3 days</p> <p>This visit will occur one month after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 7 (OLE) – Two Months \pm3 days</p> <p>This visit will occur two months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 8 (OLE) - Three Months \pm7 days</p> <p>This visit will occur three months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p>
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	<p>VISIT 9 (OLE) - Six Months ± 7 days</p> <p>This visit will occur six months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 10 (OLE) - Nine Months ± 7 days</p> <p>This visit will occur nine months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 11 – Twelve Months (OLE End of Treatment) ± 7 days</p> <p>This visit will occur twelve months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>Starting at Visit 11, patients will begin to taper down their IMP dose. The dose will be reduced by 10% of their OLE maintenance dose per day.</p> <p>VISIT 12 - OLE End of taper +3 days</p> <p>This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be</p>
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	<p>made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.</p> <p>VISIT 13 - SAFETY FOLLOW-UP CALL (OLE)</p> <p>This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.</p> <p>Monitoring of Drug Abuse Liability</p> <p>During the routine collection of AEs in this study, if AEs are reported which can illuminate an abuse potential signal (specific AEs detailed in Section 9.1.16.1.1), then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussions of the event(s) with the patient/caregiver.</p> <p>The second trigger that will require the investigator or study coordinator to discuss abuse potential signals with the patient/caregiver is drug accountability issues regarding overuse of the IMP or missing IMP bottles.</p> <p>Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.</p> <p>A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.</p>
Statistical Considerations	<p>Plasma concentration data will be analyzed to estimate PK endpoints C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{1/2}$ of the following analytes: CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites.</p> <p>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 group ratios of geometric means of C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will be done on logarithm scale using a linear mixed effect model with treatment (CLB or CLB+GWP42003-P) 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</p>

	<p>means of a PK variable falls within the interval [0.5, 2.0], a lack of meaningful effect will be declared.</p> <p>Descriptive summaries (means and standard deviations or counts [%] as appropriate) will be presented for all secondary endpoints (adverse events, laboratory data, vital signs, physical examination, C-SSRS and seizure frequency) for each phase of the study.</p>
Sponsor	<p>GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom</p>

Figure 1-1 Study Design and Treatment Schema

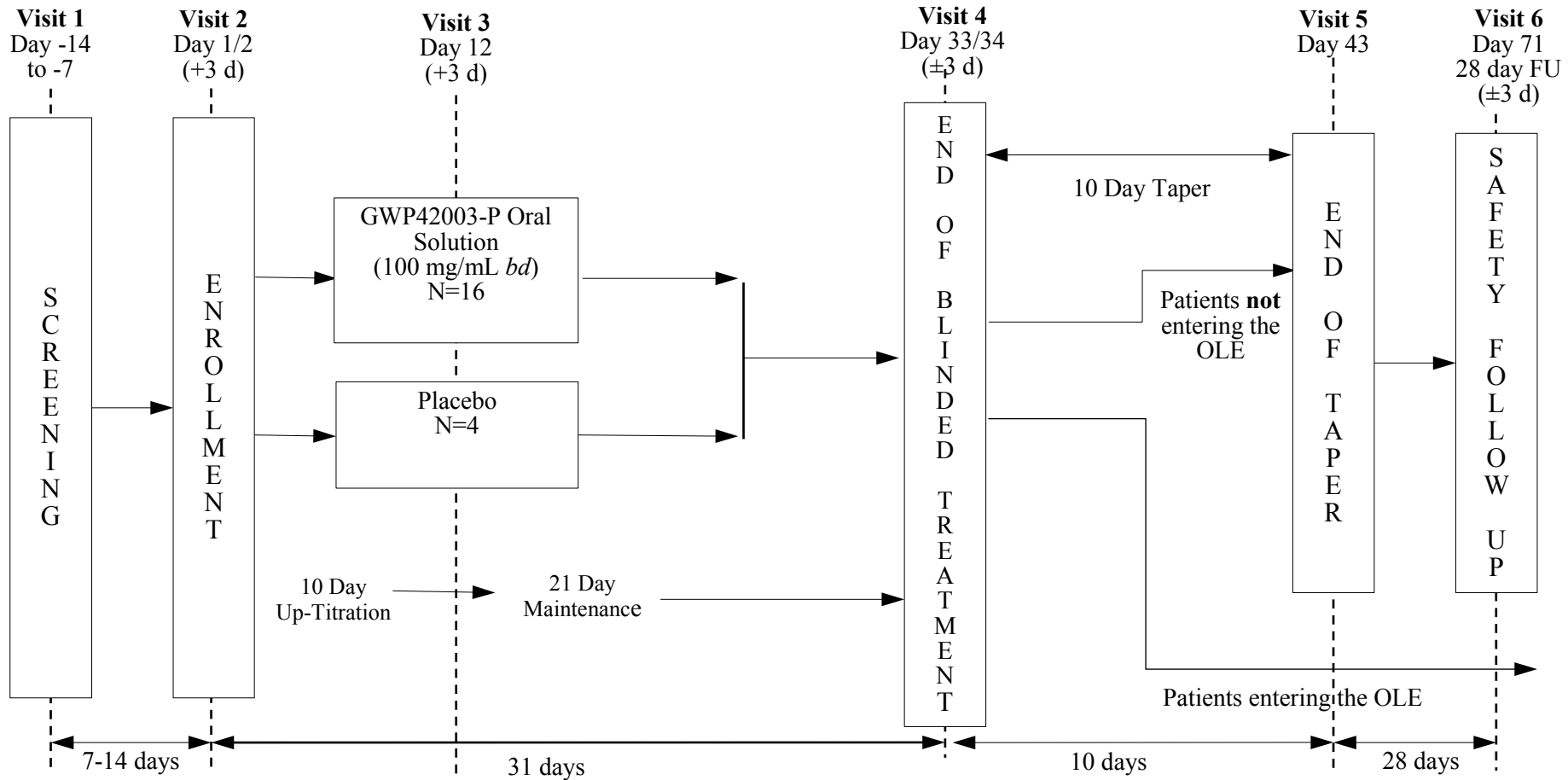


Figure 1-2 Study Design and Treatment Schema

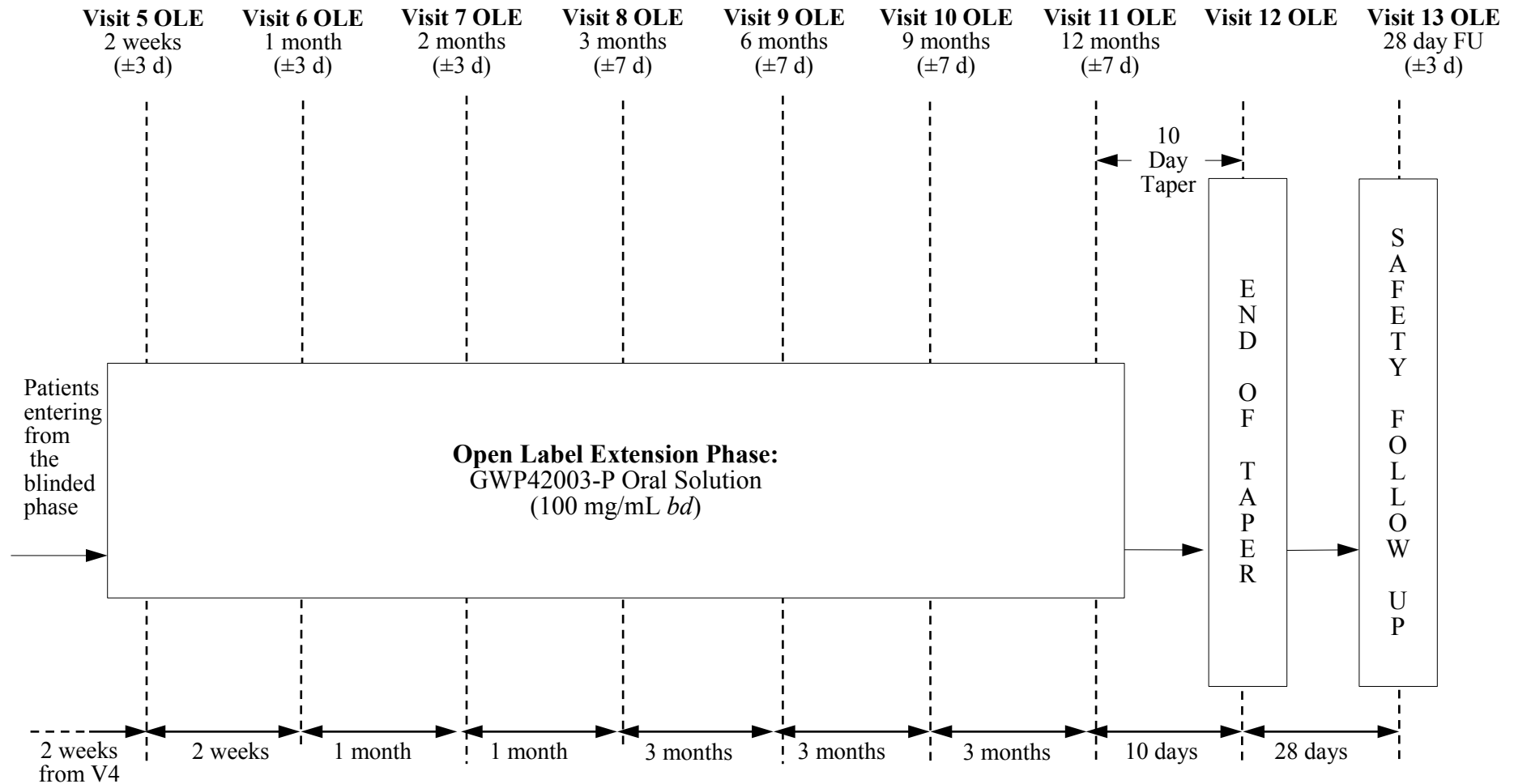


Table of Contents

Title Page	1
1. PROTOCOL SYNOPSIS.....	3
Table of Contents	18
Table of Appendices	23
List of In-text Tables	24
List of In-text Figures.....	25
List of Abbreviations	26
Definition of Terms.....	28
2. OBJECTIVES.....	29
2.1 Primary	29
2.2 Secondary	29
3. BACKGROUND AND RATIONALE	29
3.1 Disease.....	29
3.2 GWP42003-P Background.....	29
3.3 Rationale.....	30
3.3.1 Selection of Study Doses	31
3.4 Clinical Hypothesis	32
4. EXPERIMENTAL PLAN.....	32
4.1 Study Design	32
4.1.1 Primary Endpoint.....	34
4.1.2 Secondary Endpoint(s).....	34
4.2 Number of Centers	34
4.3 Number of Patients.....	34
5. INVESTIGATIONAL MEDICINAL PRODUCT	34
5.1 GWP42003-P Oral Solution.....	35
5.2 Placebo Oral Solution.....	35
5.3 Packaging, Storage and Drug Accountability (Cannabidiol/Placebo)	35
5.3.1 Packaging and Labelling.....	35
5.3.2 Storage	36
5.3.3 Supply and Return of Investigational Medicinal Product.....	36
5.3.4 Investigational Medicinal Product Accountability	36

5.4	Clobazam.....	37
6.	PARTICIPANT ELIGIBILITY	37
6.1	Inclusion Criteria.....	37
6.2	Exclusion Criteria.....	38
7.	PATIENT ENROLLMENT	40
7.1	Treatment Assignment	40
7.2	Randomization.....	40
8.	TREATMENT PROCEDURES.....	41
8.1	Investigational Medicinal Product Dosage, Administration and Schedule	41
8.1.1	Dose Administration.....	41
8.1.2	Dose Escalation and Dose Adjustments	42
8.2	Concomitant Therapy	43
8.3	Prohibited Therapy During Study Period.....	43
8.4	Compliance in Investigational Medicinal Product Administration.....	43
8.5	Access to Blinded Treatment Assignment	44
9.	STUDY PROCEDURES.....	45
9.1	Study Procedure Listing	45
9.1.1	Contraception.....	45
9.1.2	Informed Consent	45
9.1.3	Demographics	45
9.1.4	Medical History	46
9.1.5	Concomitant Medication	46
9.1.6	Physical Examination	46
9.1.7	Vital Signs	46
9.1.8	12-Lead Electrocardiogram	46
9.1.9	Clinical Laboratory Sampling.....	46
9.1.10	Pharmacokinetic Analyses.....	48
9.1.11	Genetic Testing.....	48
9.1.12	Columbia Suicide Severity Rating Scale.....	49
9.1.13	Patient Diary	49
9.1.14	Investigational Medicinal Product Accountability	49
9.1.15	Adverse Events	50

9.1.16	Monitoring of Drug Abuse Liability.....	50
9.1.16.1	Monitoring of Adverse Events.....	51
9.1.16.1.1	List of ‘Triggering Adverse Events of Interest’	51
9.1.16.1.2	Supplemental Adverse Event Form.....	51
9.1.16.2	Monitoring Drug Accountability Discrepancies	52
9.1.16.2.1	List of ‘Triggering Drug Accountability Discrepancies’	52
9.1.16.2.2	Supplemental Drug Accountability Form	53
9.1.16.3	Site Classification Form.....	53
9.1.16.4	Study Medication Use and Behavior Survey	53
9.1.16.5	Adjudication Committee — Assessment of Abuse Potential of GWP42003-P	54
9.2	Study Procedures by Visit.....	56
9.2.1	Double Blind Phase	56
9.2.1.1	Visit 1 (Day –14 to –7, Screening).....	56
9.2.1.2	Visit 2.....	56
9.2.1.2.1	Visit 2 (Day 1) – Enrollment (+3 days).....	56
9.2.1.2.2	Visit 2 (Day 2) - Enrollment.....	57
9.2.1.3	Visit 3 (Day 12 +3 days).....	57
9.2.1.4	Visit 4.....	57
9.2.1.4.1	Visit 4 (Day 33) (±3 days).....	57
9.2.1.4.2	Visit 4 (Day 34).....	58
9.2.1.5	Visit 5 (Patients not entering Open Label Extension) (Day 43 +3 days).....	58
9.2.1.6	Visit 6 - Safety Follow up Call (Day 71) (±3 days).....	59
9.2.2	Open Label Extension.....	59
9.2.2.1	Visit 5 (Open Label Extension) - Two Weeks (±3 days).....	59
9.2.2.2	Visit 6 (Open Label Extension) - One Month (±3 days).....	59
9.2.2.3	Visit 7 (Open Label Extension) - Two Months (±3 days)	60
9.2.2.4	Visit 8 (Open Label Extension) - Three Months (±7 days)	60
9.2.2.5	Visit 9 (Open Label Extension) - Six Months (±7 days)	60
9.2.2.6	Visit 10 (Open Label Extension) - Nine Months (±7 days).....	61
9.2.2.7	Visit 11 (Open Label Extension End of Treatment) - Twelve Months (±7 days)	61
9.2.2.8	Visit 12 (Open Label Extension End of Taper)	61

9.2.2.9	Safety Follow Up Call (± 3 days)	62
10.	WITHDRAWAL	62
11.	URGENT SAFETY MEASURES	63
12.	ADVERSE EVENT REPORTING	63
12.1	Definitions	63
12.1.1	Adverse Event	63
12.1.2	Investigator	64
12.2	Serious Adverse Events	64
12.3	Reporting Procedures for Serious Adverse Events	64
12.4	Pregnancy	65
12.5	Causality Assessment	65
12.6	Reporting Procedures for All Adverse Events	66
12.7	Follow up Procedures for Adverse Events	68
12.8	Potential Cases of Drug Induced Liver Injury	68
12.9	Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees	69
13.	STATISTICAL CONSIDERATIONS	71
13.1	Sample Size, Power and Significance Levels	71
13.2	Interim Analysis	71
13.3	Analysis Sets	71
13.3.1	Safety Set	71
13.3.2	Pharmacokinetic Analysis Set	71
13.3.3	Protocol Deviations	71
13.4	General Considerations	71
13.5	Accountability and Background Characteristics	72
13.5.1	Enrollment and Disposition	72
13.5.2	Baseline and Demographic Characteristics	72
13.5.3	Medical History	72
13.5.4	Concomitant Medication	72
13.6	Endpoints and Statistical Methods	72
13.6.1	Primary Endpoint(s)	72
13.6.2	Secondary Endpoint(s)	72
13.6.3	Pharmacokinetics	73

13.6.4	Safety	74
13.6.4.1	Treatment Compliance and Extent of Treatment Exposure	74
13.6.4.2	Adverse Events.....	74
13.6.4.3	Clinical Laboratory Data	74
13.6.4.4	Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data	75
13.6.4.5	Seizure Data	75
14.	DATA SAFETY MONITORING COMMITTEE	75
15.	REGULATORY AND ETHICAL OBLIGATIONS.....	76
15.1	Declaration of Helsinki	76
15.2	Informed Consent	76
15.3	Institutional Review Board/Ethics Committee.....	76
15.4	Pre-Study Documentation Requirements	77
15.5	Participant Confidentiality	77
16.	ADMINISTRATIVE AND LEGAL OBLIGATIONS.....	79
16.1	Protocol Amendments and End of Study or Termination	79
16.2	Study Documentation and Storage	79
16.3	Study Monitoring and Data Collection	80
16.4	Quality Assurance	82
16.5	Compensation.....	82
16.6	Publication Policy.....	82
16.7	Intellectual Property Rights.....	83
16.8	Confidential Information.....	83
17.	REFERENCES	84

Table of Appendices

APPENDIX 1.	Schedule of Assessments	87
APPENDIX 2.	Study Personnel	90
Appendix 3.1	Investigator Details	90
Appendix 3.2	Sponsor Contact Details	90

List of In-text Tables

Table 3.3.1-1	Epidiolex Adverse Events.....	32
Table 5.1-1	Formulation of GWP42003-P Oral Solution	35
Table 5.2-1	Formulation of Placebo Oral Solution	35
Table 8.1.2-1	Dose Up-Titration Regimen*	42
Table 9.1.9-1	Hematology, Biochemistry, Urinalysis and THC Screen	47

List of In-text Figures

Figure 1-1	Study Design and Treatment Schema.....	16
Figure 1-2	Study Design and Treatment Schema.....	17
Figure 9-1	Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization Tabulation and Analysis which can Illuminate an Abuse Potential Signal.....	55

List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic Drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC _(0-∞)	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
BP	Blood Pressure
CLB	Clobazam
CBD	Cannabidiol
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLB	Clobazam
C _{max}	Maximum measured plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	Ethics Committee
ECG	12-lead Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GW	GW Research Ltd
GWP	GW Pharma Ltd
IB	Investigator Brochure
ICH GCP	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat

IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward
MMRM	Mixed-effects Model Repeated Measures
N-CLB	N-desmethyleclobazam
OLE	Open label extension
PBPK	Physiologically-based pharmacokinetic interactions
PI	Principal Investigator
PP	Per Protocol
PVD	Pharmacovigilance Department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
TBL	Total bilirubin
THC	Δ^9 -tetrahydrocannabinol
t_{max}	Time to the maximum measured plasma concentration
ULN	Upper Limit of Normal
USA	United States of America
VNS	Vagus Nerve Stimulation

Definition of Terms

Term	Definition
Baseline period	The period from screening (Visit 1) to enrollment (Visit 2).
Convulsive seizures	Tonic-clonic, tonic, clonic or atonic seizures.
Countable partial seizures	Partial/focal seizures with a motor or behavioral component that allow such seizures to be easily identified and hence counted.
Day 1	The day a patient is enrolled and begins PK sampling.
End of treatment	Completion of the treatment period (Visit 5 or Visit 12) or withdrawal.
End of study	Last patient's last visit / last contact.
IMP	Investigational Medicinal Product (Study Medication). Used to describe both investigational active product and reference therapy (placebo).
INR	International Normalized Ratio (INR) is a calculation made to standardize prothrombin time.
Investigator	Study Principal Investigator or a formally delegated study physician.
Non-convulsive seizures	Myoclonic, partial or absence seizures.
Partial seizures	Partial (focal) seizures occur when the electrical activity remains in a limited area of the brain.
Status epilepticus	Seizures lasting for 30 minutes or longer.
Sub-types of seizures	Seizure sub-types can be tonic, clonic, tonic-clonic, atonic, myoclonic, absence (typical and atypical), countable partial and other partial.

2. OBJECTIVES

2.1 Primary

To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyclobazam (N-CLB).

2.2 Secondary

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

3. BACKGROUND AND RATIONALE

3.1 Disease

Epilepsy is a common disorder¹. Approximately 1% of the world's population is chronically affected by epilepsy². It shows no particular geographic distribution and the gender distribution is more or less equal. The incidence of epilepsy is greater in childhood and in elderly people^{2,3,4,5}. Focal seizures represent the most frequent seizure type (around 60% of all cases of epilepsy, and a substantial percentage of them are not well controlled)⁶.

Overall, and despite the introduction of a substantial number of new antiepileptic drugs (AEDs) in the last two decades, around 30% of patients remain refractory to currently available treatment^{7,8,9}. In addition, most currently approved AEDs are associated with significant motor and cognitive adverse reactions^{10,11}.

Currently available AEDs each belong to one of a large number of different classes. The principal targets for existing AEDs tend to be either modulators of voltage-dependent ion channels, enhancers of inhibitory neurotransmission, and attenuators of excitatory neurotransmission, with the aim being to reduce neuronal excitotoxicity^{12,13}.

3.2 GWP42003-P Background

The cannabis plant (*Cannabis sativa* L.) produce trichomes that synthesize a large number of pharmacologically active compounds called phytocannabinoids. The most abundant of these are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), although the amounts and proportions of the various phytocannabinoids in each plant vary by strain and can be adjusted by breeding.

The Investigational Medicinal Product (IMP), GWP42003-P, is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from

these plants are processed to yield pure (>98%) CBD that typically contains less than 0.5% (w/w) THC. The pure CBD is subsequently dissolved in excipients with added sweetener and flavoring.

The pharmacological effects of phytocannabinoids are thought to be mediated primarily via their interaction with the endocannabinoid system, which consists of cannabinoid receptors, endogenous ligands (endocannabinoids) and enzymes for endocannabinoid synthesis and degradation. Two G-protein-coupled receptors for cannabinoids have so far been identified, designated cannabinoid CB₁ and CB₂ receptors. CBD does not bind to either of these receptors with any great affinity but does modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects ion channel conductance and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1¹⁴ and the orphan receptor GPR55¹⁵. Importantly, in contrast to THC, CBD lacks detectable psychoactivity. CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity¹⁶. Very little data concerning AEs of CBD in humans exists to date. However, doses of up to 1500 mg CBD per day are reported to be well tolerated in humans¹⁷.

3.3 Rationale

CBD has shown therapeutic potential as an AED, with preclinical studies demonstrating anticonvulsant effects in a number of animal models of seizure^{16,18,19}. Although no placebo-controlled trials have been completed to date, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures while taking CBD-enriched cannabis, with over half of those reporting either >80% reduction in seizure frequency or complete seizure freedom²⁰. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness and better mood. There has been a program of expanded access by GW Pharma Ltd (GWP) in the USA, primarily in children with severe epilepsy, that has shown encouraging reports of reductions in multiple seizure types with good tolerability in 151 exposures²¹.

Population-based studies of drug utilization demonstrate that 19-24% of patients with epilepsy use polytherapy with AEDs^{22,23,24}. In recent studies of children and adults with refractory epilepsy, 64 % used polytherapy with two or more AEDs, resulting in a considerable risk of interactions^{25,26}. CLB is a widely used 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). The pharmacological action of CLB is to decrease abnormal electrical activity in the brain via allosteric activation of the ligand-gated γ -aminobutyric acid (A) receptor.

CLB is in a class of medications called benzodiazepines. Similar to other benzodiazepine medications, clobazam is metabolized by cytochrome P450 (CYP450) enzymes (mainly in the liver). This metabolism results in the formation of an active metabolite N-CLB, amongst others.

Cytochrome P450 enzymes are a family of heme-containing enzymes responsible for the metabolism of over half of all prescribed medications and interactions with these enzymes are the major source of physiologically-based pharmacokinetic (PBPK) interactions between drugs. It is anticipated that patients taking GWP42003-P may also be taking clobazam and as CBD has been shown to both inhibit CYP450 enzymes in vitro (K_i CYP3A4 = 1.5 μ M) and induce CYP450 enzymes in vitro (EC₅₀ CYP3A4 = 1.2 μ g/mL) a possibility of a pharmacokinetic (PK) interaction between CBD and clobazam exists. Furthermore, CLB has been shown to undergo PBPK interactions with other AED medications via both CYP induction (such as with felbamate where the formation of the active metabolite of clobazam, N-CLB was increased several-fold²⁷) and also CYP inhibition (such as with stiripentol where serum concentrations of CLB were increased and metabolites decreased^{28,29,30}). Given the high likelihood that patients prescribed CBD will also be using clobazam, it is the aim and purpose of this study to determine whether a PK interaction between CBD and CLB exists.

3.3.1 Selection of Study Doses

Doses up to 800 mg GWP42003-P per day for up to eight weeks have been well tolerated in adults in GW Research Ltd (GW) clinical study GWMD09112, which, assuming an average weight of 70 kg, equates to a daily dose of 11.4 mg/kg. In the literature, doses of GWP42003-P have been given up to 1500 mg GWP42003-P per day for four weeks in adults, which, in a 70 kg human equates to a daily dose of 21.4 mg/kg GWP42003-P.

Data on the safety of GWP42003-P is emerging from the physician-initiated Epidiolex[®] Expanded Access Program being conducted in the USA. This program has been running since January 2014 and at the time of writing had data on 63 patients. The mean maximum exposure achieved in this patient population of refractory epilepsies was a daily dose of 24.4 mg/kg (n=59 patients) with a maximum dose of 51 mg/kg in one patient. Please see below for a break-down of the groups:

- ≤ 20 mg/kg GWP42003-P n=13 (21%)

- >20 mg/kg - ≤30 mg/kg GWP42003-P n=40 (64%)
- >30 mg/kg - ≤40 mg/kg GWP42003-P n=4 (6%)
- >40 mg/kg GWP42003-P n=2 (3%)
- Dose not reported n=4(6%)

Eleven patients had a daily GWP42003-P dose of >25 mg/kg, of which five did not report any adverse events (AEs). Of note, the patient who received 51 mg/kg did not have any AEs at this dose. The remaining six patients experienced AEs as documented in the [Table 3.3.1-1](#) below:

Table 3.3.1-1 Epidiolex Adverse Events	
Adverse Event Term	Number of Events
Loose stools / urgent bowel movements	2
Increase in seizures	2
Drowsiness	1
Aspiration pneumonia	1
Lethargy	1
Decreased appetite	1
Dyskinesia	1
Urinary tract infection	1

Based on the above, a daily dose up to 20 mg/kg/day (given as two divided doses) has been selected for the GWP42003-P dose in the current study, including a titration period with daily increments of 2.5 mg/kg and 5 mg/kg. 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 interest. During the OLE doses may be adjusted up or down, dependent on investigator opinion, to a maximum daily dose of 30 mg/kg GWP42003-P.

3.4 Clinical Hypothesis

CBD can act as both a CYP inhibitor and inducer in human hepatocytes in vitro. Therefore, the potential for PK interactions with other drugs that are metabolized by CYP450 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.

4. EXPERIMENTAL PLAN

4.1 Study Design

This phase 2, placebo-controlled study consists of a 34 day, double-blind phase followed by an optional maximum one year 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 or equivalent of 20 mg/kg/day. 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 (Visit 2) before beginning treatment (patients will be taking CLB only).
- Day 33 (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, CBD, CBD major metabolites, THC and THC major metabolites.

Patients should try to be consistent in the timing of their food intake in relation to dosing throughout the blinded phase of the study.

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.

A study schema ([Figure 1-1](#)), presented at the end of [Section 1](#), depicts the overall study design. More detailed information on treatment and study procedures are provided in [Section 8](#) and [Section 9](#) respectively.

4.1.1 Primary Endpoint

The primary endpoints of the study are the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

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

4.1.2 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:

- 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

PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- THC
- THC major metabolites

4.2 Number of Centers

An estimated number of seven centers are expected to participate in this study.

4.3 Number of Patients

A total of 20 patients will be enrolled into the study. Recruitment for the study will be competitive between participating sites.

The sample size calculation is explained fully in [Section 13.1](#).

5. INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.1 GWP42003-P Oral Solution

GWP42003-P oral solution is presented as a pale yellow oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.1-1](#).

Table 5.1-1 Formulation of GWP42003-P Oral Solution	
Material	Quantity
CBD	100 mg/mL
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.2 Placebo Oral Solution

Placebo oral solution contains the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.2-1](#).

Table 5.2-1 Formulation of Placebo Oral Solution	
Material	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.3 Packaging, Storage and Drug Accountability (Cannabidiol/Placebo)

5.3.1 Packaging and Labelling

The IMP will be manufactured and packaged by GWP. It will be distributed by GWP or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each visit considering the weight of each patient. A unique pack identification number will be used to identify each box and the medication it contains. The pack numbers will cross check with the batch numbers held at GWP. GWP will ensure that all IMP provided is fully labelled and packaged. Label text will comply with European Union (EU) guidance on Good Manufacturing Practice, Annex 13 Labelling and will be fully described in the separate Pharmacy Manual. In addition, any local country requirements in accordance with local drug law or regulatory requirement will be included in the final label text.

Directions of use, name, address and telephone number of investigator, or main contact for information about the product or the clinical trial, will be provided separately to the patient.

5.3.2 Storage

The IMP must be stored upright at room temperature ($< 30^{\circ}\text{C}$) and must not be refrigerated or frozen. It must also be kept away from heat and direct sunlight.

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities.

Should storage conditions deviate from these specified requirements, the GW study monitor should be contacted immediately to confirm if the IMP remains suitable for use. IMP should be placed under quarantine until confirmation is received that IMP is suitable for use.

Temperature records of the storage location must be maintained on a daily basis (a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each site. These records must contain at least the minimum and maximum daily temperatures and should be made available to the appropriate GW personnel for review throughout the study.

5.3.3 Supply and Return of Investigational Medicinal Product

Once a site has been activated at study initiation, IMP will be shipped to a responsible person, such as the pharmacist, at the investigator's center, who will check the amount received and the condition of the drug. Details of the IMP received will be recorded in the IMP accountability record. The site will acknowledge IMP receipt and will complete any receipt forms required. IMP will be dispensed and returned as detailed in [Section 5.3.4](#) with further IMP shipments to be requested as necessary. As directed, all supplies, including unused, partially used, or empty containers, will be returned to GWP or destroyed at the center if agreed in writing by the study monitor.

5.3.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMPs must be kept current and should contain:

- The dates and quantities of IMP received from GWP.
- Patient's identification.
- Date and quantity of IMP dispensed.
- The initials of the dispenser.

- Date and quantity of IMP returned to the investigator/pharmacy.

A record of returned IMP must be completed and included in the shipment of used and unused IMP to GWP. At the end of the study a record/statement of reconciliation must be completed and provided to GWP.

These inventories must be made available for inspection by authorized GW or GWP representatives and local officials or regulatory agency inspectors.

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.4 Clobazam

Patients will use their own supply of Clobazam throughout the study. Clobazam usage will be recorded by the investigator. Clobazam is only an IMP for the blinded phase of the study.

6. PARTICIPANT ELIGIBILITY

Investigators will be required to maintain a log that includes limited information about all screened patients (initials, age, and gender; as allowed per local regulations) and outcome of screening.

6.1 Inclusion Criteria

For inclusion in the study patients must fulfil ALL of the following criteria:

- 6.1.1 Male or female patients aged 18 to 55 years inclusive.
- 6.1.2 Patient must have epilepsy as determined by the investigator and be taking CLB.
- 6.1.3 Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition.
- 6.1.4 Patient must have experienced at least one seizure of any type (i.e., convulsive: tonic-clonic, tonic, clonic, atonic; focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness focal seizures evolving to bilateral secondary generalization) within the two months prior to randomization.
- 6.1.5 Patients must be taking CLB and no more than two other AEDs during the course of the study.
- 6.1.6 AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study.
- 6.1.7 Intervention with vagus nerve stimulation (VNS) and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must

- be willing to maintain a stable regimen throughout the blinded phase of the study.
- 6.1.8 Patients must abstain from alcohol during the blinded phase of the study.
 - 6.1.9 Patient and/or legal representative is available to attend all PK visits within the required visit window.
 - 6.1.10 Patient and/or legal representative must be willing and able to give informed consent for participation in the study
 - 6.1.11 Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements.
 - 6.1.12 Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable.
 - 6.1.13 Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study.

6.2 Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

- 6.2.1 Patient has clinically significant unstable medical conditions other than epilepsy.
- 6.2.2 Patients on CLB at doses above 20 mg per day.
- 6.2.3 Patients taking CLB intermittently as rescue medication.
- 6.2.4 Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes.
- 6.2.5 Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening.
- 6.2.6 Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy.
- 6.2.7 Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain during the blinded phase of the study.
- 6.2.8 Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry.
- 6.2.9 Patient has any known or suspected history of any drug abuse or addiction.
- 6.2.10 Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration for the study.
- 6.2.11 Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits.
- 6.2.12 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil.

- 6.2.13 Female patient is of child bearing potential, or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.
- 6.2.14 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.
- 6.2.15 Patients who have received an IMP within the 12 weeks prior to the screening visit.
- 6.2.16 Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study.
- 6.2.17 Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator would prevent the patient from safe participation in the study.
- 6.2.18 Patient has significantly impaired hepatic function at screening (Visit 1) or enrollment (Visit 2), defined as any of the following:
- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $>5 \times$ upper limit of normal (ULN).
 - ALT or AST $>3 \times$ ULN **and** total bilirubin (TBL) $>2 \times$ ULN **or** international normalized ratio (INR) >1.5 .
 - ALT or AST $>3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion **must** be withdrawn from the study.*
- 6.2.19 Unwilling to abstain from donation of blood during the study.
- 6.2.20 Travel outside the country of residence planned during the study.
- 6.2.21 Patients previously enrolled into this study.

7. PATIENT ENROLLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center's Ethics Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent forms and other patient information material. Patients will be considered enrolled in the study from the time of providing written informed consent. All patients, or legal representatives, where appropriate, must personally sign and date the consent form prior to any procedures being performed (refer to [Section 9.1.2](#) and [Section 15.2](#)).

7.1 Treatment Assignment

At the start of Visit 1, patients will be allocated a unique patient number, consisting of a four digit GW center number and a three digit patient identification number. The three digit patient number will be assigned in ascendant numerical order at each site. The unique patient number will be preceded by a unique letter. For example, P1234001, denoting patient 001 at site 1234. GWP will provide all GWP42003-P/placebo packed and labelled. Following enrollment at Visit 2, patients will be allocated a pre-packed numbered IMP.

7.2 Randomization

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

8. TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The IMP will consist of three types of medication:

- GWP42003-P Oral Solution containing 100 mg/mL CBD.
- Placebo Oral Solution containing excipients.
- Clobazam (patient supplied).

The GWP42003-P/placebo will be presented as an oral solution containing either the active pharmaceutical ingredient and excipients (in the case of GWP42003-P) or only excipients (in the case of placebo). For details regarding GWP42003-P/placebo formulations, see [Section 5](#).

All patients will be weighed during the study visits and the daily volumes of GWP42003-P/placebo solution to be taken during the titration period, and for the remainder of the study, will be calculated and provided to the patient and/or caregiver. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Each patient will take their first dose of GWP42003-P/placebo at Visit 2, Day 2 in the clinic. Patients not entering the OLE will take their final maintenance dose of GWP42003-P/placebo at Visit 4 (Day 33) in the clinic. Patients entering the OLE will take their final dose of IMP at Visit 11 (one year after the end of the blinded phase of the study) or sooner (if marketing authorization is granted within one year).

Patients will use their own supply of Clobazam throughout the study. Patients will continue on the dose that they were on at screening for the blinded phase of the study. Clobazam will only be an IMP for the blinded section of the study.

8.1.1 Dose Administration

GWP42003-P/placebo will be administered orally by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided.

GWP42003 P/placebo should be taken immediately after the patient's usual CLB administration. The GWP42003-P/placebo should be swallowed, as per the intended commercial therapeutic route, and may be taken with other concomitant medications, as directed by the investigator.

8.1.2 Dose Escalation and Dose Adjustments

Patients will enter the blinded phase of the study and will be up-titrated over ten days (Day 2 to Day 11) to a maintenance dose or equivalent of GWP42003-P/placebo of 20 mg/kg/day. If GWP42003-P is not tolerated then the dose can be reduced accordingly at the discretion of the investigator. The titration regimen is described in [Table 8.1.2-1](#).

Table 8.1.2-1 Dose Up-Titration Regimen*		
Day - GWP42003-P/Placebo (Blinded Period)	Day - GWP42003-P only (OLE**)	Dose Level (GWP42003-P or equivalent placebo)
2	34	2.5 mg/kg
3	35	2.5 mg/kg
4	36	5.0 mg/kg
5	37	5.0 mg/kg
6	38	7.5 mg/kg
7	39	7.5 mg/kg
8	40	10.0 mg/kg
9	41	10.0 mg/kg
10	42	15.0 mg/kg
11	43	15.0 mg/kg
12 onwards	44 onwards	20.0 mg/kg

*GWP42003-P /placebo is to be taken twice daily. Total daily doses are shown.

** Only patients who were taking placebo during the double-blind period will up-titrate according to this schedule during the OLE period. Those taking GWP42003-P during the double-blind period will down-titrate their blinded IMP whilst simultaneously up-titrating with GWP42003-P, thus maintaining a daily dose of 20 mg/kg/day GWP42003-P throughout.

The titration regimen defined above should be followed to the maximum dose (20 mg/kg/day). Should an AE occur during titration which is attributable to IMP or concomitant AED, then IMP dose should be reduced to the next lower dose. Any other changes in concomitant AED therapy should be reviewed with the medical monitor before being initiated.

For those patients who do not enter the OLE the dose of GWP42003-P/placebo will taper off over 10 days beginning on Day 34. The patient will reduce the dose by 10% of the maintenance dose each day and treatment will end on Day 43.

Patients who enter the OLE period will be transitioned to the OLE treatment over a 10-day period in order to maintain blinding, simultaneously down-titrating blinded GWP42003-P /placebo whilst up-titrating open-label GWP42003-P. As such, patients who were taking GWP42003-P during the blinded period will maintain their 20 mg/kg/day dose throughout the transition from the blinded period into the OLE period and patients who received placebo during the blinded period up-titrate slowly to the 20 mg/kg/day dose in the OLE period. After this has taken place, the

maintenance dose of GWP42003-P may be adjusted up or down at the discretion of the investigator to a maximum of 30 mg/kg/day (no minimum).

8.2 Concomitant Therapy

Doses of any concomitant AEDs, including CLB, must have been stable for at least four weeks prior to screening and must remain stable throughout the blinded phase of the study. If there are symptoms of toxicity suspected to be from a drug interaction, the investigator may adjust GWP42003-P/placebo or the CLB or other AEDs after discussion with the medical monitor.

The use of rescue medication is allowed if necessary. The use of oxygen may be considered as rescue medication if used as required. Any medication, other than the IMP, taken during the study must be recorded on the Case Report Form (CRF).

Any non-pharmacological therapies (e.g., ketogenic diet, VNS) must also be stable up to four weeks prior to baseline and throughout the duration of the study.

8.3 Prohibited Therapy During Study Period

The following medications are prohibited for the duration of the study starting from acquisition of patient consent. However, any patients taking these medications after screening should not be withdrawn from the study unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered.

- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.
- Patients should not take any more than three AEDs inclusive of CLB.
- Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.

If any other IMP is taken as part of a clinical trial within twelve weeks of the screening visit or during the study, the patient must be withdrawn from this study.

8.4 Compliance in Investigational Medicinal Product Administration

Patients or their caregivers will record the total volume of IMP, administered on each treatment day, using the paper diary and will be asked to return all IMP (used and unused) at each subsequent visit. The site will check the returned IMP against the usage recorded in the diary and the projected usage. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

The investigator must inform GW promptly of all missing or unaccountable IMP.

Records of IMP accountability will be maintained according to [Section 5.3.4](#).

8.5 Access to Blinded Treatment Assignment

The identity of IMP assigned to patients will be held by the IVRS. The principal investigator (PI) at each center is responsible for all trial-related medical decisions and is responsible for ensuring that information on how to access the IVRS is available to the relevant staff in case of an emergency and unblinding is required. 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.

The investigator is encouraged to contact GW to discuss the rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of study medication will not be dependent upon the investigator receiving approval from GW (i.e., the investigator will be able to obtain the code break information independent of contacting GW).

If the investigator does unblind they must contact GW within one working day of the event and must document the time, date and reasons for unblinding in the patient's CRF.

9. STUDY PROCEDURES

A list of the required study procedures is provided in the subsections that follow, refer also to the Schedule of Assessments [APPENDIX 1](#). Assessments or tests that are not done and examinations that are not conducted must be reported as such on the CRFs.

The location of the source data for the following procedures will be documented, per center, in a signed ‘Source Data Verification plan’, for further details see [Section 16.2](#).

9.1 Study Procedure Listing

9.1.1 Contraception

To be eligible for the study, the patient must have agreed that if they or their partner are of child-bearing potential they are willing to use highly effective contraception for the duration of the study and for three months thereafter. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence⁶. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. The use of hormonal contraception must be supplemented with a barrier method (preferably male condom).

9.1.2 Informed Consent

Adult patients with an adequate level of understanding must personally sign and date the IRB/EC approved informed consent form(s) before any study specific procedures are performed or any patient related data is recorded for the study. For adult patients with an insufficient level of understanding of what is proposed, only personal legal representative consent will be sought. The informed consent process should be documented within the patient notes.

GW requires a physician to be present for consent and to also sign the consent forms.

9.1.3 Demographics

Patient demographics will be recorded at Visit 1. The following information will be obtained for each patient: date of birth, gender and race (if allowed per local regulations).

9.1.4 Medical History

Relevant, significant medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken) will be obtained during Visit 1 and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the study.

9.1.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 28 days) including AEDs will be recorded at the screening visit (Visit 1) and reviewed at each subsequent visit. AEDs used during the study should be maintained at a stable dose. Any changes in concomitant medication during the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to the screening visit, as defined in [Section 8.3](#).

9.1.6 Physical Examination

A physical examination will be performed at the screening visit (Visit 1) to ensure that the patient is eligible to enter the study. To ensure patient safety, further physical examinations will be performed at every hospital visit. Physical examinations will include height (at screening) and body weight measurements.

9.1.7 Vital Signs

Vital sign measurements, taken after five minutes rest in a sitting position, will be completed alongside the physical examination at all visits. Postural BP will be assessed after five minutes in supine position and, if possible, two minutes in standing position. The pulse rate must also be measured as part of the vital sign assessments. BP and pulse rate must be recorded using the same arm throughout the study.

9.1.8 12-Lead Electrocardiogram

An ECG will be performed, after five minutes in supine position, at all hospital visits. A physician must review the ECG and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately in the CRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

9.1.9 Clinical Laboratory Sampling

Laboratory tests will be undertaken at all hospital visits and will include hematology, biochemistry, and urinalysis (provided urine can be obtained, with the exception of

screening where a urine sample for THC screen must be obtained). A serum alcohol test will be performed at Visits 1, 2 and 4. A serum pregnancy test (if appropriate) will also be performed at Visit 1.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further laboratory based urinalysis (urinalysis, microscopy, culture and sensitivity, as applicable).

The investigator and study monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in [Table 9.1.9-1](#).

Table 9.1.9-1 Hematology, Biochemistry, Urinalysis and THC Screen				
Biochemistry (serum)	Hematology (whole blood)	Urinalysis (urine)	Pregnancy Test	THC screen (urine)
Alanine aminotransferase (ALT)	Hematocrit	Bilirubin	Serum	THC
Albumin	Hemoglobin	Blood		
Alkaline phosphatase	Mean cell volume	Glucose		
Aspartate aminotransferase (AST)	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				

All laboratory results will be reviewed and the reports signed by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. See [Section 12.8](#) for guidance on evaluation of potential drug-induced liver injury. All laboratory results considered by the investigator to represent an AE must be documented on the CRF.

Repeat samples will be taken, if required, for clinical follow up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an

investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation.

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss in the four weeks prior to screening.

9.1.10 Pharmacokinetic Analyses

The plasma concentration/time curves of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites will be assessed at Visit 2 (Day 1 and Day 2) and Visit 4 (Day 33 and Day 34). Patients will be given their daily dose of clobazam 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. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted into a forearm vein 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.

The pre-dose blood sample will be taken within 30 minutes prior to dosing. The allowable window for post-dose blood sample collection is ± 2 minutes up to and including 1 hour post-dose, ± 5 minutes from 1.5 hours up to and including 6 hours post-dose and ± 1 hour at 12 hours and 24 hours post-dose.

In the event of an AE that, in the opinion of the investigator, is related to a concomitant AED, additional blood samples may be collected.

Analysis of all PK samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

9.1.11 Genetic Testing

Genetic testing will only be conducted if specific consent is obtained from the participant. There is a separate informed consent form for this.

Genetic testing will be conducted to look at the CYP450 genes, with particular focus on CYP 2C19 and CYP 3A4, involved in the metabolism of AEDs and GWP42003-P.

9.1.12 Columbia Suicide Severity Rating Scale

The C-SSRS is to be completed by the investigator or his/her qualified designee at all hospital visits. Qualified designee is defined as physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant who is licensed and has completed the C-SSRS training within the last two years. It is a brief standardized measure that uniquely assesses the essential information (behavior, ideation, lethality and severity) and distinguishes between suicidal occurrences and non-suicidal self-injury. The survey should be completed by the same assessor, where possible, throughout the study.

If the investigator or his/her qualified designee feel that the patient is either unable to answer the questions presented in C-SSRS, or that the questions are causing undue stress to the patient, the questionnaire may be skipped and this must be documented in the patient notes.

9.1.13 Patient Diary

Patients or their caregivers will be instructed on how to complete a paper diary and will be asked to record information daily in it. The number and type of seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from screening (Visit 1) until completion of dosing or withdrawal. Information on IMP intake will also be recorded each day from enrollment (Visit 2) until completion of dosing or withdrawal.

9.1.14 Investigational Medicinal Product Accountability

GWP42003-P/placebo will be dispensed at each of the following visits during the blinded phase:

- Visit 2 (Day 2)
- Visit 4 (Day 34)

IMP will be dispensed at each of the following visits for patients entering the OLE:

- Visit 5 (Two weeks)
- Visit 6 (One month)
- Visit 7 (Two months)
- Visit 8 (Three months)
- Visit 9 (Six months)
- Visit 10 (Nine months)
- Visit 11 (12 months)

Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 2 to 12). The site will check the returned IMP against the usage recorded in the paper diary. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

9.1.15 Adverse Events

Any adverse changes in the patient's medical condition, following completion of the consent form by the patient, will be recorded on the CRF as AEs, questioning the patient further if necessary. All AEs* occurring during the study, whether or not attributed to the IMP, observed by the investigator or reported by the patient will be recorded in the CRF.

*For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures, must be documented as an AE.

Serious Adverse Events (SAEs) must be reported to GW Pharmacovigilance Department (PVD) within 24 hours of discovery or notification of the event, and recorded in the CRF.

Refer to [Section 12](#) for definitions, procedures and further information.

Inpatient hospitalizations that are, in the investigator's opinion, due to epilepsy will be recorded in the patient's CRF and through the SAE reporting process.

Refer to [Section 9.1.16.1.1](#) for the list of 'Triggering AEs of Interest' associated with monitoring of drug abuse liability.

9.1.16 Monitoring of Drug Abuse Liability

There are two triggers that will require the investigator or study coordinator to discuss abuse potential signals with the patient or their caregiver. These are either AEs of interest that may be reported by the patient/caregiver, or drug accountability issues regarding overuse of the IMP or missing bottles. Different questionnaires will be completed by the site depending upon which trigger occurs (see [Figure 9-1](#)).

Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (Visit 5 or Visit 12) or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.

Investigators and study coordinators will be provided with training on how to complete and perform the processes outlined in this section. This training must be completed and documented by the relevant site staff prior to implementation at site.

9.1.16.1 Monitoring of Adverse Events

AE information will be collected according to [Section 9.1.15](#).

9.1.16.1.1 List of ‘Triggering Adverse Events of Interest’

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 Adverse Event 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.

An AE that is consistent with the above categories will be known as a ‘triggering AE of interest’ for the purposes of this study.

9.1.16.1.2 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Adverse Event Form will then be transcribed into the patient’s CRF for the study. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the site should contact the patient/caregiver to obtain the required answers as soon as possible.

9.1.16.2 Monitoring Drug Accountability Discrepancies

Any time after enrollment until final collection of study data, drug accountability discrepancies are monitored as follows:

- At routine Drug Accountability collection times, the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the paper diary.
- At any time that the site is informed by the patient/caregiver about any overuse of IMP, suspected misuse, abuse, or diversion.

9.1.16.2.1 List of ‘Triggering Drug Accountability Discrepancies’

If there are any discrepancies in drug accountability as outlined by the criteria below, known as ‘triggering drug accountability discrepancies’, then the trained investigator or study coordinator will complete a Supplemental Drug Accountability Form and Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver. The triggering drug accountability discrepancies are as follows:

- Missing bottle(s).
- Compliance issues where one or more bottles are used compared to what was the expected use, according to the paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the paper diary.

9.1.16.2 Supplemental Drug Accountability Form

This form consists of eight questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Drug Accountability Form will then be transcribed into the patient's CRF for the study. The accountability reporting procedures will still occur. If the Supplemental Drug Accountability Form cannot be completed at the time the triggering drug accountability discrepancy is identified, then the site should contact the patient/caregiver by telephone to obtain the required answers as soon as possible (Note: IMP refers to GWP42003-P or placebo, not other concomitant medications).

9.1.16.3 Site Classification Form

The investigator should review the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then complete the Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification. The answers from the Site Classification Form will then be transcribed into the patient's CRF for the study.

9.1.16.4 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit (Visit 5 or Visit 12) or withdrawal visit. The answers on the Study Medication Use and Behavior Survey will then be transcribed into the patient's CRF for the study.

The Study Medication Use and Behavior Survey will be completed for all patients in the study and not only those that have reported a triggering AE or drug accountability discrepancy.

9.1.16.5 Adjudication Committee — Assessment of Abuse Potential of GWP42003-P

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases. Only data from patients who have completed the study will be assessed.

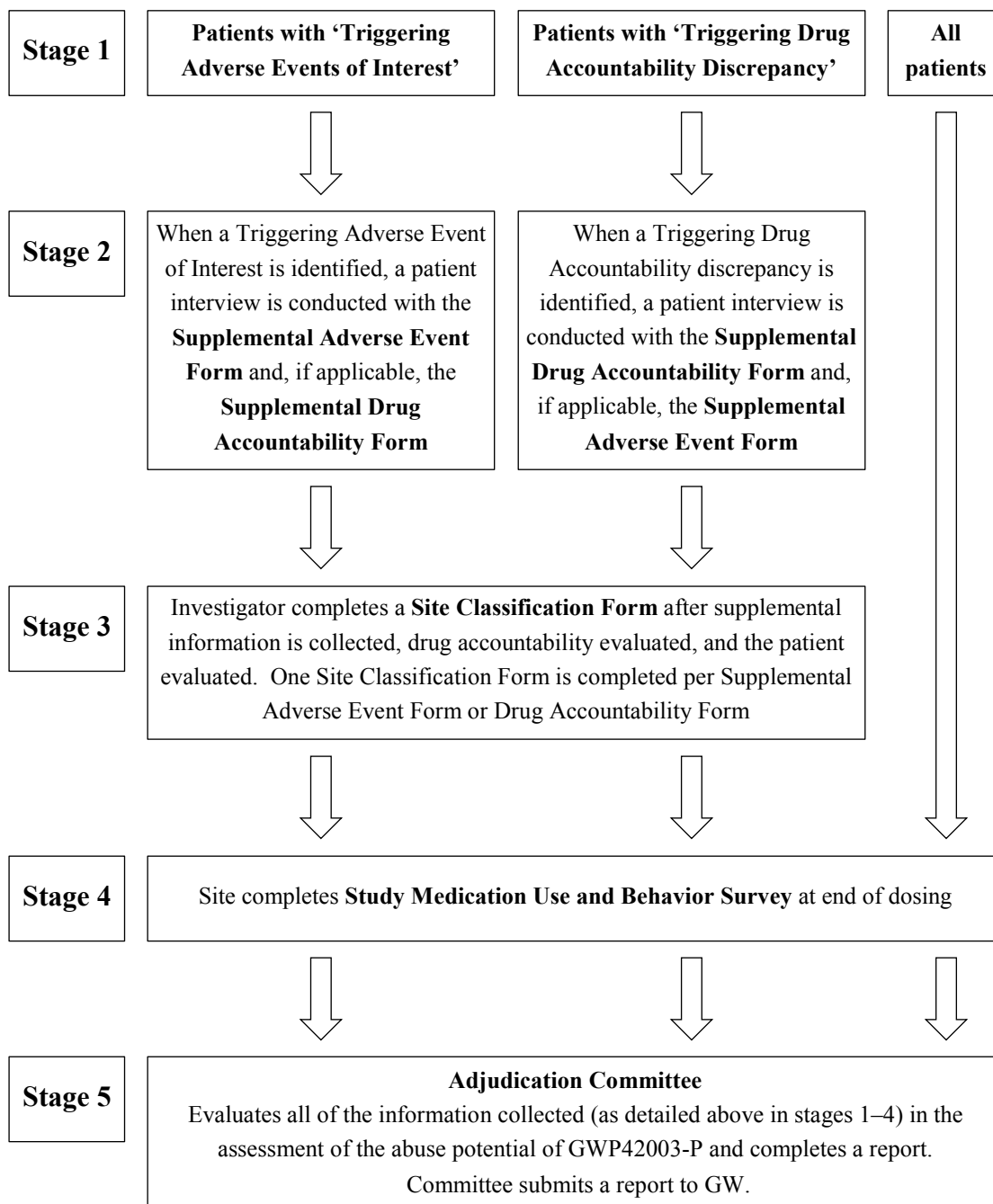
A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- All triggering AE information.
- Supplemental Adverse Event Form (if applicable).
- All triggering drug accountability discrepancies.
- Supplemental Drug Accountability Form (if applicable).
- Site Classification Form.
- Study Medication Use and Behavioral Survey.
- Additional information from site(s) as requested by the Committee.

The Adjudication Committee will assess all of the information. It will form a position on the classification of each event and will write a study-related report, detailing the conclusions and recommendations.

The overall process is summarized in [Figure 9-1](#).

Figure 9-1 **Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization Tabulation and Analysis which can Illuminate an Abuse Potential Signal**



9.2 Study Procedures by Visit

Patients and their caregivers will be invited to participate in the study and will be issued with the patient information and informed consent or the personal legal representative information and informed consent (refer to [Section 9.1.2](#) and [Section 15.2](#)). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/legal representatives who provide written informed consent at Visit 1 will be screened for entry into the study.

9.2.1 Double Blind Phase

9.2.1.1 Visit 1 (Day -14 to -7, Screening)

The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, THC testing, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.

Patients who satisfy all inclusion and none of the exclusion criteria specified in [Section 6](#) will be assigned a unique patient number and then begin the baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be instructed on how to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.

9.2.1.2 Visit 2

9.2.1.2.1 Visit 2 (Day 1) – Enrollment (+3 days)

This visit will occur 7–14 days after Visit 1.

The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including body weight), ECG, vital signs and review of patient diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. Blood samples will also be taken for genetic testing if additional consent has been obtained. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.

Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic on Day 2 ahead of additional sample collection.

9.2.1.2.2 Visit 2 (Day 2) - Enrollment

This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.

GWP42003-P/placebo will be dispensed and both the morning dose of CLB and of GWP42003-P/placebo will be taken in clinic. Patients and/or their caregivers will be provided with individual dosing schedules as described in [Section 8.1.2](#). Each patient will then receive their GWP42003-P/placebo for the 10 day titration period followed by the 21 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.

9.2.1.3 Visit 3 (Day 12 +3 days)

This visit will occur 11 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 3 (Day 12): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, AEs and review of patient diary completion.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.

9.2.1.4 Visit 4

9.2.1.4.1 Visit 4 (Day 33) (±3 days)

This visit will occur 32 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 4 (Day 33): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, and urinalysis. The C-SSRS will be administered.

Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of GWP42003-P/placebo. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. Patients are expected to remain in clinic throughout this PK sampling.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.1.4.2 Visit 4 (Day 34)

This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 33 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 34: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.

At the end of the blinded phase of the study on Day 34, providing the investigator and patient both agree, patients will be invited to continue taking GWP42003-P and to enter the OLE.

Patients who enter the OLE will be dispensed GWP42003-P on Day 34. At the point of entry to the OLE, patients will be transitioned to the OLE treatment over a 10 day period in order to maintain blinding. The dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day in the blinded phase to a maximum of 30 mg/kg/day in the OLE. Patients and/or their caregivers will be provided with individual dosing schedules as described in [Section 8.1.2](#). Patients, or their caregivers, will be instructed how to record the diary information.

Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of GWP42003-P/placebo. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42.

9.2.1.5 Visit 5 (Patients not entering Open Label Extension) (Day 43 +3 days)

This visit will occur 42 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.

All GWP42003-P/placebo (used and unused) will be collected and a check of the returned GWP42003-P/placebo against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.

9.2.1.6 Visit 6 - Safety Follow up Call (Day 71) (± 3 days)

This visit is required for patients who do not enter the OLE study on Day 34, or who withdraw from the study early. This visit should occur four weeks after Visit 5, (± 3 days) or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 71: concomitant medications (including AEDs) and AEs.

9.2.2 Open Label Extension

Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 34) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 34).

9.2.2.1 Visit 5 (Open Label Extension) - Two Weeks (± 3 days)

This visit will occur two weeks after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.2 Visit 6 (Open Label Extension) - One Month (± 3 days)

This visit will occur one month after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.3 Visit 7 (Open Label Extension) - Two Months (± 3 days)

This visit will occur two months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.4 Visit 8 (Open Label Extension) - Three Months (± 7 days)

This visit will occur three months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.5 Visit 9 (Open Label Extension) - Six Months (± 7 days)

This visit will occur six months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.6 Visit 10 (Open Label Extension) - Nine Months (± 7 days)

This visit will occur nine months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.7 Visit 11 (Open Label Extension End of Treatment) - Twelve Months (± 7 days)

This visit will occur twelve months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

Starting at Visit 11, patients will begin to taper down their IMP dose. The dose will be reduced by 10% of their OLE maintenance dose per day.

9.2.2.8 Visit 12 (Open Label Extension End of Taper)

This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.

9.2.2.9 Safety Follow Up Call (± 3 days)

This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.

10. WITHDRAWAL

In accordance with the Declaration of Helsinki³¹, the FDA regulations relating to good clinical practice (GCP) and clinical trials^{32,33,34}, the EU Clinical Trials Directive (2001/20/EC)³⁵ and/or other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

The patient must be withdrawn from the study if any of the following apply:

- Administrative decision by the investigator, GW, or a Regulatory Authority.
- Pregnancy.
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- Withdrawal of patient consent.
- Withdrawal of legal representative consent.
- Lost to follow up.
- ALT $>3 \times$ ULN or AST $>3 \times$ ULN **and** (TBL $>2 \times$ ULN **or** INR >1.5).
- ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- ALT or AST $>8 \times$ ULN.
- ALT or AST $>5 \times$ ULN for more than two weeks.
- Any other IMP is taken as part of a clinical trial during the study.

Patients may also be withdrawn from the study for any of the following:

- Patient non-compliance.
- AE, which in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Any evidence of drug abuse or diversion.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

Should a patient request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients who withdraw should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision

is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator's clinical judgment. All assessments required at Visit 4 (if the withdrawal is during the blinded phase) or Visit 11 (if the withdrawal is during the OLE) should be conducted if possible. If the tapered dose is administered, patients should return for Visit 5 (if withdrawal is during the blinded phase) or Visit 12 (if the withdrawal is during the OLE) if possible. Wherever possible, the safety follow-up visit should be conducted 28 days from the date of the last dose of IMP. Patients withdrawing due to an AE should be followed up according to [Section 12.7](#). All information should be reported on the applicable CRF pages

11. URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the investigator they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to Competent Authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the Competent Authorities and IRB/EC within three days.

12. ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this study an AE is defined as:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which is present following screening (Visit 1) throughout the study and up to the post treatment, safety follow-up visit (28 days after last dose of IMP), which may or may not be considered to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

Surgical/Investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-study existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization which prolongs their scheduled hospital stay in which case it would be considered a SAE (refer to [Section 12.2](#)).

If reporting a fatal event, the SAE term should be the underlying cause of the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

The term ‘investigator’ refers to the study PI or a formally delegated study physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported promptly to Regulatory/Competent Authorities, applicable IRB/ECs and Investigators (expedited reporting) by GW.

An AE must only be classed as serious i.e., an SAE, when the event falls into one of the following criteria:

- Results in death.
- Is life-threatening.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Medically significant.**

* The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

** Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.3 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study must be reported to GW with any other supporting information and recorded in the AE section of the CRF. Any on-going

SAEs should be followed up until resolution wherever possible. For all deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports and relevant medical reports should be sent to GW promptly.

All SAEs must be reported directly to GW PVD within 24 hours of discovery or notification of the event. All SAE information must be recorded on the SAE forms provided in the site files and faxed to GW PVD. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form, signed/dated and faxed to the GW PVD and the AE section of the CRF must be updated.

The investigator should continue to document all AEs which occur up to the last formal follow-up visit (Visit 13 for patients entering the OLE and Visit 6 for those patients that are not entering the OLE). If the investigator subsequently becomes aware of any deaths or a new IMP-related SAE after the last formal follow-up period of the study, these should still be reported to the GW PVD.

Any other problem discovered outside these time limits which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have participated in the study, then these should be treated as an SAE and reported to GW PVD. Such post study SAEs do not need to be recorded on the patient's CRF if editing rights to the CRF have been removed.

Contact details for the GW PVD are provided at the front of the site files for all study centers, and upon the GW SAE Report form.

12.4 Pregnancy

Any patient, or patient's partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD within 24 hours of first awareness. Please use the GW Pregnancy Monitoring Forms provided. Where possible the investigator should provide the outcome of the pregnancy.

The investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the investigator becomes aware of a new pregnancy outside this time limit then they should report it as above. GW PVD will follow up for all pregnancy outcomes.

12.5 Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the study medication must be reported as such. The

expression “*reasonable causal relationship*” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the investigator for all AEs is used to capture the reasonable causal relationship of an event to the study medication:

“*In your opinion is there a plausible relationship to the study medication?*” The answer is “yes” or “no”.

Events that start before the first dose of study medication (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of study medication, a new event record should be entered into the CRF.

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the investigator assess not only the possible role of the study medication but also competing etiological factors as the underlying cause. Factors for consideration may include:

- Medical history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.
- Withdrawal of study medication.
- Protocol-related procedure.

12.6 Reporting Procedures for All Adverse Events

All AEs^{*} (including SAEs) occurring during the study will be reported on the running logs in the AE section of the CRF. This includes all events from the time following screening (Visit 1) to post study follow-up (Visit 13 for patients entering the OLE and Visit 6 for those patients that are not entering the OLE), whether or not attributed to IMP and observed by the investigator or patient.

^{*}For the patient’s expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures must be documented as an AE. Any AE which meets SAE criteria should still be reported as a SAE.

The following information will need to be provided for all AEs:

A) Adverse Event (Diagnosis or Syndrome if known, or Signs and Symptoms)

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded on the AE section of the CRF. Once a diagnosis has been determined the AE section of CRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the CRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated e.g., fever and malaise due to a respiratory tract infection.

B) Adverse Event Start Date and Stop Date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given then record as much information as possible (i.e., month and year or in exceptional circumstances just year). When the actual start date becomes known the CRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one for the following categories:

- Recovered.
- Recovered with sequelae.
- Continuing.
- Patient died.

D) Severity

When describing the severity of an AE the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, for example, a headache or constipation, the change in severity should not be recorded each time, instead only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore it should not be classed as serious.

E) Causality

See [Section 12.5](#) above.

F) Action Taken with Study Medication

This question refers to the action taken with the IMP due to an AE. The action with the IMP must be classed as:

- None.
- Dose reduced temporarily.
- Dose reduced.
- Study medication interrupted.
- Study medication stopped.

12.7 Follow up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the GW PVD for any AEs reported.

AEs considered related to the IMP by the investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE, further details of withdrawal are presented in [Section 10](#). If either of these occurs, the patient must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

12.8 Potential Cases of Drug Induced Liver Injury

All investigational sites are required to submit to the GW PVD the laboratory results for any patient after randomization that meet the criteria for the selected laboratory parameters as follows:

- ALT or AST $>3 \times \text{ULN}$ **and** (TBL $>2 \times \text{ULN}$ **or** INR >1.5).
- ALT or AST $>3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- ALT or AST $>8 \times \text{ULN}$.
- ALT or AST $>5 \times \text{ULN}$ for more than two weeks.

These reports must be sent to the GW PVD using the same fax number for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the patient's baseline laboratory results with all reports to GW PVD.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol defined criteria for withdrawal and important medical events. The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL and alkaline phosphatase levels, detailed history and physical examination. Patients should be followed until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

Elevations in ALT or AST $>3 \times \text{ULN}$ or TBL $>2 \times \text{ULN}$ alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours' notice of abnormal results. If the participant cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.

12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees.

In accordance with the EU Clinical Trials Directive³⁵, relevant parts of the FDA Code of Federal Regulations and any national regulations, GW will inform investigators, regulatory authorities and relevant IRB/ECs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through three sources:

- Investigator Brochure³⁶: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study on the IMP in human participants. The IB is updated annually.
- Development Core Safety Information: this document actually forms the Safety Section of the IB³⁶, or is updated as an appendix of the IB³⁶. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).
- Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the regulatory authorities, the relevant central IRB/ECs which have approved the study and investigators. As required, the investigator should notify their regional IRB/EC of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS

reports and any additional safety documentation received from GW, in accordance with local procedures.

In the USA, investigators are normally required to promptly report to their IRBs all unanticipated problems involving risks to human patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance³² the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human patients, and reported to the IRB, *only* if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

The FDA guidance³⁷ states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW will inform investigators (regulatory authorities and applicable IRB/EC's) of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the study does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

As a minimum, the recipient will be sent all of the above and relevant updates between the period from ethics approval and final database lock.

13. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be produced prior to the database lock and analysis of the study. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

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

13.2 Interim Analysis

An interim analysis will be conducted at the end of the Double Blind phase of the study and may also be considered during the OLE phase, if long term data is required to support New Drug Application/Marketing Authorization Application submissions.

13.3 Analysis Sets

13.3.1 Safety Set

All subjects who are treated and receive at least one dose of IMP will be included. The Safety set is the primary analysis set for all safety endpoints.

13.3.2 Pharmacokinetic Analysis Set

All subjects who are treated and receive at least one dose of IMP and who provide some on-treatment data will be included.

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

13.3.3 Protocol Deviations

Any protocol deviations will be listed and reasons for exclusion from the analysis populations will be summarized

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (*n*), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category. Summaries will be presented for data recorded pre-treatment, during each 25 day dosing phase (placebo and GWP42003-P) and during the OLE phase separately.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, treated, completing the study and those prematurely terminated IMP) will be accounted for in the enrollment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Age, sex, race (as allowed per local regulations) and any other demographic or baseline characteristics will be summarized, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by system organ class, including details of the duration of epilepsy and the types of seizures currently experienced by the patients.

13.5.4 Concomitant Medication

Concomitant medications taken prior to and during the study will be summarized, by medication class and active ingredients. Summaries of medications taken during the IMP treatment phases and during OLE will be presented separately.

13.6 Endpoints and Statistical Methods

13.6.1 Primary Endpoint(s)

The primary endpoints of the study are the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

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

13.6.2 Secondary Endpoint(s)

The secondary endpoints of the study are the safety parameters (see [Section 13.6.4](#)) and the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- THC
- THC major metabolites

13.6.3 Pharmacokinetics

Calculation of PK parameters will be based on actual blood sampling times [h] (relative to the corresponding administration time) rounded to two decimal digits with negative pre-dose times set to zero. Plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites will be displayed graphically, summarized and listed. For descriptive statistics, values below the lower limit of quantification of the assay (LLOQ) will be excluded from any calculations. Descriptive statistics of concentrations will be calculated if at least half of the individual data points that have been measured are equal to or above the LLOQ.

For calculation of the PK parameters, the following rules will be applied:

At time zero and at time points in the lag-time between time zero and the first quantifiable concentration, concentrations below the LLOQ will be set to zero. All other concentrations below the LLOQ will not be used in calculations.

Variables derived from plasma concentrations:

- Concentration maximum (C_{\max}): Highest observed plasma concentration of the measured concentration-time profile. Dimension: [amount / volume].
- Terminal half-life $t_{1/2} = \ln(2)/\lambda_z$.
- The rate constant of the terminal phase λ_z will be determined by linear regression of log-transformed concentration data after the time of maximum concentration. A sequence of terminal elimination rate constants will be created by linear regression. Linear regressions are repeated using the last three points with a quantifiable concentration, the last four points, the last five points etc. For each regression, an adjusted R^2 is computed. The regression with the largest adjusted R^2 is selected to estimate the terminal half-life. Dimension: [time].
- Area under the concentration-time curve from administration until the last sampling point (t) equal or above the LLOQ $AUC_{(0-t)}$ will be calculated by the linear trapezoidal formula. Dimension: [time • amount / volume].
- Area under the concentration-time curve extrapolated to infinity: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_{\text{last}}/\lambda_z$ and C_{last} is the concentration observed at the last time point with a quantifiable concentration, λ_z refers to the terminal elimination rate constant. Dimension: [time • amount / volume].
- Time of maximum concentrations: T_{\max} will be taken as the time after administration at which C_{\max} occurs. Dimension: [time].
- PK parameters for each analyte will be summarized for the two treatment phases of the study separately, as appropriate.
- 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 group ratios of geometric means of C_{\max} , $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will be carried on logarithm scale using a linear mixed effect model with treatment

(CLB or CLB+CBD) 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.

13.6.4 Safety

13.6.4.1 Treatment Compliance and Extent of Treatment Exposure

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

13.6.4.2 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary.

A treatment emergent AE is one that started, or worsened in severity or seriousness, following the first dose of IMP.

Descriptive presentations of treatment emergent AEs will be given by preferred term and system organ class for the safety analysis set. The number of patients reporting at least one AE will be provided. Summaries will be provided for each phase of the study separately.

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.

13.6.4.3 Clinical Laboratory Data

Clinical laboratory data at screening and at the end of the 31 day treatment phase and the change from baseline to end of treatment (OLE) will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range.

13.6.4.4 Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data

The C-SSRS, vital signs, ECG and physical examination data will be summarized at screening, at the end of the 31 day treatment phase and during the OLE treatment period using appropriate summary statistics. Changes in the vital signs from baseline to end of each treatment phase will also be summarized.

13.6.4.5 Seizure Data

Seizure data collected during the 31 day treatment phase and during the OLE phase of the study will be summarized using appropriate summary statistics.

14. DATA SAFETY MONITORING COMMITTEE

GW does not plan to use an independent data safety monitoring committee as part of this study.

15. REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the^{31,35} and the clinical trial regulations adopting European Commission Directives into national legislation^{38,39,40}.

15.2 Informed Consent

Initial master informed consent forms will be provided to the investigator to prepare the informed consent documents to be used at his or her center. The GW Clinical Manager will communicate updates to the templates by letter. The written informed consent documents should be prepared in the language(s) of the potential patient population.

Before a patient's participation in the trial, the investigator is responsible for obtaining written informed consent from the patient or legal representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol specific screening procedures or any IMPs are administered. The patient, or their legal representative, should have ample time for review to consider the information provided before giving written consent; more specific definitions of ample time may be in force if required by IRB/ECs or local regulations.

The acquisition of informed consent should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient or legal representative (as applicable) and by the person who conducted the informed consent discussion. GW also requires a physician to be present for consent and to sign the consent forms as well. The original signed informed consent forms should be retained and a copy provided to the patient or legal representative.

15.3 Institutional Review Board/Ethics Committee

A copy of the protocol, proposed informed consent forms, other patient information material, any proposed advertising material and any further documentation requested, must be submitted to the IRB/EC for written approval. GW must receive a copy of the written approval of the protocol and informed consent forms before enrollment of patients into the study and shipment of IMP.

The investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent

documents. The investigator should notify the IRB/EC of deviations from the protocol or SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The investigator will be responsible for obtaining on-going IRB/EC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/EC continuance of approval must be sent to GW.

15.4 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent for entry into the study:

- Signed and dated protocol signature page.
- Copy of approved informed consent forms and other patient information material.
- Copy of the IRB/EC approval of the protocol, informed consent forms and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/EC composition and/or written statement of the IRB/EC in compliance with the FDA regulations relating to GCP and clinical trials^{32,33,34,41}, the EU Clinical Trials Directive³⁵, or International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP)⁴² where the EU Directive does not apply.
- Signed laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed clinical trial agreement (including patient/investigator indemnity insurance and financial agreement).
- FDA 1572 form.
- Completed financial disclosure statements for the PI and all sub-investigators if relevant.

15.5 Participant Confidentiality

The investigator must ensure that the patient's anonymity is maintained. On the CRFs and within the databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials and race (if allowed per local regulations) and a patient study number only. Documents that are not for submission to GW, e.g., signed informed consent forms should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to good clinical practice and clinical trials^{32,33,34,41}, and the EU Clinical Trials Directive³⁵/ICH GCP Guidelines⁴², it is

required that the investigator and institution permit authorized representatives of the company, the regulatory agencies and the IRB/EC direct access to review the patient's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the patient that his/her study related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the company.

16. ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Study or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent documents. The IRB/EC and Competent Authorities must be informed of all amendments and give approval for any substantial amendments prior to implementation. The investigator must send a copy of the approval letter from the IRB/EC to GW. Amendments for administrative changes can be submitted to the IRB/EC for information only.

Both GW and the investigator reserve the right to terminate the study, according to the clinical trial agreement. The investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to GW.

16.2 Study Documentation and Storage

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the GW delegation of authority and signature form.

Source documents are original documents, data and records from which the patient's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, electronic data captured by IVRS, microfiches, radiographs and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording; that is, there is no other written or electronic record of data. In the rare situations of this happening, then the source data from the CRF should be transcribed in the patient's notes with appropriate signature and date to provide a full audit trail. A Source Data Verification Plan, identifying the source for each data point at each site, will be agreed with each site prior to patient recruitment.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related, essential documentation (as outlined in ICH E6 Section 8.2⁴²), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consent forms and supporting copies of source documentation.

- Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see [Section 15.4](#)) and all correspondence to and from the IRB/EC and GW.
- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug related correspondence.

In addition, all original source documents supporting entries on the CRFs, paper diary data and electronic data captured by IVRS must be maintained and be readily available.

Following completion or termination of a clinical study, GW will initiate proper archive of clinical study related documentation and electronic records generated by the investigator and/or GW. All clinical trial related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 20 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by GW (EU Directive 2005/28/EC Chapter 4 Trial Master File and Archiving Article 16⁴³).

GW will inform the investigators for each site in writing of the need for record retention. No study document should be destroyed without prior written agreement between GW and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify GW in writing of the new responsible person and/or the new location.

16.3 Study Monitoring and Data Collection

The GW representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study for example, CRFs and other pertinent data provided that patient confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting the CRFs and available diary data at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor should have access to patient medical records and other study related records needed to verify the entries on the CRFs.

The investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

The investigator is responsible for ensuring the data recorded in the CRFs are accurate and complete. The CRF should be completed within five working days after the patient's visit and before review by the study monitor. Queries generated by GW or its representative are to be answered within a similar period of time. Shorter periods of time may apply during specific situations such as interim analysis or final database cleaning.

All handwritten medical records should be filled out with a black or blue ball-point pen and must be legible. Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator. No correction fluid or tape may be used. The PI will sign and date the indicated places on the CRF. These signatures will indicate that the PI inspected or reviewed the data on the CRF, the data queries and the site notifications and agrees with the content.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations^{32,33,34,41}, the ICH GCP Guideline⁴², and all other applicable regulatory requirements^{35,42}, to resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

GW's or the CRO's Clinical Data Management Department will correct the following issues in CRFs without any notification to site staff:

- Misspellings that do not change the meaning of the word, excluding AEs and medications.
- Date errors that occur at the end of the year and into the New Year.
- Temperature unit errors (Fahrenheit vs Centigrade).
- Weight unit errors (pounds vs kilograms) if a baseline weight has been established.
- Administrative data for example, event names for unscheduled visits or retests.
- Clarifying "other, specify" if data are provided for example, race, physical exam.

- If a YES or NO question for example, ‘Were there any AEs?’ is left blank yet AEs are listed on the CRF, YES will be entered in the blank.
- Correct CRF page numbers.

16.4 Quality Assurance

In accordance with the FDA regulations, EU Clinical Trials Directive/ICH GCP and the sponsor’s audit plans, representatives from GW’s Clinical Quality Assurance Department may select this study for audit. Inspection of site facilities for example, pharmacy, drug storage areas, laboratories and review of study related records will occur to evaluate the study conduct and compliance with the protocol, as per the EU Clinical Trials Directive/ICH GCP and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the study site in the event of any claim in respect of personal injury arising due to a patient’s participation in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical study patient would not otherwise have been exposed providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will co-ordinate this dissemination and may solicit input and assistance from the chief/PIs. A summary of the results of this study will be made available on <http://www.ClinicalTrials.gov>, as required by U.S. Law.

The raw data from this study may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analysis and are permitted to present such information along with methods and results of the clinical study at symposia, national or regional professional meetings, and to publish it in theses or dissertations.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this study, must be submitted to GW Medical Writing Department and, as applicable, GW Publication Committee for review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for

publication, public dissemination, or review by a publication committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

GW also reserve the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.7 Intellectual Property Rights

All Intellectual Property Rights owned by or licensed to either GW or the PIs, other than those arising from the clinical study, will remain their property. All Intellectual Property Rights arising out of the clinical study will vest in or be exclusively licensed to GW and as such, the PI should promptly disclose all knowledge to GW and refrain from using such knowledge without the prior written consent of GW.

16.8 Confidential Information

GW and the PI should ensure that only personnel directly concerned with the study should be party to confidential information and that any information coming to either party about the other during the course of the study should be kept strictly confidential and should not be disclosed to any third party or made use of without the prior written consent of the other.

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APPENDIX 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						
Enrollment		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			
Pregnancy test (if appropriate)	X							
Pharmacokinetic blood sampling**		X	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)
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 Behavior 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 Behavior Survey								X	

APPENDIX 2. STUDY PERSONNEL

Appendix 3.1 Investigator Details

At the time of protocol production, the participating investigators had not been confirmed. A list of all investigators will be maintained within the GW Master Files (electronically and added to the Trial Master File at the end of the study).

Appendix 3.2 Sponsor Contact Details

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Clinical Trials Supplies:

GW Pharma Ltd

Tel: PPD

Fax: PPD

TITLE: A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)

STUDY CODE: GWEP1428

EudraCT NUMBER: 2014-002942-33

PROTOCOL AMENDMENT NUMBER: 2

**to be incorporated into the Protocol, creating
PROTOCOL VERSION 3, DATE 08 OCT 2015**

**GW RESEARCH LTD
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Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board/Independent Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

1. PROTOCOL SYNOPSIS

Study Title	A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)
Indication	Epilepsy
Study Design	<p>This is a phase 2, double-blind, randomized, placebo-controlled study in 20 patients.</p> <ul style="list-style-type: none"> Patients will be randomized in a 4:1 ratio to receive 20 mg/kg cannabidiol (CBD) 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. Day 1 (Visit 2), patients will not be dosed with GWP42003-P/placebo but will continue to take CLB at a stable dose. Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). Day 12 (Visit 3), patients will attend the study site to check safety and compliance. After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the patient will continue to take GWP42003-P as advised by the investigator. If the patient does not enter the OLE period of the study, the patient will taper off of GWP42003-P by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with end of taper on Day 43 (Visit 5). <p>Pharmacokinetic (PK) samples will be taken on the day of enrollment (Visit 2, Day 1) and after completing 21 days treatment on GWP42003-P or placebo (Visit 4, Day 33). The PK assessments will therefore capture the following combinations of CLB and GWP42003-P:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and GWP42003-P or placebo. <p>Each PK assessment should be performed at time points in respect to a</p>

	<p>morning dose of CLB. The time points are as follows: Pre-dose, 15 min, 30 min, 1h, 1.5h, 2h, 4h, 6h, 12h and 24h. It is expected that the patient will continue to take their CLB as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The GWP42003-P/placebo should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD, CBD major metabolites, Δ^9-tetrahydrocannabinol (THC) and THC major metabolites, valproate, stiripentol, levetiracetam and topiramate. Patients will be required to keep a paper diary to note the time and dose of GWP42003-P and CLB administration each morning and evening and to record any adverse events (AEs) that may occur whilst receiving investigational medicinal product (IMP) and any other medications. Patients will also be requested to record the number and type of seizures for each day whilst on the study.</p>
Sponsor	<p>GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom</p>

2. TABLE OF CONTENTS

1.	PROTOCOL SYNOPSIS	2
2.	TABLE OF CONTENTS	4
2.1	Table of Appendices	4
3.	RATIONALE	5
3.1	Secondary Endpoints	5
3.2	Exclusion/Withdrawal Criteria	5
3.3	Laboratory tests	5
3.4	Procedures	5
3.5	Administrative Changes	6
4.	IMPLEMENTATION OF THE AMENDMENT	6
5.	PRESENTATION OF AMENDED TEXT	7

LIST OF APPENDICES

Appendix 1	Changes to Protocol Table 8.1.2-1.....	14
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3. RATIONALE

This protocol amendment 2 (will be incorporated into the Protocol creating Protocol Version 3, date 08 Oct 15) addresses the following issue(s):

3.1 Secondary Endpoints

A blood draw for CYP2C19 and CPY3A4 genotype analysis was added in protocol amendment 1. The analysis for these samples is added in protocol amendment 2 as a secondary endpoint.

3.2 Exclusion/Withdrawal Criteria

The following exclusion/withdrawal criteria have been added / amended:

- Addition of exclusion criterion: Patients taking felbamate for less than 1 year prior to screening. Aplastic anemia and liver toxicity with felbamate has the greatest risk in the first year of treatment, therefore exclusion criterion added to mitigate that risk.
- Amended exclusion criterion regarding travel outside of the country of residence to clarify that this is allowed if the patient has confirmation that the IMP is permitted in the destination country.
- Addition of exclusion criterion: Patient has a prolonged QTcB (>450 msec for males and >470 msec for females). Exclusion criterion added as a safety precaution as a formal QTc study has not yet been completed with GWP42003-P.
- Addition of withdrawal criterion: Significant change in QTcB (>60 msec) from the previous ECG or absolute QTcB of >500msec. Withdrawal criterion added as a safety precaution as a formal QTc study has not yet been completed with GWP42003-P.

3.3 Laboratory tests

The following changes have been made to the laboratory tests and PK analyses:

- PK analysis for CBD, CBD major metabolites, THC and THC major metabolites will not be conducted on the visit 2 blood samples as patients will not have been exposed to CBD at this point.
- PK analysis to be done at visit 2 and visit 4 for stiripentol, valproate, levetiracetam and topiramate if the patient is taking any of these.
- In cases of elevated liver enzymes, the patient must come back into site for repeat testing. Gamma-glutamyl transferase has been added as an analyte to the required analytes to be tested at the recommendation of the FDA.

3.4 Procedures

The following clarifications have been made to the study procedures:

- On the enrollment visit (visit 2, day 2), patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions.

- For the PK visits, clarification has been added that the evening dose of GWP42003-P/placebo and any AEDs the patient is taking must be taken after the 12 hour PK blood draw.
- Clarification that the dose of GWP42003-P can only be adjusted to 30 mg/kg/day from visit 5 onwards rather than visit 4 onwards. This is to allow all patients time to have been titrated up to 20 mg/kg/day of GWP42003-P prior to any further dose increases.

3.5 Administrative Changes

Minor spelling/formatting/consistency/administrative issues have been corrected (NB. in the interest of brevity, minor changes to grammar and punctuation are not captured in this amendment document).

4. IMPLEMENTATION OF THE AMENDMENT

This amendment will be issued as Protocol Version 3, Date 08 Oct 2015. It will be kept in the study master file at GW and in each investigator and pharmacy site file, if applicable.

5. PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 2, Dated 09 Jul 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 2 (Protocol Version 3, Dated 08 Oct 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
Protocol Synopsis, Study Design, p 4	(...) PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD, CBD major metabolites, Δ9 tetrahydrocannabinol (THC) and THC major metabolites. (...)	(...) PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD, CBD major metabolites, Δ9 tetrahydrocannabinol (THC), THC major metabolites, <u>valproate (VPA), stiripentol (STP), levetiracetam (LEV) and topiramate (TPM)</u> (...)	See section 3.3
Protocol Synopsis, Secondary Endpoint(s), p 5	(...) (...)	(...) • <u>CYP2C19 and CPY3A4 patient genotype analysis</u> (...)	See section 3.1
Protocol Synopsis, Summary of Participant Eligibility Criteria, p 5	(...) • Patient and/or legal representative is available to attend all PK visits within the required visit window. (...) (...)	(...) • Patient is available to attend all PK visits within the required visit window. (...) • <u>Patient is taking felbamate and they have been taking it for less than one year prior to screening.</u> (...) • <u>Patient has a prolonged QTcB (>450 msec for males and >470 msec for females).</u>	Patient must attend PK visits. See section 3.2 See section 3.2

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 2, Dated 09 Jul 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 2 (Protocol Version 3, Dated 08 Oct 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
	(...) <ul style="list-style-type: none"> Travel outside the country of residence planned during the study. (...)	(...) <ul style="list-style-type: none"> Travel outside the country of residence planned during the study, <u>unless the patient has confirmation that the IMP is permitted in the destination country/state.</u> (...)	See section 3.2
Protocol Synopsis, Criteria for Withdrawal, p 8	(...) (...)	(...) <ul style="list-style-type: none"> <u>Significant change in QTcB (> 60 msec) from the previous ECG or absolute QTcB of > 500 msec.</u> (...)	See section 3.2
Protocol Synopsis, Procedures, p 9-12	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. (...) (...) <p>(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. (...) (...) <p>The dose may be adjusted up or down by the investigator from the maintenance dose of 20</p></p>	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, <u>VPA, STP, LEV and TPM.</u> (...) <u>The evening dose of any AEDs must be taken after the 12 hour PK blood sample.</u> (...) (...) <p><u>Following administration of GWP42003-P/placebo, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions.</u></p> (...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, <u>VPA, STP, LEV, TPM,</u> CBD, CBD major metabolites, THC and THC major metabolites (...) <u>The evening dose of GWP42003-P/placebo and any AEDs must be taken after the 12 hour PK blood sample.</u> (...) (...) <p>(...)</p>	See section 3.3 See section 3.4 See section 3.4 See section 3.3 See section 3.4 See section 3.4

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 2, Dated 09 Jul 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 2 (Protocol Version 3, Dated 08 Oct 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
	mg/kg/day in the blinded phase to a maximum of 30 mg/kg/day in the OLE. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1. (...) (...)	(...) <u>The GWP42003-P dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day achieved at the end of the 10-day transition period, up to a maximum of 30 mg/kg/day in the OLE period.</u> (...)	See section 3.4
Protocol Synopsis, Statistical Considerations, p 15	Plasma concentration data will be analyzed to estimate PK endpoints C_{max} , t_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{1/2}$ of the following analytes: CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. (...)	Plasma concentration data will be analyzed to estimate PK endpoints C_{max} , t_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{1/2}$ of the following analytes: CLB, N-CLB, <u>VPA, STP, LEV, TPM</u> , CBD, CBD major metabolites, THC and THC major metabolites. (...)	See section 3.3
Protocol List of Abbreviations, p26	(...) (...)	(...) (...) CYP Cytochrome P450 (...) (...) LEV Levetiracetam (...) (...) QTcB Heart rate corrected QT interval using Bazett's formula (...) (...) SFU Safety follow up STP Stiripentol (...) (...)	

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 2, Dated 09 Jul 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 2 (Protocol Version 3, Dated 08 Oct 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
		TPM Topiramate (...) (...) VPA Valproate (...) (...)	
Protocol Section 4.1, Study Design, p 33	(...) PK samples will be quantitatively analyzed for CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. (...)	(...) PK samples will be quantitatively analyzed for CLB, N-CLB, <u>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 and THC major metabolites at Visit 4.</u> (...)	See section 3.3
Protocol Section 4.2, Secondary Endpoint(s), p 34	(...) (...)	(...) • <u>CYP2C19 and CPY3A4 patient genotype analysis</u> (...)	See section 3.1
Protocol Section 6.1.9, Inclusion Criteria, p 38	Patient and/or legal representative is available to attend all PK visits within the required visit window.	Patient is available to attend all PK visits within the required visit window.	Patient must attend PK visits.
Protocol Section 6.2, Exclusion Criteria, p 39	(...) (...) (...) Travel outside the country of residence planned during the study. (...)	(...) <u>Patient is taking felbamate and they have been taking it for less than one year prior to screening.</u> (...) <u>Patient has a prolonged QTcB (> 450 msec for males and > 470 msec for females).</u> (...) Travel outside the country of residence planned during the study, <u>unless the patient has confirmation that the IMP is permitted in the destination</u>	See section 3.2 See section 3.2 See section 3.2

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 2, Dated 09 Jul 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 2 (Protocol Version 3, Dated 08 Oct 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
		<u>country/state</u> . (...)	
Protocol Section 7.1, Treatment Assignment, p 41	(...) For example, P1234001, denoting patient 001 at site 1234. (...)	(...) For example, <u>W</u> 1234001, denoting patient 001 at site 1234. (...)	Unique letter at the start of patient number has been confirmed as W.
Protocol Section 8.1.2, Dose Escalation and Dose Adjustments, p 43	<<Note: For changes to Table 8.1.2-1: See Appendix I>>	<<Note: For changes to Table 8.1.2-1: See Appendix I>>	Up-titration regimen when transitioning to the OLE is different to the up-titration regimen at days 2-11.
Protocol Section 8.1.2, Dose Escalation and Dose Adjustments, p 44	(...) After this has taken place, the maintenance dose of GWP42003-P may be (...)	(...) After this has taken place <u>after Visit 5</u> , the maintenance dose of GWP42003-P may be (...)	See section 3.4
Protocol Section 9.1.10, Pharmacokinetic Analyses, p 49	The plasma concentration/time curves of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites will be assessed at Visit 2 (Day 1 and Day 2) and Visit 4 (Day 33 and Day 34). (...)	The plasma concentration/time curves of CLB, N-CLB, <u>VPA, STP, LEV</u> and <u>TPM</u> will be assessed at Visit 2 (Day 1 and Day 2) and <u>CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites at</u> Visit 4 (Day 33 and Day 34). (...)	See section 3.3
Protocol Section	(...)	(...)	

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 2, Dated 09 Jul 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 2 (Protocol Version 3, Dated 08 Oct 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
9.2.1.2.1, Visit 2 (Day 1) – Enrollment (+3 days), p 58	Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. (...) (...)	Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, <u>VPA, STP, LEV</u> and <u>TPM.</u> (...) <u>The evening dose of any AEDs must be taken after the 12 hour PK blood sample.</u> (...)	See section 3.3 See section 3.4
Protocol Section 9.2.1.2.2, Visit 2 (Day 2) – Enrollment, p 58	(...) (...)	(...) <u>Following administration of GWP42003-P/placebo, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions.</u> (...)	See section 3.4
Protocol Section 9.2.1.4.1, Visit 4 (Day 33) (±3 days), p 59	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites. (...) (...)	(...) Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, <u>VPA, STP, LEV, TPM,</u> CBD, CBD major metabolites, THC and THC major metabolites. (...) <u>The evening dose of GWP42003-P/placebo and any AEDs must be taken after the 12 hour PK blood sample.</u> (...)	See section 3.3 See section 3.4
Protocol Section 9.2.1.4.2, Visit 4 (Day 34), p 59	(...) The dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day in the blinded phase to a maximum of 30 mg/kg/day in the OLE. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1.2. Patients, or their caregivers, will be instructed how to record the diary information. (...)	(...) (...)	See section 3.4
Protocol Section 9.2.2.1, Visit 5	(...) (...)	(...) <u>The GWP42003-P dose may be adjusted up or</u>	See section 3.4

Protocol Section Number, Heading and Page Number	Original Wording from Protocol Version 2, Dated 09 Jul 15 (Deleted wording is struck through and in bold)	Revised Wording from Protocol Amendment 2 (Protocol Version 3, Dated 08 Oct 15) (Revised wording is underscored and in bold)	Rationale for the amendment.
(Open Label Extension) – Two Weeks (±3 days), p 60		<u>down by the investigator from the maintenance dose of 20 mg/kg/day achieved at the end of the 10-day transition period, up to a maximum of 30 mg/kg/day in the OLE period.</u> (...)	
Protocol Section 10, Withdrawal, p 63	(...) (...)	(...) • Significant change in QTcB (> 60 msec) from the previous ECG or absolute QTcB of > 500 msec. (...)	See section 3.2
Protocol Section 12.8, Potential Cases of Drug Induced Liver Injury, p 70	(...) The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL and alkaline phosphatase levels, (...) (...)	(...) The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase <u>and gamma-glutamyl transferase</u> levels, (...) (...)	See section 3.3
Protocol Section 13.6.3, Pharmacokinetics, p 74	(...) Plasma concentrations of CLB, N-CLB, CBD, CBD major metabolites, THC and THC major metabolites (...) (...)	(...) Plasma concentrations of CLB, N-CLB, <u>VPA, STP, LEV, TPM</u> , CBD, CBD major metabolites, THC and THC major metabolites (...) (...)	See section 3.3
Protocol Section 16.2, Study Documentation and Storage, p 80	(...) All clinical trial related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 20 years. (...)	(...) All clinical trial related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of <u>25</u> years. (...)	Update to GW Standard Operating Procedure

Appendix 1 Changes to Protocol Table 8.1.2-1

Dose Titration Regimen (Protocol V2 / Table 8.1.2-1)

Table 8.1.2-1 Dose Up-Titration Regimen*		
Day - GWP42003-P/Placebo (Blinded Period)	Day - GWP42003-P only (OLE**)	Dose Level (GWP42003-P or equivalent placebo)
2	34	2.5 mg/kg
3	35	2.5 mg/kg
4	36	5.0 mg/kg
5	37	5.0 mg/kg
6	38	7.5 mg/kg
7	39	7.5 mg/kg
8	40	10.0 mg/kg
9	41	10.0 mg/kg
10	42	15.0 mg/kg
11	43	15.0 mg/kg
12 onwards	44 onwards	20.0 mg/kg

* GWP42003-P /placebo is to be taken twice daily. Total daily doses are shown.

** Only patients who were taking placebo during the double-blind period will up-titrate according to this schedule during the OLE period. Those taking GWP42003-P during the double-blind period will down-titrate their blinded IMP whilst simultaneously up-titrating with GWP42003-P, thus maintaining a daily dose of 20 mg/kg/day GWP42003-P throughout.

Dose Titration Regimen (Protocol V3 / Table 8.1.2-1)

Table 8.1.2-1 Dose Up-titration Regimen*			
Day - GWP42003-P/Placebo (Blinded Period)	Dose Level (GWP42003-P or equivalent placebo)	Day - GWP42003-P only (OLE**)	Dose Level GWP42003-P
2	2.5 mg/kg	<u>34</u>	<u>2.0 mg/kg</u>
3	2.5 mg/kg	<u>35</u>	<u>4.0 mg/kg</u>
4	5.0 mg/kg	<u>36</u>	<u>6.0 mg/kg</u>
5	5.0 mg/kg	<u>37</u>	<u>8.0 mg/kg</u>
6	7.5 mg/kg	<u>38</u>	<u>10.0 mg/kg</u>
7	7.5 mg/kg	<u>39</u>	<u>12.0 mg/kg</u>
8	10.0 mg/kg	<u>40</u>	<u>14.0 mg/kg</u>
9	10.0 mg/kg	<u>41</u>	<u>16.0 mg/kg</u>
10	15.0 mg/kg	<u>42</u>	<u>18.0 mg/kg</u>
11	15.0 mg/kg	<u>43</u>	<u>20.0 mg/kg</u>
12 onwards	20.0 mg/kg	<u>44 onwards</u>	<u>20.0 mg/kg***</u>

* GWP42003-P /placebo is to be taken twice daily. Total daily doses are shown.

** Only patients who were taking placebo during the double-blind period will up-titrate according to this schedule during the OLE period. Those taking GWP42003-P during the double-blind period will down-titrate their blinded IMP whilst simultaneously up-titrating with GWP42003-P, thus maintaining a daily dose of 20 mg/kg/day GWP42003-P throughout.

*** The GWP42003-P dose of 20 mg/kg/day can be adjusted during the OLE period, after Visit 5, at the investigator's discretion: up to a maximum dose of 30 mg/kg/day. It may also be adjusted down (no minimum).

**TITLE: A PHASE2, DOUBLE-BLIND, RANDOMIZED,
PLACEBO-CONTROLLED STUDY TO INVESTIGATE POSSIBLE
DRUG-DRUG INTERACTIONS BETWEEN CLOBAZAM AND
CANNABIDIOL (GWP42003-P)**

STUDY CODE: GWEP1428

EudraCT NUMBER: 2014-002942-33

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Confidentiality Statement

This document contains confidential information of GW Research Ltd that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board/Independent Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Investigator Agreement

I have read the attached protocol entitled "A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)", dated version 3 date 08 Oct 15 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirements, the FDA regulations relating to good clinical practice and clinical trials and the European Union (EU) Clinical Trials Directive (2001/20/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (ICH GCP) where the EU Directive does not apply and to complete a Form 1572 if required.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Center No: _____

Print Name: _____

Principal Investigator

Date: _____

(DD Month YYYY)

Signature: _____

GW Authorization

Print Name: _____

Clinical Manager _____

Date: 08 OCT 2015

(DD Month YYYY)

Signature: _____

1. PROTOCOL SYNOPSIS

Study Title	A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)
Clinical Study Type	Phase 2
Indication	Epilepsy
Primary Objective	To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyclobazam (N-CLB).
Secondary Objective(s)	To assess the safety and tolerability of GWP42003-P in the presence of CLB.
Study Design	<p>This is a phase 2, double-blind, randomized, placebo-controlled study in 20 patients.</p> <ul style="list-style-type: none"> • 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. • Day 1 (Visit 2), patients will not be dosed with GWP42003-P/placebo but will continue to take CLB at a stable dose. • Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • Day 12 (Visit 3), patients will attend the study site to check safety and compliance. • After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). • On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the patient will continue to take GWP42003-P

	<p>as advised by the investigator.</p> <ul style="list-style-type: none"> If the patient does not enter the OLE period of the study, the patient will taper off of GWP42003-P by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with end of taper on Day 43 (Visit 5). <p>PK samples will be taken on the day of enrollment (Visit 2, Day 1) and after completing 21 days treatment on GWP42003-P or placebo (Visit 4, Day 33). The PK assessments will therefore capture the following combinations of CLB and GWP42003-P:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and GWP42003-P or placebo. <p>Each PK assessment should be performed at time points in respect to a morning dose of CLB. The time points are as follows: Pre-dose, 15 min, 30 min, 1h, 1.5h, 2h, 4h, 6h, 12h and 24h. It is expected that the patient will continue to take their CLB as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The GWP42003-P/placebo should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD, CBD major metabolites, Δ^9-tetrahydrocannabinol (THC), THC major metabolites, valproate (VPA), stiripentol (STP), levetiracetam (LEV) and topiramate (TPM). Patients will be required to keep a paper diary to note the time and dose of GWP42003-P and CLB administration each morning and evening and to record any adverse events (AEs) that may occur whilst receiving investigational medicinal product (IMP) and any other medications. Patients will also be requested to record the number and type of seizures for each day whilst on the study.</p>
Primary Endpoint	<p>The primary endpoints of the study are the PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</p> <ul style="list-style-type: none"> CLB N-desmethyleclobazam (N-CLB) CBD CBD major metabolites
Secondary Endpoint(s)	<p>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:</p> <ul style="list-style-type: none"> AEs 12-lead electrocardiogram (ECG) Clinical laboratory parameters (clinical chemistry, hematology and urinalysis) Vital signs Columbia-Suicide Severity Rating Scale (C-SSRS) Seizure frequency

	<ul style="list-style-type: none"> • Abuse liability • CYP2C19 and CPY3A4 patient genotype analysis <p>PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</p> <ul style="list-style-type: none"> • THC • THC major metabolites
Sample Size	A total of 20 patients will be enrolled in this study. Recruitment for the study will be competitive between participating sites. There is no formal sample size: Calculation and analysis is descriptive only.
Summary of Participant Eligibility Criteria	<p>For inclusion in the study patients must fulfil ALL of the following criteria:</p> <ul style="list-style-type: none"> • Male or female patients aged 18 to 55 years inclusive. • Patient must have epilepsy as determined by the investigator and be taking CLB. • Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition. • Patient must have experienced at least one seizure of any type (i.e., convulsive: tonic-clonic, tonic, clonic, atonic; focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness focal seizures evolving to bilateral secondary generalization) within the two months prior to randomization. • Patients must be taking CLB and no more than two other anti-epileptic drugs (AEDs) during the course of the study. • AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study. • Intervention with vagus nerve stimulation and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must be willing to maintain a stable regimen throughout the blinded phase of the study. • Patients must abstain from alcohol during the blinded phase of the study. • Patient is available to attend all PK visits within the required visit window. • Patient and/or legal representative must be willing and able to give informed consent for participation in the study. • Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements.

	<ul style="list-style-type: none"> • Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable. • Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study. <p>Exclusion: The patient may not enter the study if ANY of the following apply:</p> <ul style="list-style-type: none"> • Patient has clinically significant unstable medical conditions other than epilepsy. • Patients on CLB at doses above 20 mg per day. • Patients taking CLB intermittently as rescue medication. • Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes. • Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening. • Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy. • Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain during the blinded phase of the study. • Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry. • Patient has any known or suspected history of any drug abuse or addiction. • Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration of the study. • Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil. • Female patient is of child bearing potential or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal
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	<p>contraceptives, intrauterine devices/ hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.</p> <ul style="list-style-type: none"> • Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter. • Patients who have received an IMP within the 12 weeks prior to the screening visit. • Patient is taking felbamate and they have been taking it for less than one year prior to screening. • Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study. • Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator would prevent the participant from safe participation in the study. • Patient has significantly impaired hepatic function at screening (Visit 1) or enrollment (Visit 2), defined as any of the following: <ul style="list-style-type: none"> - Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $>5 \times$ upper limit of normal (ULN). - ALT or AST $>3 \times$ ULN and total bilirubin (TBL) $>2 \times$ ULN or international normalized ratio (INR) >1.5. - ALT or AST $>3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$). <p><i>This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion must be withdrawn from the study.</i></p> • Patient has a prolonged QTcB (> 450 msec for males and > 470 msec for females). • Unwilling to abstain from donation of blood during the study. • Travel outside the country of residence planned during the study, unless the patient has confirmation that the IMP is permitted in the destination country/state. • Patients previously enrolled into this study.
Criteria for Withdrawal	<p>Patients must be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Administrative decision by the investigator or GW Research Ltd or Regulatory Authority. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient.

	<ul style="list-style-type: none"> • Withdrawal of patient consent. • Withdrawal of legal representative consent. • Lost to follow up. • ALT >3 × ULN or AST >3 × ULN and (TBL >2 × ULN or INR >1.5). • ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). • ALT or AST >8 × ULN. • ALT or AST >5 × ULN for more than two weeks. • Any other IMP is taken as part of a clinical trial during the study. • Significant change in QTcB (> 60 msec) from the previous ECG or absolute QTcB of > 500 msec. <p>Patients may also be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Patient non-compliance. • AE, which in the investigator's opinion, would compromise the continued safe participation of the patient in the study. • Any evidence of drug abuse or diversion. • Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.
Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration	<p>GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring), pale yellow in color.</p> <p>Placebo oral solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring.</p> <p>The IMP should be taken orally as per intended commercial therapeutic use.</p> <p>IMP will be taken twice daily (morning and evening) following the dose schedule below:</p> <ul style="list-style-type: none"> • Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). <p>Please refer to Table 8.1.2-1 for details of the up-titration doses for GWP42003-P and placebo for the ten day taper period.</p> <p>On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the</p>

	<p>patient will continue to take GWP42003-P as advised by the investigator.</p> <p>CLB will be an IMP for the blinded section of the study. The patient's own supply of CLB will be used.</p>
Control Group	The control group will receive an equal volume of matching placebo.
Procedures	<p>VISIT 1 - Screening (Day -14 to -7)</p> <p>The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, THC testing, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.</p> <p>Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will be assigned a unique patient number and then begin the baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be instructed on how to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.</p> <p>VISIT 2 - Enrollment (Day 1) +3 days window</p> <p>This visit will occur 7-14 days after Visit 1.</p> <p>The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. Blood samples will also be taken for genetic testing if additional consent has been obtained. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.</p> <p>Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV and TPM. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of any AEDs must be taken after the 12 hour PK blood sample. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic</p>

	<p>on Day 2 ahead of additional sample collection.</p> <p>VISIT 2 - Enrollment (Day 2)</p> <p>This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose. Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.</p> <p>GWP42003-P/placebo will be dispensed and both the morning dose of CLB and GWP42003-P/placebo will be taken in clinic. Following administration of GWP42003-P/placebo, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1. Each patient will then receive their GWP42003-P/placebo for the 10 day titration period followed by the 21 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.</p> <p>VISIT 3 – Day 12 +3 day window</p> <p>This visit will occur 11 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 3: concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, AEs and review of patient diary completion.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.</p> <p>VISIT 4 - Day 33 ±3 days window</p> <p>This visit will occur 32 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 4 (Day 33): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. The C-SSRS will be administered.</p> <p>Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of GWP42003-P/placebo. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of GWP42003-P/placebo and any AEDs must be taken after the 12 hour PK blood sample. Patients are expected</p>
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	<p>to remain in clinic throughout this PK sampling process.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 4 - Day 34</p> <p>This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 33 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 34: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.</p> <p>On Day 34, providing the investigator and patient both agree, patients will be invited to continue taking GWP42003-P and to enter the OLE.</p> <p>Patients who enter the OLE will be dispensed GWP42003-P on Day 34.</p> <p>Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of GWP42003-P. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42.</p> <p>Patients Not Entering OLE</p> <p>VISIT 5 – Day 43 (End of Taper) +3 days window</p> <p>This visit will occur 42 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.</p> <p>All GWP42003-P/placebo (used and unused) will be collected and a check of the returned GWP42003-P/placebo against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.</p> <p>VISIT 6 - SAFETY FOLLOW-UP CALL - Day 71 ±3 days</p> <p>This visit is required for patients who do not enter the OLE study on Day 34, or who withdraw from the study early. This visit should occur four weeks (±3 days) after Visit 5, or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 71: concomitant medications (including AEDs) and AEs.</p> <p>Patients Entering OLE</p> <p>At the point of entry to the OLE, patients will be transitioned to the</p>
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	<p>OLE treatment over a 10 day period in order to maintain blinding. Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 34) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 34).</p> <p>VISIT 5 (OLE) – Two Weeks ± 3 days</p> <p>This visit will occur two weeks after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>The GWP42003-P dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day achieved at the end of the 10-day transition period, up to a maximum of 30 mg/kg/day in the OLE period.</p> <p>VISIT 6 (OLE) – One Month ± 3 days</p> <p>This visit will occur one month after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 7 (OLE) – Two Months ± 3 days</p> <p>This visit will occur two months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p>
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	<p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 8 (OLE) - Three Months ± 7 days</p> <p>This visit will occur three months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 9 (OLE) - Six Months ± 7 days</p> <p>This visit will occur six months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 10 (OLE) - Nine Months ± 7 days</p> <p>This visit will occur nine months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 11 – Twelve Months (OLE End of Treatment) ± 7 days</p> <p>This visit will occur twelve months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs),</p>
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	<p>physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>Starting at Visit 11, patients will begin to taper down their IMP dose. The dose will be reduced by 10% of their OLE maintenance dose per day.</p> <p>VISIT 12 - OLE End of taper +3 days</p> <p>This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.</p> <p>VISIT 13 - SAFETY FOLLOW-UP CALL (OLE)</p> <p>This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.</p> <p>Monitoring of Drug Abuse Liability</p> <p>During the routine collection of AEs in this study, if AEs are reported which can illuminate an abuse potential signal (specific AEs detailed in Section 9.1.16.1.1), then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussions of the event(s) with the patient/caregiver.</p> <p>The second trigger that will require the investigator or study coordinator to discuss abuse potential signals with the patient/caregiver is drug accountability issues regarding overuse of the IMP or missing IMP bottles.</p> <p>Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.</p> <p>A formal Adjudication Committee will be appointed and assigned to</p>
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	<p>this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.</p>
Statistical Considerations	<p>Plasma concentration data will be analyzed to estimate PK endpoints C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{1/2}$ of the following analytes: CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites.</p> <p>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 group ratios of geometric means of C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will be done on logarithm scale using a linear mixed effect model with treatment (CLB or CLB+GWP42003-P) 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.</p> <p>Descriptive summaries (means and standard deviations or counts [%] as appropriate) will be presented for all secondary endpoints (adverse events, laboratory data, vital signs, physical examination, C-SSRS and seizure frequency) for each phase of the study.</p>
Sponsor	<p>GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom</p>

Figure 1-1 Study Design and Treatment Schema

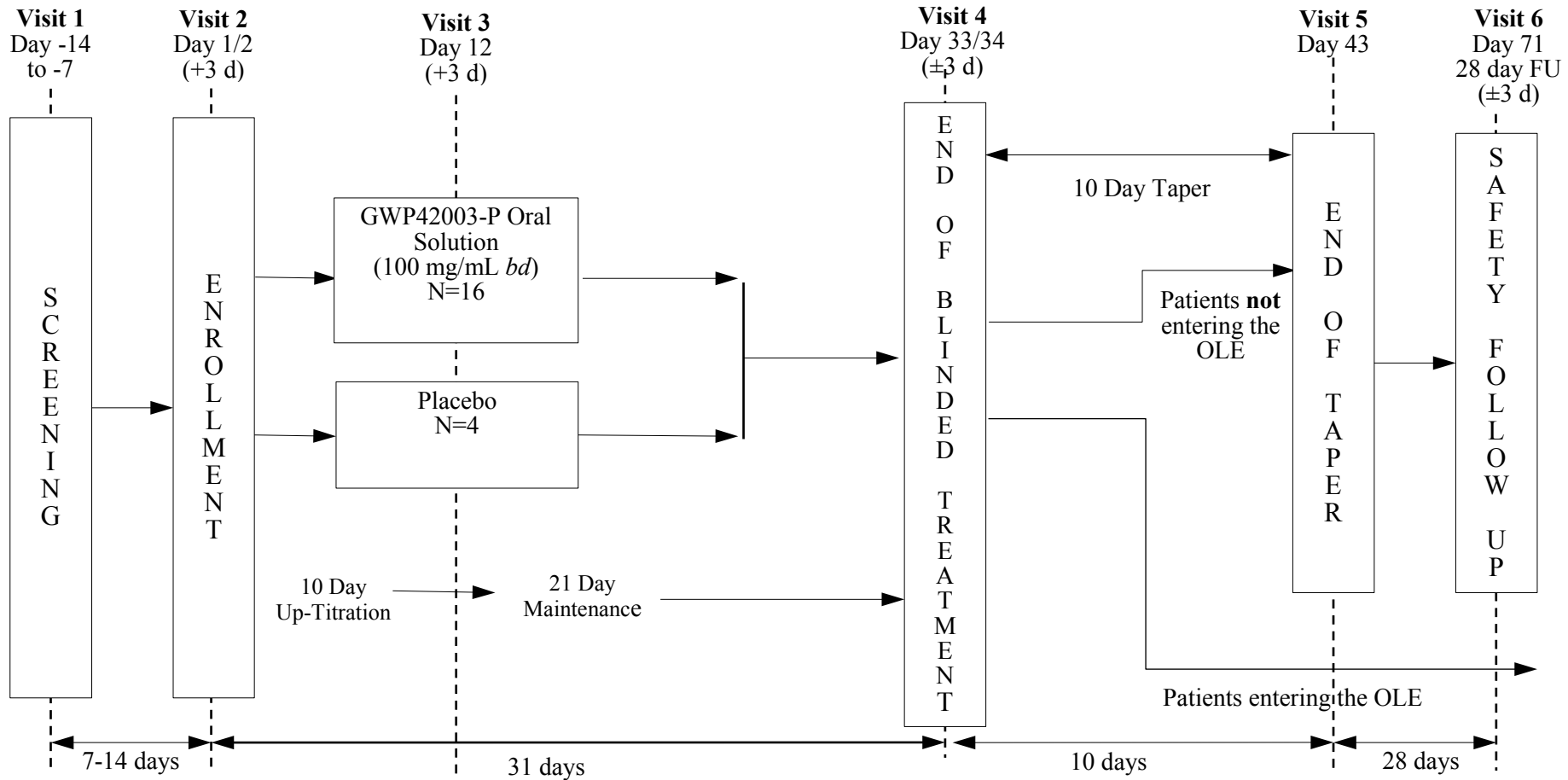


Figure 1-2 Study Design and Treatment Schema

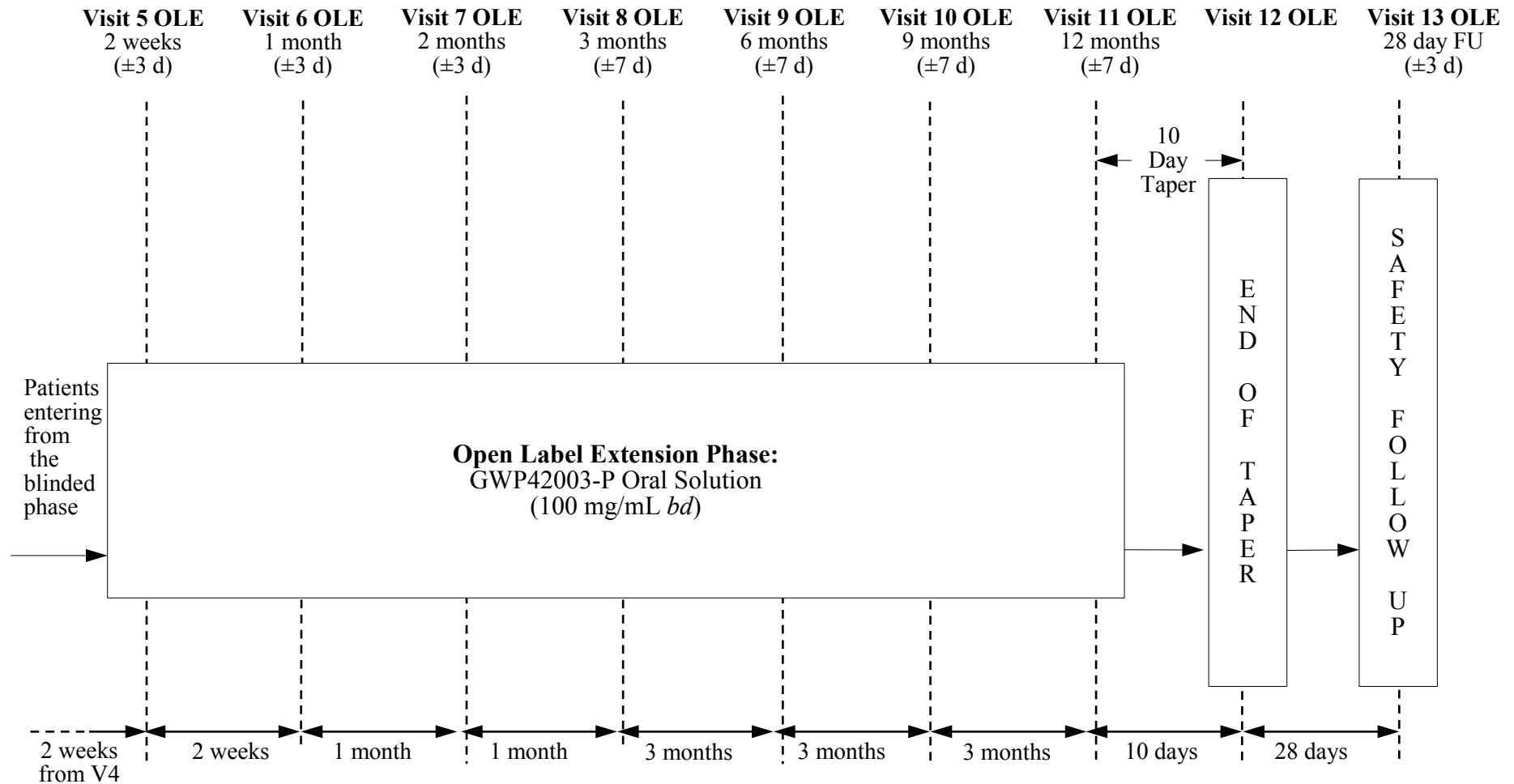


Table of Contents

Title Page	1
1. PROTOCOL SYNOPSIS.....	3
Table of Contents	18
Table of Appendices	23
List of In-text Tables	24
List of In-text Figures.....	25
List of Abbreviations	26
Definition of Terms.....	28
2. OBJECTIVES.....	29
2.1 Primary	29
2.2 Secondary	29
3. BACKGROUND AND RATIONALE	30
3.1 Disease.....	30
3.2 GWP42003-P Background.....	30
3.3 Rationale.....	31
3.3.1 Selection of Study Doses	32
3.4 Clinical Hypothesis	33
4. EXPERIMENTAL PLAN.....	34
4.1 Study Design	34
4.1.1 Primary Endpoint.....	35
4.1.2 Secondary Endpoint(s).....	35
4.2 Number of Centers	35
4.3 Number of Patients.....	36
5. INVESTIGATIONAL MEDICINAL PRODUCT	37
5.1 GWP42003-P Oral Solution.....	37
5.2 Placebo Oral Solution.....	37
5.3 Packaging, Storage and Drug Accountability (Cannabidiol/Placebo)	37
5.3.1 Packaging and Labelling.....	37
5.3.2 Storage	38
5.3.3 Supply and Return of Investigational Medicinal Product.....	38
5.3.4 Investigational Medicinal Product Accountability	38

5.4	Clobazam.....	39
6.	PARTICIPANT ELIGIBILITY	39
6.1	Inclusion Criteria.....	39
6.2	Exclusion Criteria.....	40
7.	PATIENT ENROLLMENT	42
7.1	Treatment Assignment	42
7.2	Randomization.....	42
8.	TREATMENT PROCEDURES.....	43
8.1	Investigational Medicinal Product Dosage, Administration and Schedule	43
8.1.1	Dose Administration.....	43
8.1.2	Dose Escalation and Dose Adjustments	44
8.2	Concomitant Therapy	45
8.3	Prohibited Therapy During Study Period.....	45
8.4	Compliance in Investigational Medicinal Product Administration.....	45
8.5	Access to Blinded Treatment Assignment	46
9.	STUDY PROCEDURES.....	47
9.1	Study Procedure Listing	47
9.1.1	Contraception.....	47
9.1.2	Informed Consent	47
9.1.3	Demographics	47
9.1.4	Medical History	48
9.1.5	Concomitant Medication	48
9.1.6	Physical Examination	48
9.1.7	Vital Signs	48
9.1.8	12-Lead Electrocardiogram	48
9.1.9	Clinical Laboratory Sampling.....	48
9.1.10	Pharmacokinetic Analyses.....	50
9.1.11	Genetic Testing.....	50
9.1.12	Columbia Suicide Severity Rating Scale.....	51
9.1.13	Patient Diary	51
9.1.14	Investigational Medicinal Product Accountability	51
9.1.15	Adverse Events	52

9.1.16	Monitoring of Drug Abuse Liability.....	52
9.1.16.1	Monitoring of Adverse Events.....	53
9.1.16.1.1	List of ‘Triggering Adverse Events of Interest’	53
9.1.16.1.2	Supplemental Adverse Event Form.....	53
9.1.16.2	Monitoring Drug Accountability Discrepancies	54
9.1.16.2.1	List of ‘Triggering Drug Accountability Discrepancies’	54
9.1.16.2.2	Supplemental Drug Accountability Form	55
9.1.16.3	Site Classification Form.....	55
9.1.16.4	Study Medication Use and Behavior Survey	55
9.1.16.5	Adjudication Committee — Assessment of Abuse Potential of GWP42003-P	56
9.2	Study Procedures by Visit.....	58
9.2.1	Double Blind Phase	58
9.2.1.1	Visit 1 (Day –14 to –7, Screening).....	58
9.2.1.2	Visit 2.....	58
9.2.1.2.1	Visit 2 (Day 1) – Enrollment (+3 days).....	58
9.2.1.2.2	Visit 2 (Day 2) - Enrollment.....	59
9.2.1.3	Visit 3 (Day 12 +3 days).....	59
9.2.1.4	Visit 4.....	59
9.2.1.4.1	Visit 4 (Day 33) (±3 days).....	59
9.2.1.4.2	Visit 4 (Day 34).....	60
9.2.1.5	Visit 5 (Patients not entering Open Label Extension) (Day 43 +3 days).....	60
9.2.1.6	Visit 6 - Safety Follow up Call (Day 71) (±3 days).....	61
9.2.2	Open Label Extension.....	61
9.2.2.1	Visit 5 (Open Label Extension) - Two Weeks (±3 days).....	61
9.2.2.2	Visit 6 (Open Label Extension) - One Month (±3 days).....	62
9.2.2.3	Visit 7 (Open Label Extension) - Two Months (±3 days)	62
9.2.2.4	Visit 8 (Open Label Extension) - Three Months (±7 days)	62
9.2.2.5	Visit 9 (Open Label Extension) - Six Months (±7 days)	62
9.2.2.6	Visit 10 (Open Label Extension) - Nine Months (±7 days).....	63
9.2.2.7	Visit 11 (Open Label Extension End of Treatment) - Twelve Months (±7 days)	63
9.2.2.8	Visit 12 (Open Label Extension End of Taper)	63

9.2.2.9	Safety Follow Up Call (± 3 days)	64
10.	WITHDRAWAL	64
11.	URGENT SAFETY MEASURES	65
12.	ADVERSE EVENT REPORTING	65
12.1	Definitions	65
12.1.1	Adverse Event	65
12.1.2	Investigator	66
12.2	Serious Adverse Events	66
12.3	Reporting Procedures for Serious Adverse Events	67
12.4	Pregnancy	67
12.5	Causality Assessment	68
12.6	Reporting Procedures for All Adverse Events	68
12.7	Follow up Procedures for Adverse Events	70
12.8	Potential Cases of Drug Induced Liver Injury	70
12.9	Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees	71
13.	STATISTICAL CONSIDERATIONS	73
13.1	Sample Size, Power and Significance Levels	73
13.2	Interim Analysis	73
13.3	Analysis Sets	73
13.3.1	Safety Set	73
13.3.2	Pharmacokinetic Analysis Set	73
13.3.3	Protocol Deviations	73
13.4	General Considerations	73
13.5	Accountability and Background Characteristics	74
13.5.1	Enrollment and Disposition	74
13.5.2	Baseline and Demographic Characteristics	74
13.5.3	Medical History	74
13.5.4	Concomitant Medication	74
13.6	Endpoints and Statistical Methods	74
13.6.1	Primary Endpoint(s)	74
13.6.2	Secondary Endpoint(s)	74
13.6.3	Pharmacokinetics	75

13.6.4	Safety	76
13.6.4.1	Treatment Compliance and Extent of Treatment Exposure	76
13.6.4.2	Adverse Events.....	76
13.6.4.3	Clinical Laboratory Data.....	76
13.6.4.4	Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data	77
13.6.4.5	Seizure Data	77
14.	DATA SAFETY MONITORING COMMITTEE	77
15.	REGULATORY AND ETHICAL OBLIGATIONS.....	78
15.1	Declaration of Helsinki	78
15.2	Informed Consent	78
15.3	Institutional Review Board/Ethics Committee.....	78
15.4	Pre-Study Documentation Requirements	79
15.5	Participant Confidentiality	79
16.	ADMINISTRATIVE AND LEGAL OBLIGATIONS.....	81
16.1	Protocol Amendments and End of Study or Termination	81
16.2	Study Documentation and Storage	81
16.3	Study Monitoring and Data Collection	82
16.4	Quality Assurance	84
16.5	Compensation.....	84
16.6	Publication Policy.....	84
16.7	Intellectual Property Rights.....	85
16.8	Confidential Information.....	85
17.	REFERENCES	86

Table of Appendices

APPENDIX 1.	Schedule of Assessments	89
APPENDIX 2.	Study Personnel	92
Appendix 3.1	Investigator Details	92
Appendix 3.2	Sponsor Contact Details	92

List of In-text Tables

Table 3.3.1-1	Epidiolex Adverse Events.....	33
Table 5.1-1	Formulation of GWP42003-P Oral Solution	37
Table 5.2-1	Formulation of Placebo Oral Solution	37
Table 8.1.2-1	Dose Up-titration Regimen*	44
Table 9.1.9-1	Hematology, Biochemistry, Urinalysis and THC Screen	49

List of In-text Figures

Figure 1-1	Study Design and Treatment Schema.....	16
Figure 1-2	Study Design and Treatment Schema.....	17
Figure 9-1	Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization Tabulation and Analysis which can Illuminate an Abuse Potential Signal.....	57

List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic Drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC _(0-∞)	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
BP	Blood Pressure
CBD	Cannabidiol
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLB	Clobazam
C _{max}	Maximum measured plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
EC	Ethics Committee
ECG	12-lead electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GW	GW Research Ltd
GWP	GW Pharma Ltd
IB	Investigator Brochure
ICH GCP	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat

IVRS	Interactive Voice Response System
LEV	Levetiracetam
LOCF	Last Observation Carried Forward
MMRM	Mixed-effects Model Repeated Measures
N-CLB	N-desmethyloclobazam
OLE	Open label extension
PBPK	Physiologically-based pharmacokinetic interactions
PI	Principal Investigator
PP	Per Protocol
PVD	Pharmacovigilance Department
QTcB	Heart rate corrected QT interval using Bazett's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFU	Safety follow up
STP	Stiripentol
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
TBL	Total bilirubin
THC	Δ^9 -tetrahydrocannabinol
t_{max}	Time to the maximum measured plasma concentration
TPM	Topiramate
ULN	Upper Limit of Normal
USA	United States of America
VNS	Vagus Nerve Stimulation
VPA	Valproate

Definition of Terms

Term	Definition
Baseline period	The period from screening (Visit 1) to enrollment (Visit 2).
Convulsive seizures	Tonic-clonic, tonic, clonic or atonic seizures.
Countable partial seizures	Partial/focal seizures with a motor or behavioral component that allow such seizures to be easily identified and hence counted.
Day 1	The day a patient is enrolled and begins PK sampling.
End of treatment	Completion of the treatment period (Visit 5 or Visit 12) or withdrawal.
End of study	Last patient's last visit / last contact.
IMP	Investigational Medicinal Product (Study Medication). Used to describe both investigational active product and reference therapy (placebo).
INR	International Normalized Ratio (INR) is a calculation made to standardize prothrombin time.
Investigator	Study Principal Investigator or a formally delegated study physician.
Non-convulsive seizures	Myoclonic, partial or absence seizures.
Partial seizures	Partial (focal) seizures occur when the electrical activity remains in a limited area of the brain.
Status epilepticus	Seizures lasting for 30 minutes or longer.
Sub-types of seizures	Seizure sub-types can be tonic, clonic, tonic-clonic, atonic, myoclonic, absence (typical and atypical), countable partial and other partial.

2. OBJECTIVES

2.1 Primary

To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyclobazam (N-CLB).

2.2 Secondary

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

3. BACKGROUND AND RATIONALE

3.1 Disease

Epilepsy is a common disorder¹. Approximately 1% of the world's population is chronically affected by epilepsy². It shows no particular geographic distribution and the gender distribution is more or less equal. The incidence of epilepsy is greater in childhood and in elderly people^{2,3,4,5}. Focal seizures represent the most frequent seizure type (around 60% of all cases of epilepsy, and a substantial percentage of them are not well controlled)⁶.

Overall, and despite the introduction of a substantial number of new antiepileptic drugs (AEDs) in the last two decades, around 30% of patients remain refractory to currently available treatment^{7,8,9}. In addition, most currently approved AEDs are associated with significant motor and cognitive adverse reactions^{10,11}.

Currently available AEDs each belong to one of a large number of different classes. The principal targets for existing AEDs tend to be either modulators of voltage-dependent ion channels, enhancers of inhibitory neurotransmission, and attenuators of excitatory neurotransmission, with the aim being to reduce neuronal excitotoxicity^{12,13}.

3.2 GWP42003-P Background

The cannabis plant (*Cannabis sativa* L.) produces trichomes that synthesize a large number of pharmacologically active compounds called phytocannabinoids. The most abundant of these are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), although the amounts and proportions of the various phytocannabinoids in each plant vary by strain and can be adjusted by breeding.

The Investigational Medicinal Product (IMP), GWP42003-P, is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (> 98%) CBD that typically contains less than 0.5% (w/w) THC. The pure CBD is subsequently dissolved in excipients with added sweetener and flavoring.

The pharmacological effects of phytocannabinoids are thought to be mediated primarily via their interaction with the endocannabinoid system, which consists of cannabinoid receptors, endogenous ligands (endocannabinoids) and enzymes for endocannabinoid synthesis and degradation. Two G-protein-coupled receptors for cannabinoids have so far been identified, designated cannabinoid CB₁ and CB₂.

receptors. CBD does not bind to either of these receptors with any great affinity but does modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects ion channel conductance and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1¹⁴ and the orphan receptor GPR55¹⁵. Importantly, in contrast to THC, CBD lacks detectable psychoactivity. CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity¹⁶. Very little data concerning AEs of CBD in humans exists to date. However, doses of up to 1500 mg CBD per day are reported to be well tolerated in humans¹⁷.

3.3 Rationale

CBD has shown therapeutic potential as an AED, with preclinical studies demonstrating anticonvulsant effects in a number of animal models of seizure^{16,18,19}. Although no placebo-controlled trials have been completed to date, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures while taking CBD-enriched cannabis, with over half of those reporting either > 80% reduction in seizure frequency or complete seizure freedom²⁰. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness and better mood. There has been a program of expanded access by GW Pharma Ltd (GWP) in the USA, primarily in children with severe epilepsy, that has shown encouraging reports of reductions in multiple seizure types with good tolerability in 151 exposures²¹.

Population-based studies of drug utilization demonstrate that 19-24% of patients with epilepsy use polytherapy with AEDs^{22,23,24}. In recent studies of children and adults with refractory epilepsy, 64 % used polytherapy with two or more AEDs, resulting in a considerable risk of interactions^{25,26}. CLB is a widely used 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). The pharmacological action of CLB is to decrease abnormal electrical activity in the brain via allosteric activation of the ligand-gated γ -aminobutyric acid (A) receptor.

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-CLB, amongst others.

CYP enzymes are a family of heme-containing enzymes responsible for the metabolism of over half of all prescribed medications and interactions with these enzymes are the major source of physiologically-based pharmacokinetic (PBPK) interactions between drugs. It is anticipated that patients taking GWP42003-P may also be taking CLB and as CBD has been shown to both inhibit CYP450 enzymes *in vitro* (K_i CYP3A4 = 1.5 μ M) and induce CYP450 enzymes *in vitro* (EC_{50} CYP3A4 = 1.2 μ g/mL) a possibility of a pharmacokinetic (PK) interaction between CBD and CLB exists. Furthermore, CLB has been shown to undergo PBPK interactions with other AED medications via both CYP induction (such as with felbamate where the formation of the active metabolite of CLB, N-CLB was increased several-fold²⁷) and also CYP inhibition (such as with stiripentol where serum concentrations of CLB were increased and metabolites decreased^{28,29,30}). Given the high likelihood that patients prescribed CBD will also be using CLB, it is the aim and purpose of this study to determine whether a PK interaction between CBD and CLB exists.

3.3.1 Selection of Study Doses

Doses up to 800 mg GWP42003-P per day for up to eight weeks have been well tolerated in adults in GW Research Ltd (GW) clinical study GWMD09112, which, assuming an average weight of 70 kg, equates to a daily dose of 11.4 mg/kg. In the literature, doses of GWP42003-P have been given up to 1500 mg GWP42003-P per day for four weeks in adults, which, in a 70 kg human equates to a daily dose of 21.4 mg/kg GWP42003-P.

Data on the safety of GWP42003-P is emerging from the physician-initiated Epidiolex[®] Expanded Access Program being conducted in the USA. This program has been running since January 2014 and at the time of writing had data on 63 patients. The mean maximum exposure achieved in this patient population of refractory epilepsies was a daily dose of 24.4 mg/kg (n=59 patients) with a maximum dose of 51 mg/kg in one patient. Please see below for a breakdown of the groups:

- ≤ 20 mg/kg GWP42003-P n=13 (21%)
- >20 mg/kg - ≤ 30 mg/kg GWP42003-P n=40 (64%)
- >30 mg/kg - ≤ 40 mg/kg GWP42003-P n=4 (6%)
- >40 mg/kg GWP42003-P n=2 (3%)
- Dose not reported n=4 (6%)

Eleven patients had a daily GWP42003-P dose of >25 mg/kg, of which five did not report any adverse events (AEs). Of note, the patient who received 51 mg/kg did not have any AEs at this dose. The remaining six patients experienced AEs as documented in the [Table 3.3.1-1](#) below:

Table 3.3.1-1 Epidiolex Adverse Events	
Adverse Event Term	Number of Events
Loose stools / urgent bowel movements	2
Increase in seizures	2
Drowsiness	1
Aspiration pneumonia	1
Lethargy	1
Decreased appetite	1
Dyskinesia	1
Urinary tract infection	1

Based on the above, a daily dose up to 20 mg/kg/day (given as two divided doses) has been selected for the GWP42003-P dose in the current study, including a titration period with daily increments of 2.5 mg/kg and 5 mg/kg. 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 interest. During the OLE doses may be adjusted up or down, dependent on investigator opinion, to a maximum daily dose of 30 mg/kg GWP42003-P.

3.4 Clinical Hypothesis

CBD can act as both a CYP inhibitor and inducer in human hepatocytes in vitro. Therefore, the potential for PK interactions with other drugs that are metabolized by CYP450 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.

4. EXPERIMENTAL PLAN

4.1 Study Design

This phase 2, placebo-controlled study consists of a 34 day, double-blind phase followed by an optional maximum one year 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 or equivalent of 20 mg/kg/day. 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 (Visit 2) before beginning treatment (patients will be taking CLB only).
- Day 33 (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 and THC major metabolites at Visit 4.

Patients should try to be consistent in the timing of their food intake in relation to dosing throughout the blinded phase of the study.

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.

A study schema (Figure 1-1), presented at the end of Section 1, depicts the overall study design. More detailed information on treatment and study procedures are provided in Section 8 and Section 9 respectively.

4.1.1 Primary Endpoint

The primary endpoints of the study are the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

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

4.1.2 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:

- 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 CPY3A4 patient genotype analysis

PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- THC
- THC major metabolites

4.2 Number of Centers

An estimated number of seven centers are expected to participate in this study.

4.3 Number of Patients

A total of 20 patients will be enrolled into the study. Recruitment for the study will be competitive between participating sites.

The sample size calculation is explained fully in [Section 13.1](#).

5. INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.1 GWP42003-P Oral Solution

GWP42003-P oral solution is presented as a pale yellow oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.1-1](#).

Table 5.1-1 Formulation of GWP42003-P Oral Solution	
Material	Quantity
CBD	100 mg/mL
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.2 Placebo Oral Solution

Placebo oral solution contains the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.2-1](#).

Table 5.2-1 Formulation of Placebo Oral Solution	
Material	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.3 Packaging, Storage and Drug Accountability (Cannabidiol/Placebo)

5.3.1 Packaging and Labelling

The IMP will be manufactured and packaged by GWP. It will be distributed by GWP or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each visit considering the weight of each patient. A unique pack identification number will be used to identify each box and the medication it contains. The pack numbers will cross check with the batch numbers held at GWP. GWP will ensure that all IMP provided is fully labelled and packaged. Label text will comply with European Union (EU) guidance on Good Manufacturing Practice, Annex 13 Labelling and will be fully described in the separate Pharmacy Manual. In addition, any local country

requirements in accordance with local drug law or regulatory requirement will be included in the final label text.

Directions of use, name, address and telephone number of investigator, or main contact for information about the product or the clinical trial, will be provided separately to the patient.

5.3.2 Storage

The IMP must be stored upright at room temperature ($< 30^{\circ}\text{C}$) and must not be refrigerated or frozen. It must also be kept away from heat and direct sunlight.

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities.

Should storage conditions deviate from these specified requirements, the GW study monitor should be contacted immediately to confirm if the IMP remains suitable for use. IMP should be placed under quarantine until confirmation is received that IMP is suitable for use.

Temperature records of the storage location must be maintained on a daily basis (a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each site. These records must contain at least the minimum and maximum daily temperatures and should be made available to the appropriate GW personnel for review throughout the study.

5.3.3 Supply and Return of Investigational Medicinal Product

Once a site has been activated at study initiation, IMP will be shipped to a responsible person, such as the pharmacist, at the investigator's center, who will check the amount received and the condition of the drug. Details of the IMP received will be recorded in the IMP accountability record. The site will acknowledge IMP receipt and will complete any receipt forms required. IMP will be dispensed and returned as detailed in [Section 5.3.4](#) with further IMP shipments to be requested as necessary. As directed, all supplies, including unused, partially used, or empty containers, will be returned to GWP or destroyed at the center if agreed in writing by the study monitor.

5.3.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMPs must be kept current and should contain:

- The dates and quantities of IMP received from GWP.

- Patient's identification.
- Date and quantity of IMP dispensed.
- The initials of the dispenser.
- Date and quantity of IMP returned to the investigator/pharmacy.

A record of returned IMP must be completed and included in the shipment of used and unused IMP to GWP. At the end of the study a record/statement of reconciliation must be completed and provided to GWP.

These inventories must be made available for inspection by authorized GW or GWP representatives and local officials or regulatory agency inspectors.

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.4 Clobazam

Patients will use their own supply of CLB throughout the study. CLB usage will be recorded by the investigator. CLB is only an IMP for the blinded phase of the study.

6. PARTICIPANT ELIGIBILITY

Investigators will be required to maintain a log that includes limited information about all screened patients (initials, age, and gender; as allowed per local regulations) and outcome of screening.

6.1 Inclusion Criteria

For inclusion in the study patients must fulfil ALL of the following criteria:

- 6.1.1 Male or female patients aged 18 to 55 years inclusive.
- 6.1.2 Patient must have epilepsy as determined by the investigator and be taking CLB.
- 6.1.3 Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition.
- 6.1.4 Patient must have experienced at least one seizure of any type (i.e., convulsive: tonic-clonic, tonic, clonic, atonic; focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness focal seizures evolving to bilateral secondary generalization) within the two months prior to randomization.
- 6.1.5 Patients must be taking CLB and no more than two other AEDs during the course of the study.
- 6.1.6 AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study.

- 6.1.7 Intervention with vagus nerve stimulation (VNS) and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must be willing to maintain a stable regimen throughout the blinded phase of the study.
- 6.1.8 Patients must abstain from alcohol during the blinded phase of the study.
- 6.1.9 Patient is available to attend all PK visits within the required visit window.
- 6.1.10 Patient and/or legal representative must be willing and able to give informed consent for participation in the study
- 6.1.11 Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements.
- 6.1.12 Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable.
- 6.1.13 Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study.

6.2 Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

- 6.2.1 Patient has clinically significant unstable medical conditions other than epilepsy.
- 6.2.2 Patients on CLB at doses above 20 mg per day.
- 6.2.3 Patients taking CLB intermittently as rescue medication.
- 6.2.4 Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes.
- 6.2.5 Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening.
- 6.2.6 Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy.
- 6.2.7 Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain during the blinded phase of the study.
- 6.2.8 Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry.
- 6.2.9 Patient has any known or suspected history of any drug abuse or addiction.
- 6.2.10 Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration of the study.
- 6.2.11 Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits.
- 6.2.12 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil.

- 6.2.13 Female patient is of child bearing potential, or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.
- 6.2.14 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.
- 6.2.15 Patients who have received an IMP within the 12 weeks prior to the screening visit.
- 6.2.16 Patient is taking felbamate and they have been taking it for less than one year prior to screening.
- 6.2.17 Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study.
- 6.2.18 Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator would prevent the patient from safe participation in the study.
- 6.2.19 Patient has significantly impaired hepatic function at screening (Visit 1) or enrollment (Visit 2), defined as any of the following:
- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $> 5 \times$ upper limit of normal (ULN).
 - ALT or AST $> 3 \times$ ULN **and** total bilirubin (TBL) $> 2 \times$ ULN **or** international normalized ratio (INR) > 1.5 .
 - ALT or AST $> 3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).
- This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion **must** be withdrawn from the study.*
- 6.2.20 Patient has a prolonged QTcB (> 450 msec for males and > 470 msec for females).
- 6.2.21 Unwilling to abstain from donation of blood during the study.
- 6.2.22 Travel outside the country of residence planned during the study, unless the patient has confirmation that the IMP is permitted in the destination country/state.
- 6.2.23 Patients previously enrolled into this study.

7. PATIENT ENROLLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center's Ethics Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent forms (ICFs) and other patient information material. Patients will be considered enrolled in the study from the time of providing written informed consent. All patients, or legal representatives, where appropriate, must personally sign and date the consent form prior to any procedures being performed (refer to [Section 9.1.2](#) and [Section 15.2](#)).

7.1 Treatment Assignment

At the start of Visit 1, patients will be allocated a unique patient number, consisting of a four digit GW center number and a three digit patient identification number. The three digit patient number will be assigned in ascendant numerical order at each site. The unique patient number will be preceded by a unique letter. For example, W1234001, denoting patient 001 at site 1234. GWP will provide all GWP42003-P/placebo packed and labelled. Following enrollment at Visit 2, patients will be allocated a pre-packed numbered IMP.

7.2 Randomization

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

8. TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The IMP will consist of three types of medication:

- GWP42003-P oral solution containing 100 mg/mL CBD.
- Placebo oral solution containing excipients.
- CLB (patient supplied).

The GWP42003-P/placebo will be presented as an oral solution containing either the active pharmaceutical ingredient and excipients (in the case of GWP42003-P) or only excipients (in the case of placebo). For details regarding GWP42003-P/placebo formulations, see [Section 5](#).

All patients will be weighed during the study visits and the daily volumes of GWP42003-P/placebo solution to be taken during the titration period, and for the remainder of the study, will be calculated and provided to the patient and/or caregiver. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Each patient will take their first dose of GWP42003-P/placebo at Visit 2, Day 2 in the clinic. Patients not entering the OLE will take their final maintenance dose of GWP42003-P/placebo at Visit 4 (Day 33) in the clinic. Patients entering the OLE will take their final dose of IMP at Visit 11 (one year after the end of the blinded phase of the study) or sooner (if marketing authorization is granted within one year).

Patients will use their own supply of CLB throughout the study. Patients will continue on the dose that they were on at screening for the blinded phase of the study. CLB will only be an IMP for the blinded section of the study.

8.1.1 Dose Administration

GWP42003-P/placebo will be administered orally by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided.

GWP42003 P/placebo should be taken immediately after the patient's usual CLB administration. The GWP42003-P/placebo should be swallowed, as per the intended commercial therapeutic route, and may be taken with other concomitant medications, as directed by the investigator.

8.1.2 Dose Escalation and Dose Adjustments

Patients will enter the blinded phase of the study and will be up-titrated over ten days (Day 2 to Day 11) to a maintenance dose or equivalent of GWP42003-P/placebo of 20 mg/kg/day. If GWP42003-P is not tolerated then the dose can be reduced accordingly at the discretion of the investigator. The titration regimen is described in [Table 8.1.2-1](#).

Table 8.1.2-1 Dose Up-titration Regimen*			
Day - GWP42003-P/Placebo (Blinded Period)	Dose Level (GWP42003-P or equivalent placebo)	Open label Extension** (GWP42003-P only) Day	Dose Level GWP42003-P
2	2.5 mg/kg	34	2.0 mg/kg
3	2.5 mg/kg	35	4.0 mg/kg
4	5.0 mg/kg	36	6.0 mg/kg
5	5.0 mg/kg	37	8.0 mg/kg
6	7.5 mg/kg	38	10.0 mg/kg
7	7.5 mg/kg	39	12.0 mg/kg
8	10.0 mg/kg	40	14.0 mg/kg
9	10.0 mg/kg	41	16.0 mg/kg
10	15.0 mg/kg	42	18.0 mg/kg
11	15.0 mg/kg	43	20.0 mg/kg
12 onwards	20.0 mg/kg	44	20.0 mg/kg***

* GWP42003-P /placebo is to be taken twice daily. Total daily doses are shown.

** Only patients who were taking placebo during the double-blind period will up-titrate according to this schedule during the OLE period. Those taking GWP42003-P during the double-blind period will down-titrate their blinded IMP whilst simultaneously up-titrating with GWP42003-P, thus maintaining a daily dose of 20 mg/kg/day GWP42003-P throughout.

*** The GWP42003-P dose of 20 mg/kg/day can be adjusted during the OLE period, after Visit 5, at the investigator's discretion: up to a maximum dose of 30 mg/kg/day. It may also be adjusted down (no minimum).

The titration regimen defined above should be followed to the maximum dose (20 mg/kg/day). Should an AE occur during titration which is attributable to IMP or concomitant AED, then IMP dose should be reduced to the next lower dose. Any other changes in concomitant AED therapy should be reviewed with the medical monitor before being initiated.

For those patients who do not enter the OLE the dose of GWP42003-P/placebo will taper off over 10 days beginning on Day 34. The patient will reduce the dose by 10% of the maintenance dose each day and treatment will end on Day 43.

Patients who enter the OLE period will be transitioned to the OLE treatment over a 10-day period in order to maintain blinding, simultaneously down-titrating blinded GWP42003-P /placebo whilst up-titrating open-label GWP42003-P. As such, patients

who were taking GWP42003-P during the blinded period will maintain their 20 mg/kg/day dose throughout the transition from the blinded period into the OLE period and patients who received placebo during the blinded period up-titrate slowly to the 20 mg/kg/day dose in the OLE period. After this has taken place after Visit 5, the maintenance dose of GWP42003-P may be adjusted up or down at the discretion of the investigator to a maximum of 30 mg/kg/day (no minimum).

8.2 Concomitant Therapy

Doses of any concomitant AEDs, including CLB, must have been stable for at least four weeks prior to screening and must remain stable throughout the blinded phase of the study. If there are symptoms of toxicity suspected to be from a drug interaction, the investigator may adjust GWP42003-P/placebo or the CLB or other AEDs after discussion with the medical monitor.

The use of rescue medication is allowed if necessary. The use of oxygen may be considered as rescue medication if used as required. Any medication, other than the IMP, taken during the study must be recorded on the Case Report Form (CRF).

Any non-pharmacological therapies (e.g., ketogenic diet, VNS) must also be stable up to four weeks prior to baseline and throughout the duration of the study.

8.3 Prohibited Therapy During Study Period

The following medications are prohibited for the duration of the study starting from acquisition of patient consent. However, any patients taking these medications after screening should not be withdrawn from the study unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered.

- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.
- Patients should not take any more than three AEDs inclusive of CLB.
- Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.

If any other IMP is taken as part of a clinical trial within twelve weeks of the screening visit or during the study, the patient must be withdrawn from this study.

8.4 Compliance in Investigational Medicinal Product Administration

Patients or their caregivers will record the total volume of IMP, administered on each treatment day, using the paper diary and will be asked to return all IMP (used and unused) at each subsequent visit. The site will check the returned IMP against the

usage recorded in the diary and the projected usage. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

The investigator must inform GW promptly of all missing or unaccountable IMP.

Records of IMP accountability will be maintained according to [Section 5.3.4](#).

8.5 Access to Blinded Treatment Assignment

The identity of IMP assigned to patients will be held by the IVRS. The principal investigator (PI) at each center is responsible for all trial-related medical decisions and is responsible for ensuring that information on how to access the IVRS is available to the relevant staff in case of an emergency and unblinding is required. 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.

The investigator is encouraged to contact GW to discuss the rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of study medication will not be dependent upon the investigator receiving approval from GW (i.e., the investigator will be able to obtain the code break information independent of contacting GW).

If the investigator does unblind they must contact GW within one working day of the event and must document the time, date and reasons for unblinding in the patient's CRF.

9. STUDY PROCEDURES

A list of the required study procedures is provided in the subsections that follow; refer also to the Schedule of Assessments in [APPENDIX 1](#). Assessments or tests that are not done and examinations that are not conducted must be reported as such on the CRFs.

The location of the source data for the following procedures will be documented, per center, in a signed ‘Source Data Verification plan’, for further details see [Section 16.2](#).

9.1 Study Procedure Listing

9.1.1 Contraception

To be eligible for the study, the patient must have agreed that if they or their partner are of child-bearing potential they are willing to use highly effective contraception for the duration of the study and for three months thereafter. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence⁶. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. The use of hormonal contraception must be supplemented with a barrier method (preferably male condom).

9.1.2 Informed Consent

Adult patients with an adequate level of understanding must personally sign and date the IRB/EC approved ICF(s) before any study specific procedures are performed or any patient related data is recorded for the study. For adult patients with an insufficient level of understanding of what is proposed, only personal legal representative consent will be sought. The informed consent process should be documented within the patient notes.

GW requires a physician to be present for consent and to also sign the ICFs.

9.1.3 Demographics

Patient demographics will be recorded at Visit 1. The following information will be obtained for each patient: date of birth, gender and race (if allowed per local regulations).

9.1.4 Medical History

Relevant, significant medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken) will be obtained during Visit 1 and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the study.

9.1.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 28 days) including AEDs will be recorded at the screening visit (Visit 1) and reviewed at each subsequent visit. AEDs used during the study should be maintained at a stable dose. Any changes in concomitant medication during the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to the screening visit, as defined in [Section 8.3](#).

9.1.6 Physical Examination

A physical examination will be performed at the screening visit (Visit 1) to ensure that the patient is eligible to enter the study. To ensure patient safety, further physical examinations will be performed at every hospital visit. Physical examinations will include height (at screening) and body weight measurements.

9.1.7 Vital Signs

Vital sign measurements, taken after five minutes rest in a sitting position, will be completed alongside the physical examination at all visits. Postural BP will be assessed after five minutes in supine position and, if possible, two minutes in standing position. The pulse rate must also be measured as part of the vital sign assessments. BP and pulse rate must be recorded using the same arm throughout the study.

9.1.8 12-Lead Electrocardiogram

An ECG will be performed, after five minutes in supine position, at all hospital visits. A physician must review the ECG and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately in the CRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

9.1.9 Clinical Laboratory Sampling

Laboratory tests will be undertaken at all hospital visits and will include hematology, biochemistry, and urinalysis (provided urine can be obtained, with the exception of

screening where a urine sample for THC screen must be obtained). A serum alcohol test will be performed at Visits 1, 2 and 4. A serum pregnancy test (if appropriate) will also be performed at Visit 1.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further laboratory based urinalysis (urinalysis, microscopy, culture and sensitivity, as applicable).

The investigator and study monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in [Table 9.1.9-1](#).

Table 9.1.9-1 Hematology, Biochemistry, Urinalysis and THC Screen				
Biochemistry (serum)	Hematology (whole blood)	Urinalysis (urine)	Pregnancy Test	THC screen (urine)
Alanine aminotransferase (ALT)	Hematocrit	Bilirubin	Serum	THC
Albumin	Hemoglobin	Blood		
Alkaline phosphatase	Mean cell volume	Glucose		
Aspartate aminotransferase (AST)	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				

All laboratory results will be reviewed and the reports signed by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. See [Section 12.8](#) for guidance on evaluation of potential drug-induced liver injury. All laboratory results considered by the investigator to represent an AE must be documented on the CRF.

Repeat samples will be taken, if required, for clinical follow up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an

investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation.

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss in the four weeks prior to screening.

9.1.10 Pharmacokinetic Analyses

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. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted into a forearm vein 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.

The pre-dose blood sample will be taken within 30 minutes prior to dosing. The allowable window for post-dose blood sample collection is ± 2 minutes up to and including 1 hour post-dose, ± 5 minutes from 1.5 hours up to and including 6 hours post-dose and ± 1 hour at 12 hours and 24 hours post-dose.

In the event of an AE that, in the opinion of the investigator, is related to a concomitant AED, additional blood samples may be collected.

Analysis of all PK samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

9.1.11 Genetic Testing

Genetic testing will only be conducted if specific consent is obtained from the participant or their legal representative. There is a separate ICF for this.

Genetic testing will be conducted to look at the CYP450 genes, with particular focus on CYP 2C19 and CYP 3A4, involved in the metabolism of AEDs and GWP42003-P.

9.1.12 Columbia Suicide Severity Rating Scale

The C-SSRS is to be completed by the investigator or his/her qualified designee at all hospital visits. Qualified designee is defined as physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant who is licensed and has completed the C-SSRS training within the last two years. It is a brief standardized measure that uniquely assesses the essential information (behavior, ideation, lethality and severity) and distinguishes between suicidal occurrences and non-suicidal self-injury. The survey should be completed by the same assessor, where possible, throughout the study.

If the investigator or his/her qualified designee feel that the patient is either unable to answer the questions presented in C-SSRS, or that the questions are causing undue stress to the patient, the questionnaire may be skipped and this must be documented in the patient notes.

9.1.13 Patient Diary

Patients or their caregivers will be instructed on how to complete a paper diary and will be asked to record information daily in it. The number and type of seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from screening (Visit 1) until completion of dosing or withdrawal. Information on IMP intake will also be recorded each day from enrollment (Visit 2) until completion of dosing or withdrawal.

9.1.14 Investigational Medicinal Product Accountability

GWP42003-P/placebo will be dispensed at each of the following visits during the blinded phase:

- Visit 2 (Day 2)
- Visit 4 (Day 34)

IMP will be dispensed at each of the following visits for patients entering the OLE:

- Visit 5 (Two weeks)
- Visit 6 (One month)
- Visit 7 (Two months)
- Visit 8 (Three months)
- Visit 9 (Six months)
- Visit 10 (Nine months)
- Visit 11 (12 months)

Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 2 to 12). The site will check the returned IMP against the usage recorded in the paper diary. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

9.1.15 Adverse Events

Any adverse changes in the patient's medical condition, following completion of the consent form by the patient, will be recorded on the CRF as AEs, questioning the patient further if necessary. All AEs* occurring during the study, whether or not attributed to the IMP, observed by the investigator or reported by the patient will be recorded in the CRF.

*For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures, must be documented as an AE.

Serious Adverse Events (SAEs) must be reported to GW Pharmacovigilance Department (PVD) within 24 hours of discovery or notification of the event, and recorded in the CRF.

Refer to [Section 12](#) for definitions, procedures and further information.

Inpatient hospitalizations that are, in the investigator's opinion, due to epilepsy will be recorded in the patient's CRF and through the SAE reporting process.

Refer to [Section 9.1.16.1.1](#) for the list of 'Triggering AEs of Interest' associated with monitoring of drug abuse liability.

9.1.16 Monitoring of Drug Abuse Liability

There are two triggers that will require the investigator or study coordinator to discuss abuse potential signals with the patient or their caregiver. These are either AEs of interest that may be reported by the patient/caregiver, or drug accountability issues regarding overuse of the IMP or missing bottles. Different questionnaires will be completed by the site depending upon which trigger occurs (see [Figure 9-1](#)).

Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (Visit 5 or Visit 12) or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.

Investigators and study coordinators will be provided with training on how to complete and perform the processes outlined in this section. This training must be completed and documented by the relevant site staff prior to implementation at site.

9.1.16.1 Monitoring of Adverse Events

AE information will be collected according to [Section 9.1.15](#).

9.1.16.1.1 List of ‘Triggering Adverse Events of Interest’

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 Adverse Event 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.

An AE that is consistent with the above categories will be known as a ‘triggering AE of interest’ for the purposes of this study.

9.1.16.1.2 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Adverse Event Form will then be transcribed into the patient’s CRF for the study. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the site should contact the patient/caregiver to obtain the required answers as soon as possible.

9.1.16.2 Monitoring Drug Accountability Discrepancies

Any time after enrollment until final collection of study data, drug accountability discrepancies are monitored as follows:

- At routine Drug Accountability collection times, the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the paper diary.
- At any time that the site is informed by the patient/caregiver about any overuse of IMP, suspected misuse, abuse, or diversion.

9.1.16.2.1 List of ‘Triggering Drug Accountability Discrepancies’

If there are any discrepancies in drug accountability as outlined by the criteria below, known as ‘triggering drug accountability discrepancies’, then the trained investigator or study coordinator will complete a Supplemental Drug Accountability Form and Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver. The triggering drug accountability discrepancies are as follows:

- Missing bottle(s).
- Compliance issues where one or more bottles are used compared to what was the expected use, according to the paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the paper diary.

9.1.16.2 Supplemental Drug Accountability Form

This form consists of eight questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Drug Accountability Form will then be transcribed into the patient's CRF for the study. The accountability reporting procedures will still occur. If the Supplemental Drug Accountability Form cannot be completed at the time the triggering drug accountability discrepancy is identified, then the site should contact the patient/caregiver by telephone to obtain the required answers as soon as possible (Note: IMP refers to GWP42003-P or placebo, not other concomitant medications).

9.1.16.3 Site Classification Form

The investigator should review the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then complete the Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification. The answers from the Site Classification Form will then be transcribed into the patient's CRF for the study.

9.1.16.4 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit (Visit 5 or Visit 12) or withdrawal visit. The answers on the Study Medication Use and Behavior Survey will then be transcribed into the patient's CRF for the study.

The Study Medication Use and Behavior Survey will be completed for all patients in the study and not only those that have reported a triggering AE or drug accountability discrepancy.

9.1.16.5 Adjudication Committee — Assessment of Abuse Potential of GWP42003-P

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases. Only data from patients who have completed the study will be assessed.

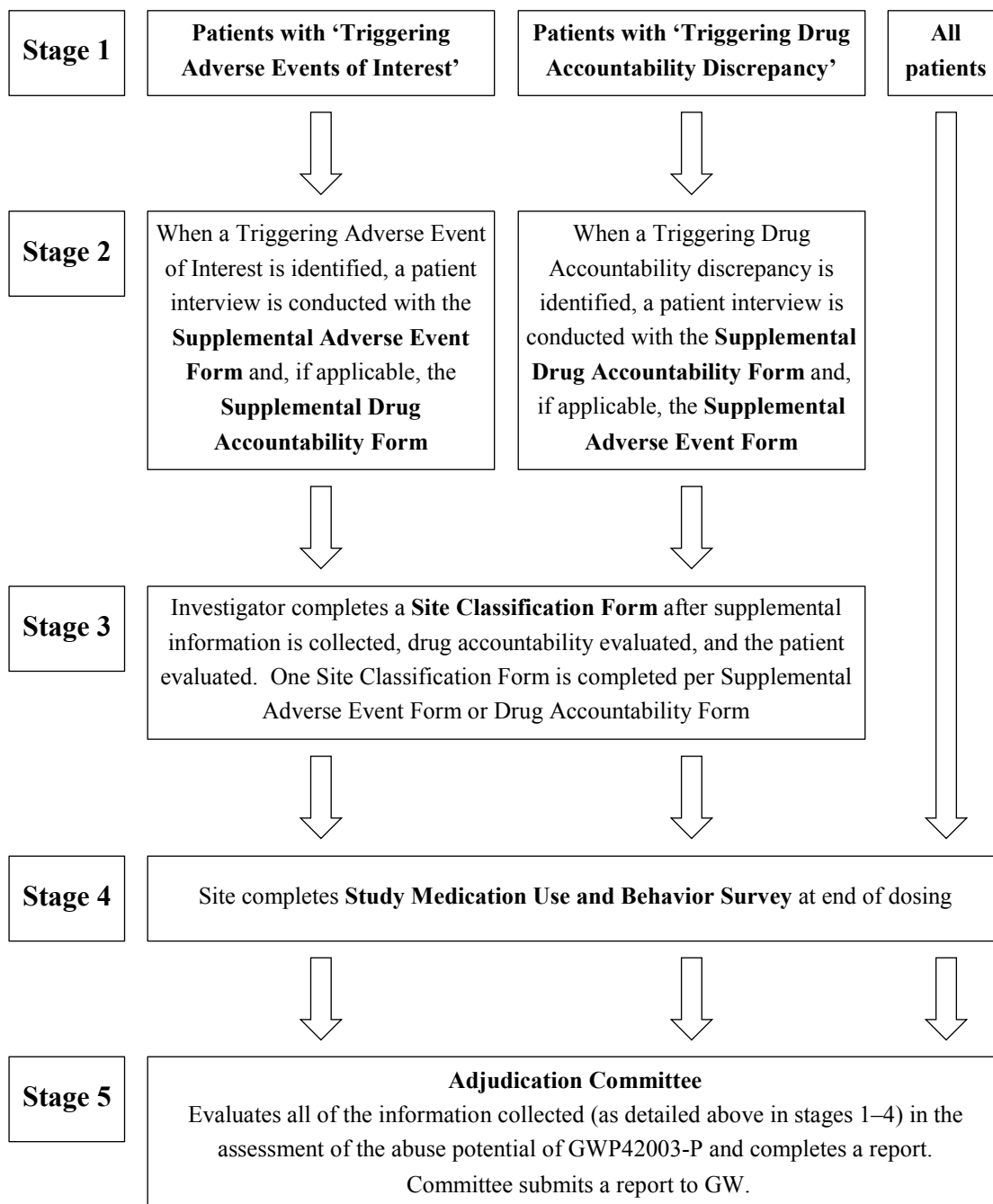
A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- All triggering AE information.
- Supplemental Adverse Event Form (if applicable).
- All triggering drug accountability discrepancies.
- Supplemental Drug Accountability Form (if applicable).
- Site Classification Form.
- Study Medication Use and Behavioral Survey.
- Additional information from site(s) as requested by the Committee.

The Adjudication Committee will assess all of the information. It will form a position on the classification of each event and will write a study-related report, detailing the conclusions and recommendations.

The overall process is summarized in [Figure 9-1](#).

Figure 9-1 **Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization Tabulation and Analysis which can Illuminate an Abuse Potential Signal**



9.2 Study Procedures by Visit

Patients and their caregivers will be invited to participate in the study and will be issued with the patient information and informed consent or the personal legal representative information and informed consent (refer to [Section 9.1.2](#) and [Section 15.2](#)). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/legal representatives who provide written informed consent at Visit 1 will be screened for entry into the study.

9.2.1 Double Blind Phase

9.2.1.1 Visit 1 (Day -14 to -7, Screening)

The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, THC testing, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.

Patients who satisfy all inclusion and none of the exclusion criteria specified in [Section 6](#) will be assigned a unique patient number and then begin the baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be instructed on how to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.

9.2.1.2 Visit 2

9.2.1.2.1 Visit 2 (Day 1) – Enrollment (+3 days)

This visit will occur 7–14 days after Visit 1.

The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including body weight), ECG, vital signs and review of patient diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. Blood samples will also be taken for genetic testing if additional consent has been obtained. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.

Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV and TPM. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of any AEDs must be taken after the 12 hour PK blood sample. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic on Day 2 ahead of additional sample collection.

9.2.1.2.2 Visit 2 (Day 2) - Enrollment

This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.

GWP42003-P/placebo will be dispensed and both the morning dose of CLB and of GWP42003-P/placebo will be taken in clinic. Following administration of GWP42003-P/placebo, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions. Patients and/or their caregivers will be provided with individual dosing schedules as described in [Section 8.1.2](#). Each patient will then receive their GWP42003-P/placebo for the 10 day titration period followed by the 21 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.

9.2.1.3 Visit 3 (Day 12 +3 days)

This visit will occur 11 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 3 (Day 12): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, AEs and review of patient diary completion.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.

9.2.1.4 Visit 4

9.2.1.4.1 Visit 4 (Day 33) (±3 days)

This visit will occur 32 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at

Visit 4 (Day 33): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, and urinalysis. The C-SSRS will be administered.

Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of GWP42003-P/placebo. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of GWP42003-P/placebo and any AEDs must be taken after the 12 hour PK blood sample. Patients are expected to remain in clinic throughout this PK sampling.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.1.4.2 Visit 4 (Day 34)

This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 33 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 34: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.

At the end of the blinded phase of the study on Day 34, providing the investigator and patient both agree, patients will be invited to continue taking GWP42003-P and to enter the OLE.

Patients who enter the OLE will be dispensed GWP42003-P on Day 34. At the point of entry to the OLE, patients will be transitioned to the OLE treatment over a 10 day period in order to maintain blinding.

Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of GWP42003-P/placebo. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42.

9.2.1.5 Visit 5 (Patients not entering Open Label Extension) (Day 43 +3 days)

This visit will occur 42 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.

All GWP42003-P/placebo (used and unused) will be collected and a check of the returned GWP42003-P/placebo against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.

9.2.1.6 Visit 6 - Safety Follow up Call (Day 71) (± 3 days)

This visit is required for patients who do not enter the OLE study on Day 34, or who withdraw from the study early. This visit should occur four weeks after Visit 5, (± 3 days) or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 71: concomitant medications (including AEDs) and AEs.

9.2.2 Open Label Extension

Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 34) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 34).

9.2.2.1 Visit 5 (Open Label Extension) - Two Weeks (± 3 days)

This visit will occur two weeks after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

The GWP42003-P dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day achieved at the end of the 10-day transition period, up to a maximum of 30 mg/kg/day in the OLE period.

9.2.2.2 Visit 6 (Open Label Extension) - One Month (± 3 days)

This visit will occur one month after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.3 Visit 7 (Open Label Extension) - Two Months (± 3 days)

This visit will occur two months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.4 Visit 8 (Open Label Extension) - Three Months (± 7 days)

This visit will occur three months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.5 Visit 9 (Open Label Extension) - Six Months (± 7 days)

This visit will occur six months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE):

concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.6 Visit 10 (Open Label Extension) - Nine Months (± 7 days)

This visit will occur nine months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.7 Visit 11 (Open Label Extension End of Treatment) - Twelve Months (± 7 days)

This visit will occur twelve months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

Starting at Visit 11, patients will begin to taper down their IMP dose. The dose will be reduced by 10% of their OLE maintenance dose per day.

9.2.2.8 Visit 12 (Open Label Extension End of Taper)

This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be

administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.

9.2.2.9 Safety Follow Up Call (±3 days)

This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.

10. WITHDRAWAL

In accordance with the Declaration of Helsinki³¹, the FDA regulations relating to good clinical practice (GCP) and clinical trials^{32,33,34}, the EU Clinical Trials Directive (2001/20/EC)³⁵ and/or other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

The patient must be withdrawn from the study if any of the following apply:

- Administrative decision by the investigator, GW, or a Regulatory Authority.
- Pregnancy.
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- Withdrawal of patient consent.
- Withdrawal of legal representative consent.
- Lost to follow up.
- ALT >3 × ULN or AST >3 × ULN **and** (TBL >2 × ULN **or** INR >1.5).
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- ALT or AST >8 × ULN.
- ALT or AST >5 × ULN for more than two weeks.
- Any other IMP is taken as part of a clinical trial during the study.
- Significant change in QTcB (> 60 msec) from the previous ECG or absolute QTcB of > 500 msec.

Patients may also be withdrawn from the study for any of the following:

- Patient non-compliance.

- AE, which in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Any evidence of drug abuse or diversion.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

Should a patient request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients who withdraw should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator's clinical judgment. All assessments required at Visit 4 (if the withdrawal is during the blinded phase) or Visit 11 (if the withdrawal is during the OLE) should be conducted if possible. If the tapered dose is administered, patients should return for Visit 5 (if withdrawal is during the blinded phase) or Visit 12 (if the withdrawal is during the OLE) if possible. Wherever possible, the safety follow-up visit should be conducted 28 days from the date of the last dose of IMP. Patients withdrawing due to an AE should be followed up according to [Section 12.7](#). All information should be reported on the applicable CRF pages

11. URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the investigator they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to Competent Authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the Competent Authorities and IRB/EC within three days.

12. ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this study an AE is defined as:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which is present following screening (Visit 1) throughout the study and up to the post treatment, safety follow-up visit (28 days after last dose of IMP), which may or may not be considered

to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

Surgical/Investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-study existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization which prolongs their scheduled hospital stay in which case it would be considered a SAE (refer to [Section 12.2](#)).

If reporting a fatal event, the SAE term should be the underlying cause of the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

The term ‘investigator’ refers to the study PI or a formally delegated study physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported promptly to Regulatory/Competent Authorities, applicable IRB/ECs and Investigators (expedited reporting) by GW.

An AE must only be classed as serious i.e., an SAE, when the event falls into one of the following criteria:

- Results in death.
- Is life-threatening.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Medically significant.**

* The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

** Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of

such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.3 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study must be reported to GW with any other supporting information and recorded in the AE section of the CRF. Any on-going SAEs should be followed up until resolution wherever possible. For all deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports and relevant medical reports should be sent to GW promptly.

All SAEs must be reported directly to GW PVD within 24 hours of discovery or notification of the event. All SAE information must be recorded on the SAE forms provided in the site files and faxed to GW PVD. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form, signed/dated and faxed to the GW PVD and the AE section of the CRF must be updated.

The investigator should continue to document all AEs which occur up to the last formal follow-up visit (Visit 13 for patients entering the OLE and Visit 6 for those patients that are not entering the OLE). If the investigator subsequently becomes aware of any deaths or a new IMP-related SAE after the last formal follow-up period of the study, these should still be reported to the GW PVD.

Any other problem discovered outside these time limits which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have participated in the study, then these should be treated as an SAE and reported to GW PVD. Such post study SAEs do not need to be recorded on the patient's CRF if editing rights to the CRF have been removed.

Contact details for the GW PVD are provided at the front of the site files for all study centers, and upon the GW SAE Report form.

12.4 Pregnancy

Any patient, or patient's partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD within 24 hours of first awareness. Please use the GW Pregnancy Monitoring Forms provided. Where possible the investigator should provide the outcome of the pregnancy.

The investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the investigator becomes

aware of a new pregnancy outside this time limit then they should report it as above. GW PVD will follow up for all pregnancy outcomes.

12.5 Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the study medication must be reported as such. The expression “*reasonable causal relationship*” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the investigator for all AEs is used to capture the reasonable causal relationship of an event to the study medication:

“In your opinion is there a plausible relationship to the study medication?” The answer is “yes” or “no”.

Events that start before the first dose of study medication (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of study medication, a new event record should be entered into the CRF.

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the investigator assess not only the possible role of the study medication but also competing etiological factors as the underlying cause. Factors for consideration may include:

- Medical history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.
- Withdrawal of study medication.
- Protocol-related procedure.

12.6 Reporting Procedures for All Adverse Events

All AEs* (including SAEs) occurring during the study will be reported on the running logs in the AE section of the CRF. This includes all events from the time following screening (Visit 1) to post study follow-up (Visit 13 for patients entering the OLE and Visit 6 for those patients that are not entering the OLE). whether or not attributed to IMP and observed by the investigator or patient.

* For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures must be documented as an AE. Any AE which meets SAE criteria should still be reported as a SAE.

The following information will need to be provided for all AEs:

A) Adverse Event (Diagnosis or Syndrome if known, or Signs and Symptoms)

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded on the AE section of the CRF. Once a diagnosis has been determined the AE section of CRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the CRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated e.g., fever and malaise due to a respiratory tract infection.

B) Adverse Event Start Date and Stop Date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given then record as much information as possible (i.e., month and year or in exceptional circumstances just year). When the actual start date becomes known the CRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one for the following categories:

- Recovered.
- Recovered with sequelae.
- Continuing.
- Patient died.

D) Severity

When describing the severity of an AE the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, for example, a headache or constipation, the change in severity should not be recorded each time, instead only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore it should not be classed as serious.

E) Causality

See [Section 12.5](#) above.

F) Action Taken with Study Medication

This question refers to the action taken with the IMP due to an AE. The action with the IMP must be classed as:

- None.
- Dose reduced temporarily.
- Dose reduced.
- Study medication interrupted.
- Study medication stopped.

12.7 Follow up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the GW PVD for any AEs reported.

AEs considered related to the IMP by the investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE, further details of withdrawal are presented in [Section 10](#). If either of these occurs, the patient must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

12.8 Potential Cases of Drug Induced Liver Injury

All investigational sites are required to submit to the GW PVD the laboratory results for any patient after randomization that meet the criteria for the selected laboratory parameters as follows:

- ALT or AST $>3 \times$ ULN **and** (TBL $>2 \times$ ULN **or** INR >1.5).

- ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- ALT or AST $>8 \times$ ULN.
- ALT or AST $>5 \times$ ULN for more than two weeks.

These reports must be sent to the GW PVD using the same fax number for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the patient's baseline laboratory results with all reports to GW PVD.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol defined criteria for withdrawal and important medical events. The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase and gamma-glutamyl transferase levels, detailed history and physical examination. Patients should be followed until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

Elevations in ALT or AST $>3 \times$ ULN or TBL $>2 \times$ ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours' notice of abnormal results. If the participant cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.

12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees.

In accordance with the EU Clinical Trials Directive³⁵, relevant parts of the FDA Code of Federal Regulations and any national regulations, GW will inform investigators, regulatory authorities and relevant IRB/ECs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through three sources:

- Investigator Brochure³⁶: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study on the IMP in human participants. The IB is updated annually.
- Development Core Safety Information: this document actually forms the Safety Section of the IB³⁶, or is updated as an appendix of the IB³⁶. This

document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).

- Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the regulatory authorities, the relevant central IRB/ECs which have approved the study and investigators. As required, the investigator should notify their regional IRB/EC of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the USA, investigators are normally required to promptly report to their IRBs all unanticipated problems involving risks to human patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance³² the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human patients, and reported to the IRB, *only* if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

The FDA guidance³⁷ states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW will inform investigators (regulatory authorities and applicable IRB/EC's) of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the study does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

As a minimum, the recipient will be sent all of the above and relevant updates between the period from ethics approval and final database lock.

13. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be produced prior to the database lock and analysis of the study. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

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

13.2 Interim Analysis

An interim analysis will be conducted at the end of the Double Blind phase of the study and may also be considered during the OLE phase, if long term data is required to support New Drug Application/Marketing Authorization Application submissions.

13.3 Analysis Sets

13.3.1 Safety Set

All subjects who are treated and receive at least one dose of IMP will be included. The Safety set is the primary analysis set for all safety endpoints.

13.3.2 Pharmacokinetic Analysis Set

All subjects who are treated and receive at least one dose of IMP and who provide some on-treatment data will be included.

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

13.3.3 Protocol Deviations

Any protocol deviations will be listed and reasons for exclusion from the analysis populations will be summarized

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (n), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category. Summaries will be presented for data recorded pre-treatment, during each 25 day dosing phase (placebo and GWP42003-P) and during the OLE phase separately.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, treated, completing the study and those prematurely terminated IMP) will be accounted for in the enrollment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Age, sex, race (as allowed per local regulations) and any other demographic or baseline characteristics will be summarized, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by system organ class, including details of the duration of epilepsy and the types of seizures currently experienced by the patients.

13.5.4 Concomitant Medication

Concomitant medications taken prior to and during the study will be summarized, by medication class and active ingredients. Summaries of medications taken during the IMP treatment phases and during OLE will be presented separately.

13.6 Endpoints and Statistical Methods

13.6.1 Primary Endpoint(s)

The primary endpoints of the study are the PK parameters (C_{max} , t_{max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

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

13.6.2 Secondary Endpoint(s)

The secondary endpoints of the study are the safety parameters (see [Section 13.6.4](#)) and the PK parameters (C_{max} , t_{max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- THC
- THC major metabolites

13.6.3 Pharmacokinetics

Calculation of PK parameters will be based on actual blood sampling times [h] (relative to the corresponding administration time) rounded to two decimal digits with negative pre-dose times set to zero. Plasma concentrations of CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites will be displayed graphically, summarized and listed. For descriptive statistics, values below the lower limit of quantification of the assay (LLOQ) will be excluded from any calculations. Descriptive statistics of concentrations will be calculated if at least half of the individual data points that have been measured are equal to or above the LLOQ.

For calculation of the PK parameters, the following rules will be applied:

At time zero and at time points in the lag-time between time zero and the first quantifiable concentration, concentrations below the LLOQ will be set to zero. All other concentrations below the LLOQ will not be used in calculations.

Variables derived from plasma concentrations:

- Concentration maximum (C_{\max}): Highest observed plasma concentration of the measured concentration-time profile. Dimension: [amount / volume].
- Terminal half-life $t_{1/2} = \ln(2)/\lambda_z$.
- The rate constant of the terminal phase λ_z will be determined by linear regression of log-transformed concentration data after the time of maximum concentration. A sequence of terminal elimination rate constants will be created by linear regression. Linear regressions are repeated using the last three points with a quantifiable concentration, the last four points, the last five points etc. For each regression, an adjusted R^2 is computed. The regression with the largest adjusted R^2 is selected to estimate the terminal half-life. Dimension: [time].
- Area under the concentration-time curve from administration until the last sampling point (t) equal or above the LLOQ $AUC_{(0-t)}$ will be calculated by the linear trapezoidal formula. Dimension: [time • amount / volume].
- Area under the concentration-time curve extrapolated to infinity: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_{\text{last}}/\lambda_z$ and C_{last} is the concentration observed at the last time point with a quantifiable concentration, λ_z refers to the terminal elimination rate constant. Dimension: [time • amount / volume].
- Time of maximum concentrations: T_{\max} will be taken as the time after administration at which C_{\max} occurs. Dimension: [time].
- PK parameters for each analyte will be summarized for the two treatment phases of the study separately, as appropriate.
- 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 group ratios of geometric means of C_{\max} , $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will

be carried on logarithm scale using a linear mixed effect model with treatment (CLB or CLB+CBD) 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.

13.6.4 Safety

13.6.4.1 Treatment Compliance and Extent of Treatment Exposure

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

13.6.4.2 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary.

A treatment emergent AE is one that started, or worsened in severity or seriousness, following the first dose of IMP.

Descriptive presentations of treatment emergent AEs will be given by preferred term and system organ class for the safety analysis set. The number of patients reporting at least one AE will be provided. Summaries will be provided for each phase of the study separately.

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.

13.6.4.3 Clinical Laboratory Data

Clinical laboratory data at screening and at the end of the 31 day treatment phase and the change from baseline to end of treatment (OLE) will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range.

13.6.4.4 Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data

The C-SSRS, vital signs, ECG and physical examination data will be summarized at screening, at the end of the 31 day treatment phase and during the OLE treatment period using appropriate summary statistics. Changes in the vital signs from baseline to end of each treatment phase will also be summarized.

13.6.4.5 Seizure Data

Seizure data collected during the 31 day treatment phase and during the OLE phase of the study will be summarized using appropriate summary statistics.

14. DATA SAFETY MONITORING COMMITTEE

GW does not plan to use an independent data safety monitoring committee as part of this study.

15. REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the^{31,35} and the clinical trial regulations adopting European Commission Directives into national legislation^{38,39,40}.

15.2 Informed Consent

Initial master ICFs will be provided to the investigator to prepare the informed consent documents to be used at his or her center. The GW Clinical Manager will communicate updates to the templates by letter. The written informed consent documents should be prepared in the language(s) of the potential patient population.

Before a patient's participation in the trial, the investigator is responsible for obtaining written informed consent from the patient or legal representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol specific screening procedures or any IMPs are administered. The patient, or their legal representative, should have ample time for review to consider the information provided before giving written consent; more specific definitions of ample time may be in force if required by IRB/ECs or local regulations.

The acquisition of informed consent should be documented in the patient's medical records and the ICF should be signed and personally dated by the patient or legal representative (as applicable) and by the person who conducted the informed consent discussion. GW also requires a physician to be present for consent and to sign the consent forms as well. The original signed ICFs should be retained and a copy provided to the patient or legal representative.

15.3 Institutional Review Board/Ethics Committee

A copy of the protocol, proposed ICFs, other patient information material, any proposed advertising material and any further documentation requested, must be submitted to the IRB/EC for written approval. GW must receive a copy of the written approval of the protocol and ICFs before enrollment of patients into the study and shipment of IMP.

The investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent documents. The investigator should notify the IRB/EC of deviations from the protocol

or SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The investigator will be responsible for obtaining on-going IRB/EC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/EC continuance of approval must be sent to GW.

15.4 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent for entry into the study:

- Signed and dated protocol signature page.
- Copy of approved ICFs and other patient information material.
- Copy of the IRB/EC approval of the protocol, ICFs and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/EC composition and/or written statement of the IRB/EC in compliance with the FDA regulations relating to GCP and clinical trials^{32,33,34,41}, the EU Clinical Trials Directive³⁵, or International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP)⁴² where the EU Directive does not apply.
- Signed laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed clinical trial agreement (including patient/investigator indemnity insurance and financial agreement).
- FDA 1572 form.
- Completed financial disclosure statements for the PI and all sub-investigators if relevant.

15.5 Participant Confidentiality

The investigator must ensure that the patient's anonymity is maintained. On the CRFs and within the databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials and race (if allowed per local regulations) and a patient study number only. Documents that are not for submission to GW, e.g., signed ICFs should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to good clinical practice and clinical trials^{32,33,34,41}, and the EU Clinical Trials Directive³⁵/ICH GCP Guidelines⁴², it is required that the investigator and institution permit authorized representatives of the company, the regulatory agencies and the IRB/EC direct access to review the patient's original medical records for verification of study related procedures and data. Direct

access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the patient that his/her study related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the company.

16. ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Study or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent documents. The IRB/EC and Competent Authorities must be informed of all amendments and give approval for any substantial amendments prior to implementation. The investigator must send a copy of the approval letter from the IRB/EC to GW. Amendments for administrative changes can be submitted to the IRB/EC for information only.

Both GW and the investigator reserve the right to terminate the study, according to the clinical trial agreement. The investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to GW.

16.2 Study Documentation and Storage

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the GW delegation of authority and signature form.

Source documents are original documents, data and records from which the patient's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, electronic data captured by IVRS, microfiches, radiographs and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording; that is, there is no other written or electronic record of data. In the rare situations of this happening, then the source data from the CRF should be transcribed in the patient's notes with appropriate signature and date to provide a full audit trail. A Source Data Verification Plan, identifying the source for each data point at each site, will be agreed with each site prior to patient recruitment.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related, essential documentation (as outlined in ICH E6 Section 8.2⁴²), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, ICFs and supporting copies of source documentation.

- Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see [Section 15.4](#)) and all correspondence to and from the IRB/EC and GW.
- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug related correspondence.

In addition, all original source documents supporting entries on the CRFs, paper diary data and electronic data captured by IVRS must be maintained and be readily available.

Following completion or termination of a clinical study, GW will initiate proper archive of clinical study related documentation and electronic records generated by the investigator and/or GW. All clinical trial related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 25 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by GW (EU Directive 2005/28/EC Chapter 4 Trial Master File and Archiving Article 16⁴³).

GW will inform the investigators for each site in writing of the need for record retention. No study document should be destroyed without prior written agreement between GW and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify GW in writing of the new responsible person and/or the new location.

16.3 Study Monitoring and Data Collection

The GW representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study for example, CRFs and other pertinent data provided that patient confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting the CRFs and available diary data at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor should have access to patient medical records and other study related records needed to verify the entries on the CRFs.

The investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

The investigator is responsible for ensuring the data recorded in the CRFs are accurate and complete. The CRF should be completed within five working days after the patient's visit and before review by the study monitor. Queries generated by GW or its representative are to be answered within a similar period of time. Shorter periods of time may apply during specific situations such as interim analysis or final database cleaning.

All handwritten medical records should be filled out with a black or blue ball-point pen and must be legible. Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator. No correction fluid or tape may be used. The PI will sign and date the indicated places on the CRF. These signatures will indicate that the PI inspected or reviewed the data on the CRF, the data queries and the site notifications and agrees with the content.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations^{32,33,34,41}, the ICH GCP Guideline⁴², and all other applicable regulatory requirements^{35,42}, to resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

GW's or the CRO's Clinical Data Management Department will correct the following issues in CRFs without any notification to site staff:

- Misspellings that do not change the meaning of the word, excluding AEs and medications.
- Date errors that occur at the end of the year and into the New Year.
- Temperature unit errors (Fahrenheit vs Centigrade).
- Weight unit errors (pounds vs kilograms) if a baseline weight has been established.
- Administrative data for example, event names for unscheduled visits or retests.
- Clarifying "other, specify" if data are provided for example, race, physical exam.

- If a YES or NO question for example, ‘Were there any AEs?’ is left blank yet AEs are listed on the CRF, YES will be entered in the blank.
- Correct CRF page numbers.

16.4 Quality Assurance

In accordance with the FDA regulations, EU Clinical Trials Directive/ICH GCP and the sponsor’s audit plans, representatives from GW’s Clinical Quality Assurance Department may select this study for audit. Inspection of site facilities for example, pharmacy, drug storage areas, laboratories and review of study related records will occur to evaluate the study conduct and compliance with the protocol, as per the EU Clinical Trials Directive/ICH GCP and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the study site in the event of any claim in respect of personal injury arising due to a patient’s participation in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical study patient would not otherwise have been exposed providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will co-ordinate this dissemination and may solicit input and assistance from the chief/PIs. A summary of the results of this study will be made available on <http://www.ClinicalTrials.gov>, as required by U.S. Law.

The raw data from this study may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analysis and are permitted to present such information along with methods and results of the clinical study at symposia, national or regional professional meetings, and to publish it in theses or dissertations.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this study, must be submitted to GW Medical Writing Department and, as applicable, GW Publication Committee for review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for

publication, public dissemination, or review by a publication committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

GW also reserve the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.7 Intellectual Property Rights

All Intellectual Property Rights owned by or licensed to either GW or the PIs, other than those arising from the clinical study, will remain their property. All Intellectual Property Rights arising out of the clinical study will vest in or be exclusively licensed to GW and as such, the PI should promptly disclose all knowledge to GW and refrain from using such knowledge without the prior written consent of GW.

16.8 Confidential Information

GW and the PI should ensure that only personnel directly concerned with the study should be party to confidential information and that any information coming to either party about the other during the course of the study should be kept strictly confidential and should not be disclosed to any third party or made use of without the prior written consent of the other.

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APPENDIX 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						
Enrollment		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			
Pregnancy test (if appropriate)	X							
Pharmacokinetic blood sampling**		X	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)
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 Behavior 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 Behavior Survey								X	

APPENDIX 2. STUDY PERSONNEL

Appendix 3.1 Investigator Details

At the time of protocol production, the participating investigators had not been confirmed. A list of all investigators will be maintained within the GW Master Files (electronically and added to the Trial Master File at the end of the study).

Appendix 3.2 Sponsor Contact Details

Pharmacovigilance Department — SAE
Reporting:

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PPD

Tel: PPD

Sponsor:

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Clinical Project Manager/Clinical Operations
Director:

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Tel: PPD

Fax: PPD

Clinical Trials Supplies:

GW Pharma Ltd

Tel: PPD

Fax: PPD

**TITLE: A phase 2, double-blind, randomized, placebo-controlled
study to investigate possible drug-drug interactions between
clobazam and cannabidiol (GWP42003-P)**

Study Code: GWEP1428

EudraCT Number: 2014-002942-33

CLINICAL PROTOCOL AMENDMENT NUMBER: 3

**to be incorporated into the Protocol, creating
CLINICAL PROTOCOL VERSION 4,
DATE 04 FEB 16**

**GW Research Ltd
Sovereign House
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Tel: PPD [REDACTED]
Fax: PPD [REDACTED]

Confidentiality Statement

This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board or independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW.

1 PROTOCOL SYNOPSIS

Study Title	A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P).
Indication	Epilepsy
Study Design	<p>This is a phase 2, double-blind, randomized, placebo-controlled study in 20 patients.</p> <ul style="list-style-type: none"> 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. Day 1 (Visit 2), patients will not be dosed with GWP42003-P/placebo but will continue to take clobazam (CLB) at a stable dose. Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). Day 12 (Visit 3), patients will attend the study site to check safety and compliance. After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the patient will continue to take GWP42003-P as advised by the investigator. If the patient does not enter the OLE period of the study, the patient will taper off of GWP42003-P by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with end of taper on Day 43 (Visit 5). <p>Pharmacokinetic (PK) samples will be taken on the day of enrollment (Visit 2, Day 1) and after completing 21 days treatment on GWP42003-P or placebo (Visit 4, Day 33). The PK assessments will therefore capture the following combinations of CLB and GWP42003-P:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and GWP42003-P or placebo.

	<p>Each PK assessment should be performed at time points in respect to a morning dose of CLB. The time points are as follows: Pre-dose, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 12 h and 24 h. It is expected that the patient will continue to take their CLB as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The GWP42003-P/placebo should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze the amount of CLB, the CLB primary metabolite N-desmethyleclobazam, cannabidiol (CBD), CBD major metabolites, Δ^9-tetrahydrocannabinol (THC) and THC major metabolites, valproate (VPA), stiripentol (STP), levetiracetam (LEV) and topiramate (TPM). Patients will be required to keep a paper diary to note the time and dose of GWP42003-P and CLB administration each morning and evening and to record any adverse events that may occur whilst receiving investigational medicinal product and any other medications. Patients will also be requested to record the number and type of seizures for each day whilst on the study.</p>
Sponsor	<p>GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom</p>

Table of Contents

Title Page	1
1 PROTOCOL SYNOPSIS.....	2
Table of Contents	4
List of Appendices.....	5
2 RATIONALE	6
2.1 Inclusion Criteria	6
2.2 Procedures	6
2.3 Administrative Changes	6
3 IMPLEMENTATION OF THE AMENDMENT.....	7
4 PRESENTATION OF AMENDED TEXT	8
5 REFERENCES	11

List of Appendices

APPENDIX 1	Schedule of Assessments	12
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2 RATIONALE

This clinical protocol amendment 3 (will be incorporated into the Protocol creating Clinical Protocol Version 4 Date 04 February 2016) addresses the following issue(s):

2.1 Inclusion Criteria

The following inclusion criterion, relating to age limit, has been amended:

- Inclusion criterion 6.1.1 has been amended to increase the upper age limit to 65, to expand the study to more patients.

2.2 Procedures

The following clarifications have been made to the study procedures:

- For patients entering the OLE, it has been clarified that they must remain in clinic for at least 30 minutes following administration of GWP42003-P as this may be their first exposure to the study drug if they had previously been taking placebo.
- In the OLE, it has been clarified that 1 month is equal to 28 days or 4 weeks for the purpose of scheduling.

2.3 Administrative Changes

Administrative updates have been made throughout the protocol (N.B. in the interest of brevity, minor changes to grammar, punctuation or formatting are not captured in this amendment document).

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 4, Date 04 February 2016. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 3, Dated 08 Oct 15 <i>(Deleted wording is struck through and in bold)</i>	Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol Version 4, Dated 04 Feb 16) <i>(Revised wording is underscored and in bold)</i>	Rationale for the Amendment
Protocol Synopsis, Summary of Participant Eligibility Criteria, pg 5	(...) Male or female patients aged 18 to 55 years inclusive. (...)	(...) Male or female patients aged 18 to <u>65</u> years inclusive. (...)	See Section 2.1
Protocol Synopsis, Procedures, pg 11	(...) Patients who enter the OLE will be dispensed GWP42003-P on Day 34. (...)	(...) Patients who enter the OLE will be dispensed GWP42003-P on Day 34 <u>and the first dose will be taken in clinic. Following administration of GWP42003-P, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions.</u> (...)	See Section 2.2

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 3, Dated 08 Oct 15 <i>(Deleted wording is struck through and in bold)</i>	Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol Version 4, Dated 04 Feb 16) <i>(Revised wording is underscored and in bold)</i>	Rationale for the Amendment
Protocol Synopsis, Procedures, pg 12	This visit will occur one month after Visit 4 (Day 34). (...)	This visit will occur one month <u>(one month is considered as 28 days)</u> after Visit 4 (Day 34). (...)	See Section 2.2
Protocol Section 6.1, Inclusion Criteria, pg 39	(...) Male or female patients aged 18 to 55 years inclusive. (...)	(...) Male or female patients aged 18 to <u>65</u> years inclusive. (...)	See Section 2.1
Protocol Section 9.2.1.4.2, Visit 4 (Day 34), pg 60	(...) Patients who enter the OLE will be dispensed GWP42003-P on Day 34. (...)	(...) Patients who enter the OLE will be dispensed GWP42003-P on Day 34 <u>and the first dose will be taken in clinic. Following administration of GWP42003-P, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions.</u> (...)	See Section 2.2
Protocol Section 9.2.2.2, Visit 6 (Open Label Extension) – One	This visit will occur one month after Visit 4 (Day 34). (...) (...)	This visit will occur one month <u>(one month is considered as 28 days)</u> after Visit 4 (Day 34). (...) (...)	See Section 2.2

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 3, Dated 08 Oct 15 <i>(Deleted wording is struck through and in bold)</i>	Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol Version 4, Dated 04 Feb 16) <i>(Revised wording is underscored and in bold)</i>	Rationale for the Amendment
Month (± 3 days), pg 62			
APPENDIX 1, Schedule of Assessments, pg 92	<< Note: See Appendix 1 for detailed changes >>	<< Note: See Appendix 1 for detailed changes >>	See Section 2.2

5 REFERENCES

N/A

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open Label Extension Schedule of Assessments (Protocol V3/ Appendix1)

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 Behavior Survey								X	

Open Label Extension Schedule of Assessments (Protocol V4/ Appendix1)

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 Behavior Survey								X	

*** For the purpose of scheduling, each month is considered as 4 weeks (28 days).**

**TITLE: A PHASE2, DOUBLE-BLIND, RANDOMIZED,
PLACEBO-CONTROLLED STUDY TO INVESTIGATE POSSIBLE
DRUG-DRUG INTERACTIONS BETWEEN CLOBAZAM AND
CANNABIDIOL (GWP42003-P)**

STUDY CODE: GWEP1428

EudraCT NUMBER: 2014-002942-33

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Confidentiality Statement

This document contains confidential information of GW Research Ltd that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board/Independent Ethics Committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Investigator Agreement

I have read the attached protocol entitled "A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P)", dated version 4 date 04 Feb 16 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirements, the FDA regulations relating to good clinical practice and clinical trials and the European Union (EU) Clinical Trials Directive (2001/20/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (ICH GCP) where the EU Directive does not apply and to complete a Form 1572 if required.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Center No: _____

Print Name: _____

Date: _____

Principal Investigator

(DD Month YYYY)

Signature: _____

GW Authorization

Print Name: 

Date: 04 FEB 2016

Clinical Manager 

(DD Month YYYY)

Signature: 

1. PROTOCOL SYNOPSIS

Study Title	A phase 2, double-blind, randomized, placebo-controlled study to investigate possible drug-drug interactions between clobazam and cannabidiol (GWP42003-P).
Clinical Study Type	Phase 2
Indication	Epilepsy
Primary Objective	To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyclobazam (N-CLB).
Secondary Objective(s)	To assess the safety and tolerability of GWP42003-P in the presence of CLB.
Study Design	<p>This is a phase 2, double-blind, randomized, placebo-controlled study in 20 patients.</p> <ul style="list-style-type: none"> • 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. • Day 1 (Visit 2), patients will not be dosed with GWP42003-P/placebo but will continue to take CLB at a stable dose. • Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • Day 12 (Visit 3), patients will attend the study site to check safety and compliance. • After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). • On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the patient will continue to take GWP42003-P

	<p>as advised by the investigator.</p> <ul style="list-style-type: none"> If the patient does not enter the OLE period of the study, the patient will taper off of GWP42003-P by reducing the dose by approximately 10% of the maintenance dose each day until dosing has ceased, with end of taper on Day 43 (Visit 5). <p>PK samples will be taken on the day of enrollment (Visit 2, Day 1) and after completing 21 days treatment on GWP42003-P or placebo (Visit 4, Day 33). The PK assessments will therefore capture the following combinations of CLB and GWP42003-P:</p> <ul style="list-style-type: none"> First PK Assessment: CLB only. Second PK Assessment: CLB and GWP42003-P or placebo. <p>Each PK assessment should be performed at time points in respect to a morning dose of CLB. The time points are as follows: Pre-dose, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 12 h and 24 h. It is expected that the patient will continue to take their CLB as advised by their physician and PK assessments will be scheduled in order to accommodate this dosing schedule. The GWP42003-P/placebo should be taken twice daily immediately following their CLB dose.</p> <p>PK assessments will analyze the amount of CLB, the CLB primary metabolite N-CLB, CBD, CBD major metabolites, Δ^9-tetrahydrocannabinol (THC), THC major metabolites, valproate (VPA), stiripentol (STP), levetiracetam (LEV) and topiramate (TPM). Patients will be required to keep a paper diary to note the time and dose of GWP42003-P and CLB administration each morning and evening and to record any adverse events (AEs) that may occur whilst receiving investigational medicinal product (IMP) and any other medications. Patients will also be requested to record the number and type of seizures for each day whilst on the study.</p>
Primary Endpoint	<p>The primary endpoints of the study are the PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</p> <ul style="list-style-type: none"> CLB N-CLB CBD CBD major metabolites
Secondary Endpoint(s)	<p>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:</p> <ul style="list-style-type: none"> AEs 12-lead electrocardiogram (ECG) Clinical laboratory parameters (clinical chemistry, hematology and urinalysis) Vital signs Columbia-Suicide Severity Rating Scale (C-SSRS) Seizure frequency

	<ul style="list-style-type: none"> • Abuse liability • CYP2C19 and CPY3A4 patient genotype analysis <p>PK parameters (C_{max}, t_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:</p> <ul style="list-style-type: none"> • THC • THC major metabolites
Sample Size	A total of 20 patients will be enrolled in this study. Recruitment for the study will be competitive between participating sites. There is no formal sample size: Calculation and analysis is descriptive only.
Summary of Participant Eligibility Criteria	<p>For inclusion in the study patients must fulfil ALL of the following criteria:</p> <ul style="list-style-type: none"> • Male or female patients aged 18 to 65 years inclusive. • Patient must have epilepsy as determined by the investigator and be taking CLB. • Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition. • Patient must have experienced at least one seizure of any type (i.e., convulsive: tonic-clonic, tonic, clonic, atonic; focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness focal seizures evolving to bilateral secondary generalization) within the two months prior to randomization. • Patients must be taking CLB and no more than two other antiepileptic drugs (AEDs) during the course of the study. • AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study. • Intervention with vagus nerve stimulation and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must be willing to maintain a stable regimen throughout the blinded phase of the study. • Patients must abstain from alcohol during the blinded phase of the study. • Patient is available to attend all PK visits within the required visit window. • Patient and/or legal representative must be willing and able to give informed consent for participation in the study. • Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements.

	<ul style="list-style-type: none"> • Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable. • Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study. <p>Exclusion: The patient may not enter the study if ANY of the following apply:</p> <ul style="list-style-type: none"> • Patient has clinically significant unstable medical conditions other than epilepsy. • Patients on CLB at doses above 20 mg per day. • Patients taking CLB intermittently as rescue medication. • Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes. • Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening. • Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy. • Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain during the blinded phase of the study. • Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry. • Patient has any known or suspected history of any drug abuse or addiction. • Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration of the study. • Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil. • Female patient is of child bearing potential or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal
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	<p>contraceptives, intrauterine devices/ hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.</p> <ul style="list-style-type: none"> • Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter. • Patients who have received an IMP within the 12 weeks prior to the screening visit. • Patient is taking felbamate and they have been taking it for less than one year prior to screening. • Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study. • Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator would prevent the participant from safe participation in the study. • Patient has significantly impaired hepatic function at screening (Visit 1) or enrollment (Visit 2), defined as any of the following: <ul style="list-style-type: none"> - Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $> 5 \times$ upper limit of normal (ULN). - ALT or AST $> 3 \times$ ULN and total bilirubin (TBL) $> 2 \times$ ULN or international normalized ratio (INR) > 1.5. - ALT or AST $> 3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$). <p><i>This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion must be withdrawn from the study.</i></p> • Patient has a prolonged QTcB (> 450 msec for males and > 470 msec for females). • Unwilling to abstain from donation of blood during the study. • Travel outside the country of residence planned during the study, unless the patient has confirmation that the IMP is permitted in the destination country/state. • Patients previously enrolled into this study.
Criteria for Withdrawal	<p>Patients must be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Administrative decision by the investigator or GW Research Ltd or Regulatory Authority. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient.

	<ul style="list-style-type: none"> • Withdrawal of patient consent. • Withdrawal of legal representative consent. • Lost to follow up. • ALT > 3 × ULN or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5). • ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • ALT or AST > 8 × ULN. • ALT or AST > 5 × ULN for more than two weeks. • Any other IMP is taken as part of a clinical trial during the study. • Significant change in QTcB (> 60 msec) from the previous ECG or absolute QTcB of > 500 msec. <p>Patients may also be withdrawn from the study if any of the following apply:</p> <ul style="list-style-type: none"> • Patient non-compliance. • AE, which in the investigator's opinion, would compromise the continued safe participation of the patient in the study. • Any evidence of drug abuse or diversion. • Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.
Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration	<p>GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring), pale yellow in color.</p> <p>Placebo oral solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring.</p> <p>The IMP should be taken orally as per intended commercial therapeutic use.</p> <p>IMP will be taken twice daily (morning and evening) following the dose schedule below:</p> <ul style="list-style-type: none"> • Day 2 (Visit 2), patients will begin the up-titration with GWP42003-P or placebo to a maintenance dose or an equivalent maintenance dose of 20 mg/kg/day over a period of 10 days (Days 2 to 11). • After up-titration with GWP42003-P or placebo, the patients will remain on the maintenance dose for 21 days (Days 12 to 32). <p>Please refer to Table 8.1.2-1 for details of the up-titration doses for GWP42003-P and placebo for the ten day taper period.</p> <p>On Day 34 (Visit 4), patients will be invited to receive GWP42003-P in the OLE period. If the patient enters the OLE period of the study, the</p>

	<p>patient will continue to take GWP42003-P as advised by the investigator.</p> <p>CLB will be an IMP for the blinded section of the study. The patient's own supply of CLB will be used.</p>
Control Group	The control group will receive an equal volume of matching placebo.
Procedures	<p>VISIT 1 - Screening (Day -14 to -7)</p> <p>The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, THC testing, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.</p> <p>Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will be assigned a unique patient number and then begin the baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be instructed on how to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.</p> <p>VISIT 2 - Enrollment (Day 1) + 3 days window</p> <p>This visit will occur 7–14 days after Visit 1.</p> <p>The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. Blood samples will also be taken for genetic testing if additional consent has been obtained. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.</p> <p>Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV and TPM. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of any AEDs must be taken after the 12 hour PK blood sample. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic</p>

	<p>on Day 2 ahead of additional sample collection.</p> <p>VISIT 2 - Enrollment (Day 2)</p> <p>This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose. Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.</p> <p>GWP42003-P/placebo will be dispensed and both the morning dose of CLB and GWP42003-P/placebo will be taken in clinic. Following administration of GWP42003-P/placebo, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions. Patients and/or their caregivers will be provided with individual dosing schedules as described in Section 8.1. Each patient will then receive their GWP42003-P/placebo for the 10 day titration period followed by the 21 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.</p> <p>VISIT 3 – Day 12 + 3 day window</p> <p>This visit will occur 11 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 3: concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, AEs and review of patient diary completion.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.</p> <p>VISIT 4 - Day 33 ± 3 days window</p> <p>This visit will occur 32 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 4 (Day 33): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. The C-SSRS will be administered.</p> <p>Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of GWP42003-P/placebo. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of GWP42003-P/placebo and any AEDs must be taken after the 12 hour PK blood sample. Patients are expected</p>
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	<p>to remain in clinic throughout this PK sampling process.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 4 - Day 34</p> <p>This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 33 morning CLB dose.</p> <p>Following completion of the PK sampling process the following observations will be made on Day 34: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.</p> <p>On Day 34, providing the investigator and patient both agree, patients will be invited to continue taking GWP42003-P and to enter the OLE. Patients who enter the OLE will be dispensed GWP42003-P on Day 34 and the first dose will be taken in clinic. Following administration of GWP42003-P, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions.</p> <p>Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of GWP42003-P. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42.</p> <p>Patients Not Entering OLE</p> <p>VISIT 5 – Day 43 (End of Taper) + 3 days window</p> <p>This visit will occur 42 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.</p> <p>All GWP42003-P/placebo (used and unused) will be collected and a check of the returned GWP42003-P/placebo against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.</p> <p>VISIT 6 - SAFETY FOLLOW-UP CALL - Day 71 ± 3 days</p> <p>This visit is required for patients who do not enter the OLE study on Day 34, or who withdraw from the study early. This visit should occur four weeks (± 3 days) after Visit 5, or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 71: concomitant medications (including AEDs) and AEs.</p>
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	<p>Patients Entering OLE</p> <p>At the point of entry to the OLE, patients will be transitioned to the OLE treatment over a 10 day period in order to maintain blinding. Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 34) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 34).</p> <p>VISIT 5 (OLE) – Two Weeks \pm 3 days</p> <p>This visit will occur two weeks after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>The GWP42003-P dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day achieved at the end of the 10-day transition period, up to a maximum of 30 mg/kg/day in the OLE period.</p> <p>VISIT 6 (OLE) – One Month \pm 3 days</p> <p>This visit will occur one month (one month is considered as 28 days) after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 7 (OLE) – Two Months \pm 3 days</p> <p>This visit will occur two months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for</p>
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	<p>hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 8 (OLE) - Three Months \pm 7 days</p> <p>This visit will occur three months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 9 (OLE) - Six Months \pm 7 days</p> <p>This visit will occur six months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 10 (OLE) - Nine Months \pm 7 days</p> <p>This visit will occur nine months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>VISIT 11 – Twelve Months (OLE End of Treatment) \pm 7 days</p>
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	<p>This visit will occur twelve months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.</p> <p>The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.</p> <p>Starting at Visit 11, patients will begin to taper down their IMP dose. The dose will be reduced by 10% of their OLE maintenance dose per day.</p> <p>VISIT 12 - OLE End of taper + 3 days</p> <p>This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.</p> <p>Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.</p> <p>VISIT 13 - SAFETY FOLLOW-UP CALL (OLE)</p> <p>This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.</p> <p>Monitoring of Drug Abuse Liability</p> <p>During the routine collection of AEs in this study, if AEs are reported which can illuminate an abuse potential signal (specific AEs detailed in Section 9.1.16.1.1), then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussions of the event(s) with the patient/caregiver.</p> <p>The second trigger that will require the investigator or study coordinator to discuss abuse potential signals with the patient/caregiver is drug accountability issues regarding overuse of the IMP or missing IMP bottles.</p> <p>Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit or withdrawal visit and a Study Medication Use</p>
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	<p>and Behavior Survey will be completed by the investigator or study coordinator.</p> <p>A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.</p>
Statistical Considerations	<p>Plasma concentration data will be analyzed to estimate PK endpoints C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{1/2}$ of the following analytes: CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites.</p> <p>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 group ratios of geometric means of C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will be done on logarithm scale using a linear mixed effect model with treatment (CLB or CLB+GWP42003-P) 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.</p> <p>Descriptive summaries (means and standard deviations or counts [%] as appropriate) will be presented for all secondary endpoints (adverse events, laboratory data, vital signs, physical examination, C-SSRS and seizure frequency) for each phase of the study.</p>
Sponsor	<p>GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom</p>

Figure 1-1 Study Design and Treatment Schema

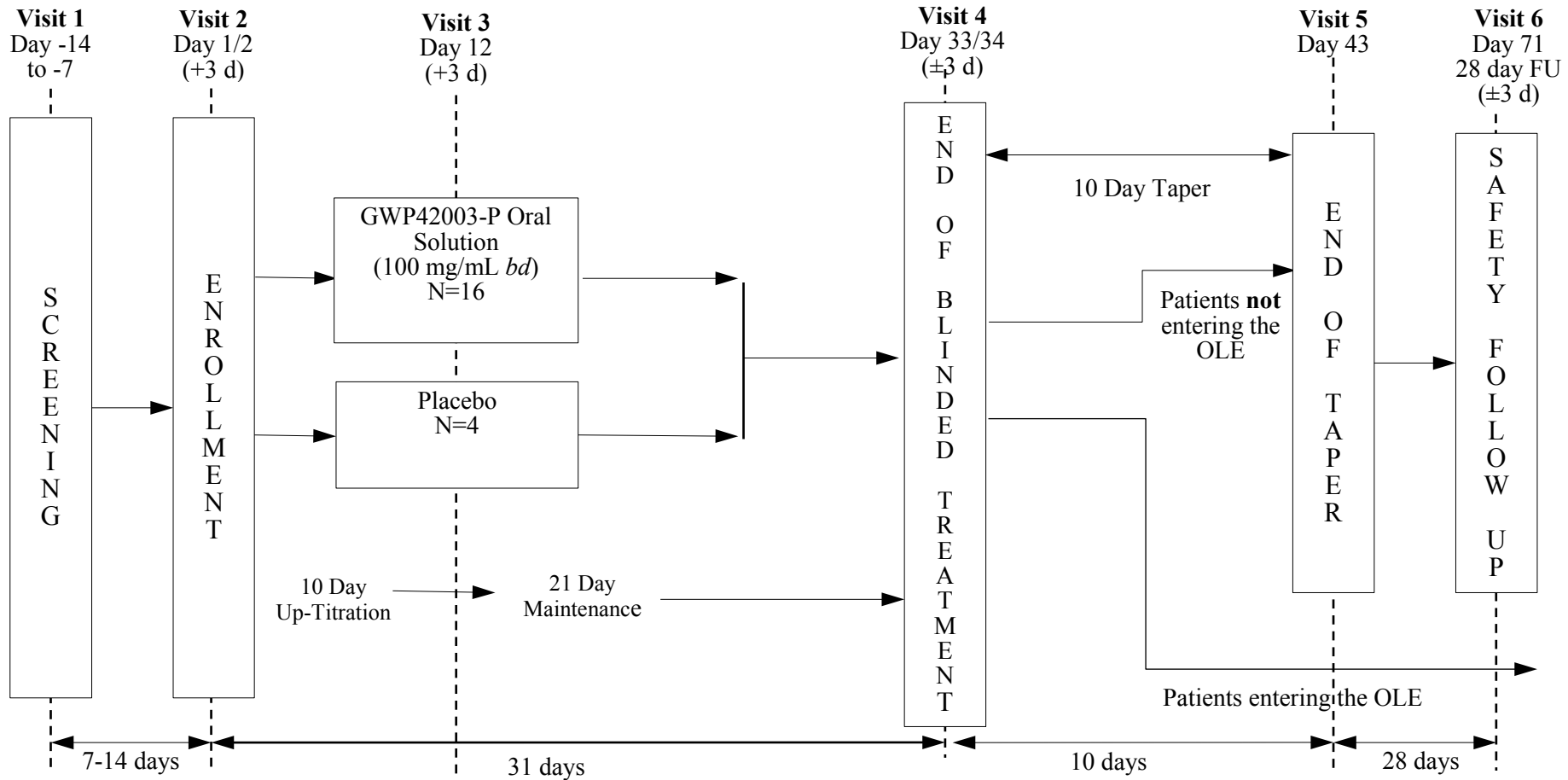


Figure 1-2 Study Design and Treatment Schema

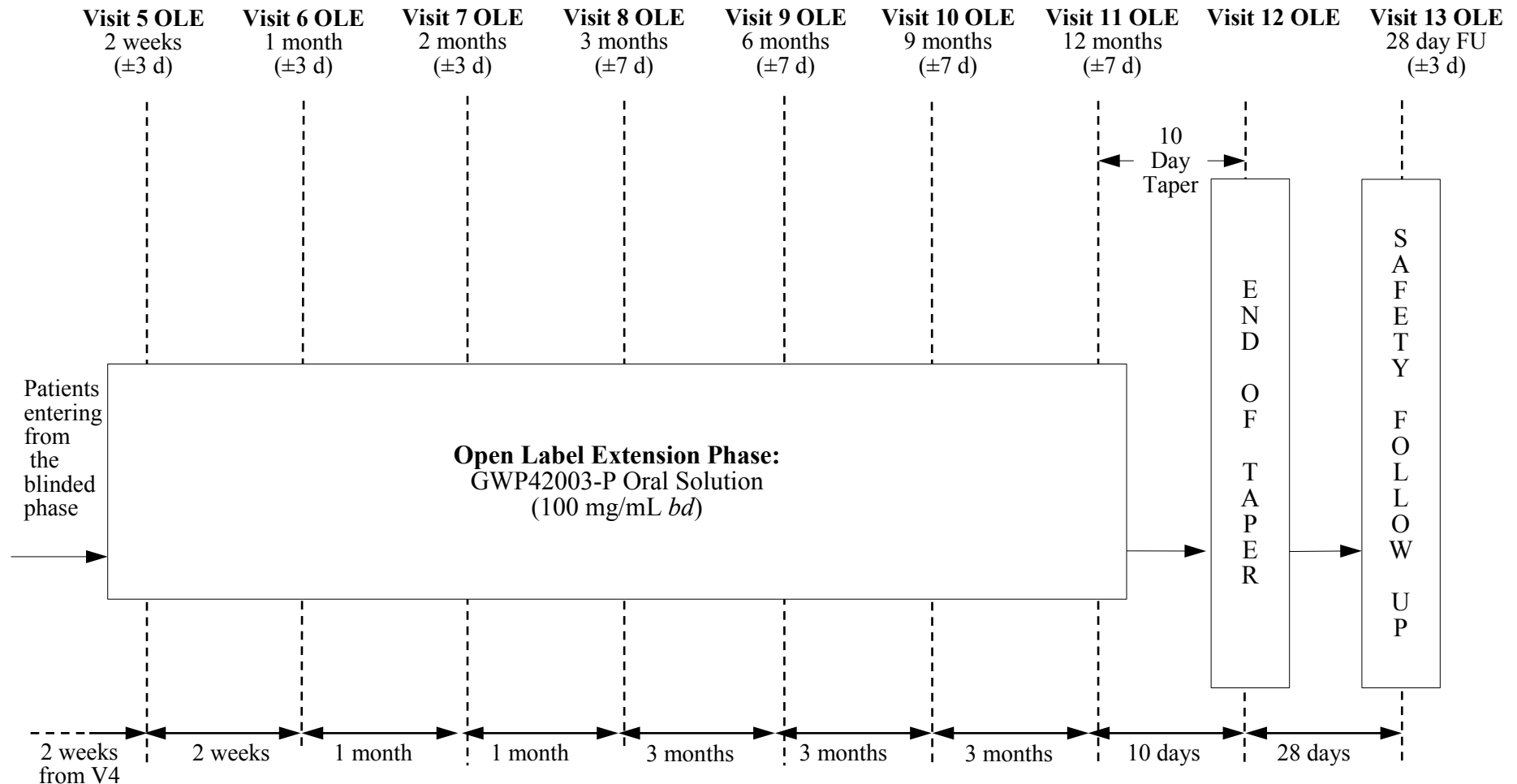


Table of Contents

Title Page	1
1. PROTOCOL SYNOPSIS.....	3
Table of Contents	18
Table of Appendices	23
List of In-text Tables	24
List of In-text Figures.....	25
List of Abbreviations	26
Definition of Terms.....	28
2. OBJECTIVES.....	29
2.1 Primary	29
2.2 Secondary	29
3. BACKGROUND AND RATIONALE	30
3.1 Disease.....	30
3.2 GWP42003-P Background.....	30
3.3 Rationale.....	31
3.3.1 Selection of Study Doses	32
3.4 Clinical Hypothesis	33
4. EXPERIMENTAL PLAN.....	34
4.1 Study Design	34
4.1.1 Primary Endpoint.....	35
4.1.2 Secondary Endpoint(s).....	35
4.2 Number of Centers	35
4.3 Number of Patients.....	36
5. INVESTIGATIONAL MEDICINAL PRODUCT	37
5.1 GWP42003-P Oral Solution.....	37
5.2 Placebo Oral Solution.....	37
5.3 Packaging, Storage and Drug Accountability (Cannabidiol/Placebo)	37
5.3.1 Packaging and Labelling.....	37
5.3.2 Storage	38
5.3.3 Supply and Return of Investigational Medicinal Product.....	38
5.3.4 Investigational Medicinal Product Accountability	38

5.4	Clobazam.....	39
6.	PARTICIPANT ELIGIBILITY.....	39
6.1	Inclusion Criteria.....	39
6.2	Exclusion Criteria.....	40
7.	PATIENT ENROLLMENT	42
7.1	Treatment Assignment	42
7.2	Randomization.....	42
8.	TREATMENT PROCEDURES.....	43
8.1	Investigational Medicinal Product Dosage, Administration and Schedule	43
8.1.1	Dose Administration.....	43
8.1.2	Dose Escalation and Dose Adjustments	44
8.2	Concomitant Therapy	45
8.3	Prohibited Therapy During Study Period.....	45
8.4	Compliance in Investigational Medicinal Product Administration.....	45
8.5	Access to Blinded Treatment Assignment	46
9.	STUDY PROCEDURES.....	47
9.1	Study Procedure Listing.....	47
9.1.1	Contraception.....	47
9.1.2	Informed Consent	47
9.1.3	Demographics	47
9.1.4	Medical History	48
9.1.5	Concomitant Medication	48
9.1.6	Physical Examination	48
9.1.7	Vital Signs	48
9.1.8	12-Lead Electrocardiogram	48
9.1.9	Clinical Laboratory Sampling.....	48
9.1.10	Pharmacokinetic Analyses.....	50
9.1.11	Genetic Testing.....	50
9.1.12	Columbia Suicide Severity Rating Scale.....	51
9.1.13	Patient Diary	51
9.1.14	Investigational Medicinal Product Accountability	51
9.1.15	Adverse Events	52

9.1.16	Monitoring of Drug Abuse Liability.....	52
9.1.16.1	Monitoring of Adverse Events.....	53
9.1.16.1.1	List of ‘Triggering Adverse Events of Interest’	53
9.1.16.1.2	Supplemental Adverse Event Form.....	53
9.1.16.2	Monitoring Drug Accountability Discrepancies	54
9.1.16.2.1	List of ‘Triggering Drug Accountability Discrepancies’	54
9.1.16.2.2	Supplemental Drug Accountability Form	55
9.1.16.3	Site Classification Form.....	55
9.1.16.4	Study Medication Use and Behavior Survey	55
9.1.16.5	Adjudication Committee — Assessment of Abuse Potential of GWP42003-P	56
9.2	Study Procedures by Visit.....	58
9.2.1	Double Blind Phase	58
9.2.1.1	Visit 1 (Day –14 to –7, Screening).....	58
9.2.1.2	Visit 2.....	58
9.2.1.2.1	Visit 2 (Day 1) – Enrollment (+3 days).....	58
9.2.1.2.2	Visit 2 (Day 2) - Enrollment.....	59
9.2.1.3	Visit 3 (Day 12 +3 days).....	59
9.2.1.4	Visit 4.....	59
9.2.1.4.1	Visit 4 (Day 33) (±3 days).....	59
9.2.1.4.2	Visit 4 (Day 34).....	60
9.2.1.5	Visit 5 (Patients not entering Open Label Extension) (Day 43 +3 days).....	61
9.2.1.6	Visit 6 - Safety Follow up Call (Day 71) (±3 days).....	61
9.2.2	Open Label Extension.....	61
9.2.2.1	Visit 5 (Open Label Extension) - Two Weeks (±3 days).....	61
9.2.2.2	Visit 6 (Open Label Extension) - One Month (±3 days).....	62
9.2.2.3	Visit 7 (Open Label Extension) - Two Months (±3 days)	62
9.2.2.4	Visit 8 (Open Label Extension) - Three Months (±7 days)	62
9.2.2.5	Visit 9 (Open Label Extension) - Six Months (±7 days)	63
9.2.2.6	Visit 10 (Open Label Extension) - Nine Months (±7 days).....	63
9.2.2.7	Visit 11 (Open Label Extension End of Treatment) - Twelve Months (±7 days)	63
9.2.2.8	Visit 12 (Open Label Extension End of Taper)	64

9.2.2.9	Safety Follow Up Call (± 3 days)	64
10.	WITHDRAWAL	64
11.	URGENT SAFETY MEASURES	65
12.	ADVERSE EVENT REPORTING	66
12.1	Definitions	66
12.1.1	Adverse Event	66
12.1.2	Investigator	66
12.2	Serious Adverse Events	66
12.3	Reporting Procedures for Serious Adverse Events	67
12.4	Pregnancy	68
12.5	Causality Assessment	68
12.6	Reporting Procedures for All Adverse Events	69
12.7	Follow up Procedures for Adverse Events	70
12.8	Potential Cases of Drug Induced Liver Injury	71
12.9	Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees	71
13.	STATISTICAL CONSIDERATIONS	74
13.1	Sample Size, Power and Significance Levels	74
13.2	Interim Analysis	74
13.3	Analysis Sets	74
13.3.1	Safety Set	74
13.3.2	Pharmacokinetic Analysis Set	74
13.3.3	Protocol Deviations	74
13.4	General Considerations	74
13.5	Accountability and Background Characteristics	75
13.5.1	Enrollment and Disposition	75
13.5.2	Baseline and Demographic Characteristics	75
13.5.3	Medical History	75
13.5.4	Concomitant Medication	75
13.6	Endpoints and Statistical Methods	75
13.6.1	Primary Endpoint(s)	75
13.6.2	Secondary Endpoint(s)	75
13.6.3	Pharmacokinetics	76

13.6.4	Safety	77
13.6.4.1	Treatment Compliance and Extent of Treatment Exposure	77
13.6.4.2	Adverse Events.....	77
13.6.4.3	Clinical Laboratory Data.....	77
13.6.4.4	Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data	78
13.6.4.5	Seizure Data	78
14.	DATA SAFETY MONITORING COMMITTEE	78
15.	REGULATORY AND ETHICAL OBLIGATIONS.....	79
15.1	Declaration of Helsinki	79
15.2	Informed Consent	79
15.3	Institutional Review Board/Ethics Committee.....	79
15.4	Pre-Study Documentation Requirements	80
15.5	Participant Confidentiality	80
16.	ADMINISTRATIVE AND LEGAL OBLIGATIONS.....	82
16.1	Protocol Amendments and End of Study or Termination	82
16.2	Study Documentation and Storage	82
16.3	Study Monitoring and Data Collection	83
16.4	Quality Assurance	85
16.5	Compensation.....	85
16.6	Publication Policy.....	85
16.7	Intellectual Property Rights.....	86
16.8	Confidential Information.....	86
17.	REFERENCES	87

Table of Appendices

APPENDIX 1.	Schedule of Assessments	90
APPENDIX 2.	Study Personnel	93
Appendix 3.1	Investigator Details	93
Appendix 3.2	Sponsor Contact Details	93

List of In-text Tables

Table 3.3.1-1	Epidiolex Adverse Events.....	33
Table 5.1-1	Formulation of GWP42003-P Oral Solution	37
Table 5.2-1	Formulation of Placebo Oral Solution	37
Table 8.1.2-1	Dose Up-titration Regimen*	44
Table 9.1.9-1	Hematology, Biochemistry, Urinalysis and THC Screen	49

List of In-text Figures

Figure 1-1	Study Design and Treatment Schema.....	16
Figure 1-2	Study Design and Treatment Schema.....	17
Figure 9-1	Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization Tabulation and Analysis which can Illuminate an Abuse Potential Signal.....	57

List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic Drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC _(0-∞)	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
BP	Blood Pressure
CBD	Cannabidiol
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLB	Clobazam
C _{max}	Maximum measured plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
EC	Ethics Committee
ECG	12-lead electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GW	GW Research Ltd
GWP	GW Pharma Ltd
IB	Investigator Brochure
ICH GCP	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat

IVRS	Interactive Voice Response System
LEV	Levetiracetam
LOCF	Last Observation Carried Forward
MMRM	Mixed-effects Model Repeated Measures
N-CLB	N-desmethyloclobazam
OLE	Open label extension
PBPK	Physiologically-based pharmacokinetic interactions
PI	Principal Investigator
PP	Per Protocol
PVD	Pharmacovigilance Department
QTcB	Heart rate corrected QT interval using Bazett's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFU	Safety follow up
STP	Stiripentol
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
TBL	Total bilirubin
THC	Δ^9 -tetrahydrocannabinol
t_{max}	Time to the maximum measured plasma concentration
TPM	Topiramate
ULN	Upper Limit of Normal
USA	United States of America
VNS	Vagus Nerve Stimulation
VPA	Valproate

Definition of Terms

Term	Definition
Baseline period	The period from screening (Visit 1) to enrollment (Visit 2).
Convulsive seizures	Tonic-clonic, tonic, clonic or atonic seizures.
Countable partial seizures	Partial/focal seizures with a motor or behavioral component that allow such seizures to be easily identified and hence counted.
Day 1	The day a patient is enrolled and begins PK sampling.
End of treatment	Completion of the treatment period (Visit 5 or Visit 12) or withdrawal.
End of study	Last patient's last visit / last contact.
IMP	Investigational Medicinal Product (Study Medication). Used to describe both investigational active product and reference therapy (placebo).
INR	International Normalized Ratio (INR) is a calculation made to standardize prothrombin time.
Investigator	Study Principal Investigator or a formally delegated study physician.
Non-convulsive seizures	Myoclonic, partial or absence seizures.
Partial seizures	Partial (focal) seizures occur when the electrical activity remains in a limited area of the brain.
Status epilepticus	Seizures lasting for 30 minutes or longer.
Sub-types of seizures	Seizure sub-types can be tonic, clonic, tonic-clonic, atonic, myoclonic, absence (typical and atypical), countable partial and other partial.

2. OBJECTIVES

2.1 Primary

To determine whether GWP42003-P affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethyclobazam (N-CLB).

2.2 Secondary

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

3. BACKGROUND AND RATIONALE

3.1 Disease

Epilepsy is a common disorder¹. Approximately 1% of the world's population is chronically affected by epilepsy². It shows no particular geographic distribution and the gender distribution is more or less equal. The incidence of epilepsy is greater in childhood and in elderly people^{2,3,4,5}. Focal seizures represent the most frequent seizure type (around 60% of all cases of epilepsy, and a substantial percentage of them are not well controlled)⁶.

Overall, and despite the introduction of a substantial number of new antiepileptic drugs (AEDs) in the last two decades, around 30% of patients remain refractory to currently available treatment^{7,8,9}. In addition, most currently approved AEDs are associated with significant motor and cognitive adverse reactions^{10,11}.

Currently available AEDs each belong to one of a large number of different classes. The principal targets for existing AEDs tend to be either modulators of voltage-dependent ion channels, enhancers of inhibitory neurotransmission, and attenuators of excitatory neurotransmission, with the aim being to reduce neuronal excitotoxicity^{12,13}.

3.2 GWP42003-P Background

The cannabis plant (*Cannabis sativa* L.) produces trichomes that synthesize a large number of pharmacologically active compounds called phytocannabinoids. The most abundant of these are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), although the amounts and proportions of the various phytocannabinoids in each plant vary by strain and can be adjusted by breeding.

The Investigational Medicinal Product (IMP), GWP42003-P, is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (> 98%) CBD that typically contains less than 0.5% (w/w) THC. The pure CBD is subsequently dissolved in excipients with added sweetener and flavoring.

The pharmacological effects of phytocannabinoids are thought to be mediated primarily via their interaction with the endocannabinoid system, which consists of cannabinoid receptors, endogenous ligands (endocannabinoids) and enzymes for endocannabinoid synthesis and degradation. Two G-protein-coupled receptors for cannabinoids have so far been identified, designated cannabinoid CB₁ and CB₂.

receptors. CBD does not bind to either of these receptors with any great affinity but does modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects ion channel conductance and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1¹⁴ and the orphan receptor GPR55¹⁵. Importantly, in contrast to THC, CBD lacks detectable psychoactivity. CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity¹⁶. Very little data concerning AEs of CBD in humans exists to date. However, doses of up to 1500 mg CBD per day are reported to be well tolerated in humans¹⁷.

3.3 Rationale

CBD has shown therapeutic potential as an AED, with preclinical studies demonstrating anticonvulsant effects in a number of animal models of seizure^{16,18,19}. Although no placebo-controlled trials have been completed to date, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures while taking CBD-enriched cannabis, with over half of those reporting either > 80% reduction in seizure frequency or complete seizure freedom²⁰. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness and better mood. There has been a program of expanded access by GW Pharma Ltd (GWP) in the USA, primarily in children with severe epilepsy, that has shown encouraging reports of reductions in multiple seizure types with good tolerability in 151 exposures²¹.

Population-based studies of drug utilization demonstrate that 19–24% of patients with epilepsy use polytherapy with AEDs^{22,23,24}. In recent studies of children and adults with refractory epilepsy, 64% used polytherapy with two or more AEDs, resulting in a considerable risk of interactions^{25,26}. CLB is a widely used 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). The pharmacological action of CLB is to decrease abnormal electrical activity in the brain via allosteric activation of the ligand-gated γ -aminobutyric acid (A) receptor.

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-CLB, amongst others.

CYP enzymes are a family of heme-containing enzymes responsible for the metabolism of over half of all prescribed medications and interactions with these enzymes are the major source of physiologically-based pharmacokinetic (PBPK) interactions between drugs. It is anticipated that patients taking GWP42003-P may also be taking CLB and as CBD has been shown to both inhibit CYP450 enzymes *in vitro* (K_i CYP3A4 = 1.5 μ M) and induce CYP450 enzymes *in vitro* (EC_{50} CYP3A4 = 1.2 μ g/mL) a possibility of a pharmacokinetic (PK) interaction between CBD and CLB exists. Furthermore, CLB has been shown to undergo PBPK interactions with other AED medications via both CYP induction (such as with felbamate where the formation of the active metabolite of CLB, N-CLB was increased several-fold²⁷) and also CYP inhibition (such as with stiripentol where serum concentrations of CLB were increased and metabolites decreased^{28,29,30}). Given the high likelihood that patients prescribed CBD will also be using CLB, it is the aim and purpose of this study to determine whether a PK interaction between CBD and CLB exists.

3.3.1 Selection of Study Doses

Doses up to 800 mg GWP42003-P per day for up to eight weeks have been well tolerated in adults in GW Research Ltd (GW) clinical study GWMD09112, which, assuming an average weight of 70 kg, equates to a daily dose of 11.4 mg/kg. In the literature, doses of GWP42003-P have been given up to 1500 mg GWP42003-P per day for four weeks in adults, which, in a 70 kg human equates to a daily dose of 21.4 mg/kg GWP42003-P.

Data on the safety of GWP42003-P is emerging from the physician-initiated Epidiolex[®] Expanded Access Program being conducted in the USA. This program has been running since January 2014 and at the time of writing had data on 63 patients. The mean maximum exposure achieved in this patient population of refractory epilepsies was a daily dose of 24.4 mg/kg (n=59 patients) with a maximum dose of 51 mg/kg in one patient. Please see below for a breakdown of the groups:

- ≤ 20 mg/kg GWP42003-P n=13 (21%)
- > 20 mg/kg– ≤ 30 mg/kg GWP42003-P n=40 (64%)
- > 30 mg/kg– ≤ 40 mg/kg GWP42003-P n=4 (6%)
- > 40 mg/kg GWP42003-P n=2 (3%)
- Dose not reported n=4 (6%)

Eleven patients had a daily GWP42003-P dose of > 25 mg/kg, of which five did not report any adverse events (AEs). Of note, the patient who received 51 mg/kg did not have any AEs at this dose. The remaining six patients experienced AEs as documented in the [Table 3.3.1-1](#) below:

Table 3.3.1-1 Epidiolex Adverse Events	
Adverse Event Term	Number of Events
Loose stools / urgent bowel movements	2
Increase in seizures	2
Drowsiness	1
Aspiration pneumonia	1
Lethargy	1
Decreased appetite	1
Dyskinesia	1
Urinary tract infection	1

Based on the above, a daily dose up to 20 mg/kg/day (given as two divided doses) has been selected for the GWP42003-P dose in the current study, including a titration period with daily increments of 2.5 mg/kg and 5 mg/kg. 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 interest. During the OLE doses may be adjusted up or down, dependent on investigator opinion, to a maximum daily dose of 30 mg/kg GWP42003-P.

3.4 Clinical Hypothesis

CBD can act as both a CYP inhibitor and inducer in human hepatocytes in vitro. Therefore, the potential for PK interactions with other drugs that are metabolized by CYP450 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.

4. EXPERIMENTAL PLAN

4.1 Study Design

This phase 2, placebo-controlled study consists of a 34 day, double-blind phase followed by an optional maximum one year 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 or equivalent of 20 mg/kg/day. 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 (Visit 2) before beginning treatment (patients will be taking CLB only).
- Day 33 (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, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 12 h and 24 h. 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 and THC major metabolites at Visit 4.

Patients should try to be consistent in the timing of their food intake in relation to dosing throughout the blinded phase of the study.

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.

A study schema (Figure 1-1), presented at the end of Section 1, depicts the overall study design. More detailed information on treatment and study procedures are provided in Section 8 and Section 9 respectively.

4.1.1 Primary Endpoint

The primary endpoints of the study are the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

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

4.1.2 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:

- 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 CPY3A4 patient genotype analysis

PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- THC
- THC major metabolites

4.2 Number of Centers

An estimated number of seven centers are expected to participate in this study.

4.3 Number of Patients

A total of 20 patients will be enrolled into the study. Recruitment for the study will be competitive between participating sites.

The sample size calculation is explained fully in [Section 13.1](#).

5. INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.1 GWP42003-P Oral Solution

GWP42003-P oral solution is presented as a pale yellow oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.1-1](#).

Table 5.1-1 Formulation of GWP42003-P Oral Solution	
Material	Quantity
CBD	100 mg/mL
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.2 Placebo Oral Solution

Placebo oral solution contains the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring [Table 5.2-1](#).

Table 5.2-1 Formulation of Placebo Oral Solution	
Material	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.3 Packaging, Storage and Drug Accountability (Cannabidiol/Placebo)

5.3.1 Packaging and Labelling

The IMP will be manufactured and packaged by GWP. It will be distributed by GWP or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each visit considering the weight of each patient. A unique pack identification number will be used to identify each box and the medication it contains. The pack numbers will cross check with the batch numbers held at GWP. GWP will ensure that all IMP provided is fully labelled and packaged. Label text will comply with European Union (EU) guidance on Good Manufacturing Practice, Annex 13 Labelling and will be fully described in the separate Pharmacy Manual. In addition, any local

country requirements in accordance with local drug law or regulatory requirement will be included in the final label text.

Directions of use, name, address and telephone number of investigator, or main contact for information about the product or the clinical trial, will be provided separately to the patient.

5.3.2 Storage

The IMP must be stored upright at room temperature ($< 30^{\circ}\text{C}$) and must not be refrigerated or frozen. It must also be kept away from heat and direct sunlight.

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities.

Should storage conditions deviate from these specified requirements, the GW study monitor should be contacted immediately to confirm if the IMP remains suitable for use. IMP should be placed under quarantine until confirmation is received that IMP is suitable for use.

Temperature records of the storage location must be maintained on a daily basis (a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each site. These records must contain at least the minimum and maximum daily temperatures and should be made available to the appropriate GW personnel for review throughout the study.

5.3.3 Supply and Return of Investigational Medicinal Product

Once a site has been activated at study initiation, IMP will be shipped to a responsible person, such as the pharmacist, at the investigator's center, who will check the amount received and the condition of the drug. Details of the IMP received will be recorded in the IMP accountability record. The site will acknowledge IMP receipt and will complete any receipt forms required. IMP will be dispensed and returned as detailed in [Section 5.3.4](#) with further IMP shipments to be requested as necessary. As directed, all supplies, including unused, partially used, or empty containers, will be returned to GWP or destroyed at the center if agreed in writing by the study monitor.

5.3.4 Investigational Medicinal Product Accountability

The investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMPs must be kept current and should contain:

- The dates and quantities of IMP received from GWP.

- Patient's identification.
- Date and quantity of IMP dispensed.
- The initials of the dispenser.
- Date and quantity of IMP returned to the investigator/pharmacy.

A record of returned IMP must be completed and included in the shipment of used and unused IMP to GWP. At the end of the study a record/statement of reconciliation must be completed and provided to GWP.

These inventories must be made available for inspection by authorized GW or GWP representatives and local officials or regulatory agency inspectors.

Please refer to the separate Pharmacy Manual for more detailed information on the IMP.

5.4 Clobazam

Patients will use their own supply of CLB throughout the study. CLB usage will be recorded by the investigator. CLB is only an IMP for the blinded phase of the study.

6. PARTICIPANT ELIGIBILITY

Investigators will be required to maintain a log that includes limited information about all screened patients (initials, age, and gender; as allowed per local regulations) and outcome of screening.

6.1 Inclusion Criteria

For inclusion in the study patients must fulfil ALL of the following criteria:

- 6.1.1 Male or female patients aged 18 to 65 years inclusive.
- 6.1.2 Patient must have epilepsy as determined by the investigator and be taking CLB.
- 6.1.3 Patient must have a documented magnetic resonance imaging/computerized tomography of the brain that ruled out a progressive neurologic condition.
- 6.1.4 Patient must have experienced at least one seizure of any type (i.e., convulsive: tonic-clonic, tonic, clonic, atonic; focal: focal seizures with retained consciousness and a motor component, focal seizures with impaired consciousness focal seizures evolving to bilateral secondary generalization) within the two months prior to randomization.
- 6.1.5 Patients must be taking CLB and no more than two other AEDs during the course of the study.
- 6.1.6 AED(s), including CLB, must be stable for four weeks prior to screening and regimen must remain stable throughout the duration of the blinded phase of the study.

- 6.1.7 Intervention with vagus nerve stimulation (VNS) and/or ketogenic diet must be stable for four weeks prior to baseline and patient/caregiver must be willing to maintain a stable regimen throughout the blinded phase of the study.
- 6.1.8 Patients must abstain from alcohol during the blinded phase of the study.
- 6.1.9 Patient is available to attend all PK visits within the required visit window.
- 6.1.10 Patient and/or legal representative must be willing and able to give informed consent for participation in the study
- 6.1.11 Patient and/or legal representative must be willing and able (in the investigator's opinion) to comply with all study requirements.
- 6.1.12 Patient is willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable.
- 6.1.13 Patient is willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study.

6.2 Exclusion Criteria

The patient may not enter the study if ANY of the following apply:

- 6.2.1 Patient has clinically significant unstable medical conditions other than epilepsy.
- 6.2.2 Patients on CLB at doses above 20 mg per day.
- 6.2.3 Patients taking CLB intermittently as rescue medication.
- 6.2.4 Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure (BP) due to postural changes.
- 6.2.5 Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS in the last month or at screening.
- 6.2.6 Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or enrollment, other than epilepsy.
- 6.2.7 Patient has consumed alcohol during the seven days prior to enrollment and is unwilling to abstain during the blinded phase of the study.
- 6.2.8 Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex[®]) within the three months prior to study entry.
- 6.2.9 Patient has any known or suspected history of any drug abuse or addiction.
- 6.2.10 Patient is unwilling to abstain from recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) for the duration of the study.
- 6.2.11 Patient has consumed grapefruit or grapefruit juice seven days prior to enrollment and is unwilling to abstain from drinking grapefruit juice within seven days of PK visits.
- 6.2.12 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, e.g., sesame oil.

- 6.2.13 Female patient is of child bearing potential, or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.
- 6.2.14 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.
- 6.2.15 Patients who have received an IMP within the 12 weeks prior to the screening visit.
- 6.2.16 Patient is taking felbamate and they have been taking it for less than one year prior to screening.
- 6.2.17 Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or the patient's ability to participate in the study.
- 6.2.18 Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator would prevent the patient from safe participation in the study.
- 6.2.19 Patient has significantly impaired hepatic function at screening (Visit 1) or enrollment (Visit 2), defined as any of the following:
- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $> 5 \times$ upper limit of normal (ULN).
 - ALT or AST $> 3 \times$ ULN **and** total bilirubin (TBL) $> 2 \times$ ULN **or** international normalized ratio (INR) > 1.5 .
 - ALT or AST $> 3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).
- This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found to meet this criterion **must** be withdrawn from the study.*
- 6.2.20 Patient has a prolonged QTcB (> 450 msec for males and > 470 msec for females).
- 6.2.21 Unwilling to abstain from donation of blood during the study.
- 6.2.22 Travel outside the country of residence planned during the study, unless the patient has confirmation that the IMP is permitted in the destination country/state.
- 6.2.23 Patients previously enrolled into this study.

7. PATIENT ENROLLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center's Ethics Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent forms (ICFs) and other patient information material. Patients will be considered enrolled in the study from the time of providing written informed consent. All patients, or legal representatives, where appropriate, must personally sign and date the consent form prior to any procedures being performed (refer to [Section 9.1.2](#) and [Section 15.2](#)).

7.1 Treatment Assignment

At the start of Visit 1, patients will be allocated a unique patient number, consisting of a four digit GW center number and a three digit patient identification number. The three digit patient number will be assigned in ascendant numerical order at each site. The unique patient number will be preceded by a unique letter. For example, W1234001, denoting patient 001 at site 1234. GWP will provide all GWP42003-P/placebo packed and labelled. Following enrollment at Visit 2, patients will be allocated a pre-packed numbered IMP.

7.2 Randomization

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

8. TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The IMP will consist of three types of medication:

- GWP42003-P oral solution containing 100 mg/mL CBD.
- Placebo oral solution containing excipients.
- CLB (patient supplied).

The GWP42003-P/placebo will be presented as an oral solution containing either the active pharmaceutical ingredient and excipients (in the case of GWP42003-P) or only excipients (in the case of placebo). For details regarding GWP42003-P/placebo formulations, see [Section 5](#).

All patients will be weighed during the study visits and the daily volumes of GWP42003-P/placebo solution to be taken during the titration period, and for the remainder of the study, will be calculated and provided to the patient and/or caregiver. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Each patient will take their first dose of GWP42003-P/placebo at Visit 2, Day 2 in the clinic. Patients not entering the OLE will take their final maintenance dose of GWP42003-P/placebo at Visit 4 (Day 33) in the clinic. Patients entering the OLE will take their final dose of IMP at Visit 11 (one year after the end of the blinded phase of the study) or sooner (if marketing authorization is granted within one year).

Patients will use their own supply of CLB throughout the study. Patients will continue on the dose that they were on at screening for the blinded phase of the study. CLB will only be an IMP for the blinded section of the study.

8.1.1 Dose Administration

GWP42003-P/placebo will be administered orally by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided.

GWP42003 P/placebo should be taken immediately after the patient's usual CLB administration. The GWP42003-P/placebo should be swallowed, as per the intended commercial therapeutic route, and may be taken with other concomitant medications, as directed by the investigator.

8.1.2 Dose Escalation and Dose Adjustments

Patients will enter the blinded phase of the study and will be up-titrated over ten days (Day 2 to Day 11) to a maintenance dose or equivalent of GWP42003-P/placebo of 20 mg/kg/day. If GWP42003-P is not tolerated then the dose can be reduced accordingly at the discretion of the investigator. The titration regimen is described in [Table 8.1.2-1](#).

Table 8.1.2-1 Dose Up-titration Regimen*			
Day - GWP42003-P/Placebo (Blinded Period)	Dose Level (GWP42003-P or equivalent placebo)	Open label Extension** (GWP42003-P only) Day	Dose Level GWP42003-P
2	2.5 mg/kg	34	2.0 mg/kg
3	2.5 mg/kg	35	4.0 mg/kg
4	5.0 mg/kg	36	6.0 mg/kg
5	5.0 mg/kg	37	8.0 mg/kg
6	7.5 mg/kg	38	10.0 mg/kg
7	7.5 mg/kg	39	12.0 mg/kg
8	10.0 mg/kg	40	14.0 mg/kg
9	10.0 mg/kg	41	16.0 mg/kg
10	15.0 mg/kg	42	18.0 mg/kg
11	15.0 mg/kg	43	20.0 mg/kg
12 onwards	20.0 mg/kg	44	20.0 mg/kg***

* GWP42003-P /placebo is to be taken twice daily. Total daily doses are shown.

** Only patients who were taking placebo during the double-blind period will up-titrate according to this schedule during the OLE period. Those taking GWP42003-P during the double-blind period will down-titrate their blinded IMP whilst simultaneously up-titrating with GWP42003-P, thus maintaining a daily dose of 20 mg/kg/day GWP42003-P throughout.

*** The GWP42003-P dose of 20 mg/kg/day can be adjusted during the OLE period, after Visit 5, at the investigator's discretion: up to a maximum dose of 30 mg/kg/day. It may also be adjusted down (no minimum).

The titration regimen defined above should be followed to the maximum dose (20 mg/kg/day). Should an AE occur during titration which is attributable to IMP or concomitant AED, then IMP dose should be reduced to the next lower dose. Any other changes in concomitant AED therapy should be reviewed with the medical monitor before being initiated.

For those patients who do not enter the OLE the dose of GWP42003-P/placebo will taper off over 10 days beginning on Day 34. The patient will reduce the dose by 10% of the maintenance dose each day and treatment will end on Day 43.

Patients who enter the OLE period will be transitioned to the OLE treatment over a 10-day period in order to maintain blinding, simultaneously down-titrating blinded GWP42003-P /placebo whilst up-titrating open-label GWP42003-P. As such, patients

who were taking GWP42003-P during the blinded period will maintain their 20 mg/kg/day dose throughout the transition from the blinded period into the OLE period and patients who received placebo during the blinded period up-titrate slowly to the 20 mg/kg/day dose in the OLE period. After this has taken place after Visit 5, the maintenance dose of GWP42003-P may be adjusted up or down at the discretion of the investigator to a maximum of 30 mg/kg/day (no minimum).

8.2 Concomitant Therapy

Doses of any concomitant AEDs, including CLB, must have been stable for at least four weeks prior to screening and must remain stable throughout the blinded phase of the study. If there are symptoms of toxicity suspected to be from a drug interaction, the investigator may adjust GWP42003-P/placebo or the CLB or other AEDs after discussion with the medical monitor.

The use of rescue medication is allowed if necessary. The use of oxygen may be considered as rescue medication if used as required. Any medication, other than the IMP, taken during the study must be recorded on the Case Report Form (CRF).

Any non-pharmacological therapies (e.g., ketogenic diet, VNS) must also be stable up to four weeks prior to baseline and throughout the duration of the study.

8.3 Prohibited Therapy During Study Period

The following medications are prohibited for the duration of the study starting from acquisition of patient consent. However, any patients taking these medications after screening should not be withdrawn from the study unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered.

- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.
- Patients should not take any more than three AEDs inclusive of CLB.
- Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.

If any other IMP is taken as part of a clinical trial within twelve weeks of the screening visit or during the study, the patient must be withdrawn from this study.

8.4 Compliance in Investigational Medicinal Product Administration

Patients or their caregivers will record the total volume of IMP, administered on each treatment day, using the paper diary and will be asked to return all IMP (used and unused) at each subsequent visit. The site will check the returned IMP against the

usage recorded in the diary and the projected usage. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

The investigator must inform GW promptly of all missing or unaccountable IMP.

Records of IMP accountability will be maintained according to [Section 5.3.4](#).

8.5 Access to Blinded Treatment Assignment

The identity of IMP assigned to patients will be held by the IVRS. The principal investigator (PI) at each center is responsible for all trial-related medical decisions and is responsible for ensuring that information on how to access the IVRS is available to the relevant staff in case of an emergency and unblinding is required. 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.

The investigator is encouraged to contact GW to discuss the rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of study medication will not be dependent upon the investigator receiving approval from GW (i.e., the investigator will be able to obtain the code break information independent of contacting GW).

If the investigator does unblind they must contact GW within one working day of the event and must document the time, date and reasons for unblinding in the patient's CRF.

9. STUDY PROCEDURES

A list of the required study procedures is provided in the subsections that follow; refer also to the Schedule of Assessments in [APPENDIX 1](#). Assessments or tests that are not done and examinations that are not conducted must be reported as such on the CRFs.

The location of the source data for the following procedures will be documented, per center, in a signed 'Source Data Verification Plan', for further details see [Section 16.2](#).

9.1 Study Procedure Listing

9.1.1 Contraception

To be eligible for the study, the patient must have agreed that if they or their partner are of child-bearing potential they are willing to use highly effective contraception for the duration of the study and for three months thereafter. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as combined or progesterone only oral contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner or sexual abstinence⁶. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. The use of hormonal contraception must be supplemented with a barrier method (preferably male condom).

9.1.2 Informed Consent

Adult patients with an adequate level of understanding must personally sign and date the IRB/EC approved ICF(s) before any study specific procedures are performed or any patient related data is recorded for the study. For adult patients with an insufficient level of understanding of what is proposed, only personal legal representative consent will be sought. The informed consent process should be documented within the patient notes.

GW requires a physician to be present for consent and to also sign the ICFs.

9.1.3 Demographics

Patient demographics will be recorded at Visit 1. The following information will be obtained for each patient: date of birth, gender and race (if allowed per local regulations).

9.1.4 Medical History

Relevant, significant medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken) will be obtained during Visit 1 and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the study.

9.1.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 28 days) including AEDs will be recorded at the screening visit (Visit 1) and reviewed at each subsequent visit. AEDs used during the study should be maintained at a stable dose. Any changes in concomitant medication during the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to the screening visit, as defined in [Section 8.3](#).

9.1.6 Physical Examination

A physical examination will be performed at the screening visit (Visit 1) to ensure that the patient is eligible to enter the study. To ensure patient safety, further physical examinations will be performed at every hospital visit. Physical examinations will include height (at screening) and body weight measurements.

9.1.7 Vital Signs

Vital sign measurements, taken after five minutes rest in a sitting position, will be completed alongside the physical examination at all visits. Postural BP will be assessed after five minutes in supine position and, if possible, two minutes in standing position. The pulse rate must also be measured as part of the vital sign assessments. BP and pulse rate must be recorded using the same arm throughout the study.

9.1.8 12-Lead Electrocardiogram

An ECG will be performed, after five minutes in supine position, at all hospital visits. A physician must review the ECG and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately in the CRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

9.1.9 Clinical Laboratory Sampling

Laboratory tests will be undertaken at all hospital visits and will include hematology, biochemistry, and urinalysis (provided urine can be obtained, with the exception of

screening where a urine sample for THC screen must be obtained). A serum alcohol test will be performed at Visits 1, 2 and 4. A serum pregnancy test (if appropriate) will also be performed at Visit 1.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further laboratory based urinalysis (urinalysis, microscopy, culture and sensitivity, as applicable).

The investigator and study monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in [Table 9.1.9-1](#).

Table 9.1.9-1 Hematology, Biochemistry, Urinalysis and THC Screen				
Biochemistry (serum)	Hematology (whole blood)	Urinalysis (urine)	Pregnancy Test	THC screen (urine)
Alanine aminotransferase (ALT)	Hematocrit	Bilirubin	Serum	THC
Albumin	Hemoglobin	Blood		
Alkaline phosphatase	Mean cell volume	Glucose		
Aspartate aminotransferase (AST)	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				

All laboratory results will be reviewed and the reports signed by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. See [Section 12.8](#) for guidance on evaluation of potential drug-induced liver injury. All laboratory results considered by the investigator to represent an AE must be documented on the CRF.

Repeat samples will be taken, if required, for clinical follow up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an

investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation.

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss in the four weeks prior to screening.

9.1.10 Pharmacokinetic Analyses

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. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted into a forearm vein 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.

The pre-dose blood sample will be taken within 30 minutes prior to dosing. The allowable window for post-dose blood sample collection is ± 2 minutes up to and including 1 hour post-dose, ± 5 minutes from 1.5 hours up to and including 6 hours post-dose and ± 1 hour at 12 hours and 24 hours post-dose.

In the event of an AE that, in the opinion of the investigator, is related to a concomitant AED, additional blood samples may be collected.

Analysis of all PK samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

9.1.11 Genetic Testing

Genetic testing will only be conducted if specific consent is obtained from the participant or their legal representative. There is a separate ICF for this.

Genetic testing will be conducted to look at the CYP450 genes, with particular focus on CYP 2C19 and CYP 3A4, involved in the metabolism of AEDs and GWP42003-P.

9.1.12 Columbia Suicide Severity Rating Scale

The C-SSRS is to be completed by the investigator or his/her qualified designee at all hospital visits. Qualified designee is defined as physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant who is licensed and has completed the C-SSRS training within the last two years. It is a brief standardized measure that uniquely assesses the essential information (behavior, ideation, lethality and severity) and distinguishes between suicidal occurrences and non-suicidal self-injury. The survey should be completed by the same assessor, where possible, throughout the study.

If the investigator or his/her qualified designee feel that the patient is either unable to answer the questions presented in C-SSRS, or that the questions are causing undue stress to the patient, the questionnaire may be skipped and this must be documented in the patient notes.

9.1.13 Patient Diary

Patients or their caregivers will be instructed on how to complete a paper diary and will be asked to record information daily in it. The number and type of seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from screening (Visit 1) until completion of dosing or withdrawal. Information on IMP intake will also be recorded each day from enrollment (Visit 2) until completion of dosing or withdrawal.

9.1.14 Investigational Medicinal Product Accountability

GWP42003-P/placebo will be dispensed at each of the following visits during the blinded phase:

- Visit 2 (Day 2)
- Visit 4 (Day 34)

IMP will be dispensed at each of the following visits for patients entering the OLE:

- Visit 5 (Two weeks)
- Visit 6 (One month)
- Visit 7 (Two months)
- Visit 8 (Three months)
- Visit 9 (Six months)
- Visit 10 (Nine months)
- Visit 11 (12 months)

Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 2 to 12). The site will check the returned IMP against the usage recorded in the paper diary. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

9.1.15 Adverse Events

Any adverse changes in the patient's medical condition, following completion of the consent form by the patient, will be recorded on the CRF as AEs, questioning the patient further if necessary. All AEs* occurring during the study, whether or not attributed to the IMP, observed by the investigator or reported by the patient will be recorded in the CRF.

*For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures, must be documented as an AE.

Serious Adverse Events (SAEs) must be reported to GW Pharmacovigilance Department (PVD) within 24 hours of discovery or notification of the event, and recorded in the CRF.

Refer to [Section 12](#) for definitions, procedures and further information.

Inpatient hospitalizations that are, in the investigator's opinion, due to epilepsy will be recorded in the patient's CRF and through the SAE reporting process.

Refer to [Section 9.1.16.1.1](#) for the list of 'Triggering AEs of Interest' associated with monitoring of drug abuse liability.

9.1.16 Monitoring of Drug Abuse Liability

There are two triggers that will require the investigator or study coordinator to discuss abuse potential signals with the patient or their caregiver. These are either AEs of interest that may be reported by the patient/caregiver, or drug accountability issues regarding overuse of the IMP or missing bottles. Different questionnaires will be completed by the site depending upon which trigger occurs (see [Figure 9-1](#)).

Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (Visit 5 or Visit 12) or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.

Investigators and study coordinators will be provided with training on how to complete and perform the processes outlined in this section. This training must be completed and documented by the relevant site staff prior to implementation at site.

9.1.16.1 Monitoring of Adverse Events

AE information will be collected according to [Section 9.1.15](#).

9.1.16.1.1 List of ‘Triggering Adverse Events of Interest’

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 Adverse Event 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.

An AE that is consistent with the above categories will be known as a ‘triggering AE of interest’ for the purposes of this study.

9.1.16.1.2 Supplemental Adverse Event Form

This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Adverse Event Form will then be transcribed into the patient’s CRF for the study. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the site should contact the patient/caregiver to obtain the required answers as soon as possible.

9.1.16.2 Monitoring Drug Accountability Discrepancies

Any time after enrollment until final collection of study data, drug accountability discrepancies are monitored as follows:

- At routine drug accountability collection times, the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the paper diary.
- At any time that the site is informed by the patient/caregiver about any overuse of IMP, suspected misuse, abuse, or diversion.

9.1.16.2.1 List of ‘Triggering Drug Accountability Discrepancies’

If there are any discrepancies in drug accountability as outlined by the criteria below, known as ‘triggering drug accountability discrepancies’, then the trained investigator or study coordinator will complete a Supplemental Drug Accountability Form and Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver. The triggering drug accountability discrepancies are as follows:

- Missing bottle(s).
- Compliance issues where one or more bottles are used compared to what was the expected use, according to the paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the paper diary.

9.1.16.2 Supplemental Drug Accountability Form

This form consists of eight questions regarding various aspects of drug accountability and patient usage. It is completed as part of an interview with the patient/caregiver when a triggering drug accountability discrepancy is identified. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Drug Accountability Form will then be transcribed into the patient's CRF for the study. The accountability reporting procedures will still occur. If the Supplemental Drug Accountability Form cannot be completed at the time the triggering drug accountability discrepancy is identified, then the site should contact the patient/caregiver by telephone to obtain the required answers as soon as possible (Note: IMP refers to GWP42003-P or placebo, not other concomitant medications).

9.1.16.3 Site Classification Form

The investigator should review the applicable Supplemental Adverse Event Form or Supplemental Drug Accountability Form, and then complete the Site Classification Form. For each Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed, there should be an associated Site Classification Form.

The Site Classification Form requires the investigator to assign the finding to an appropriate classification and then to also assign the possible relationship to the IMP. The investigator is also required to indicate the level of the certainty of the classification. The answers from the Site Classification Form will then be transcribed into the patient's CRF for the study.

9.1.16.4 Study Medication Use and Behavior Survey

This form consists of 18 questions regarding the use of the IMP. The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit (Visit 5 or Visit 12) or withdrawal visit. The answers on the Study Medication Use and Behavior Survey will then be transcribed into the patient's CRF for the study.

The Study Medication Use and Behavior Survey will be completed for all patients in the study and not only those that have reported a triggering AE or drug accountability discrepancy.

9.1.16.5 Adjudication Committee — Assessment of Abuse Potential of GWP42003-P

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases. Only data from patients who have completed the study will be assessed.

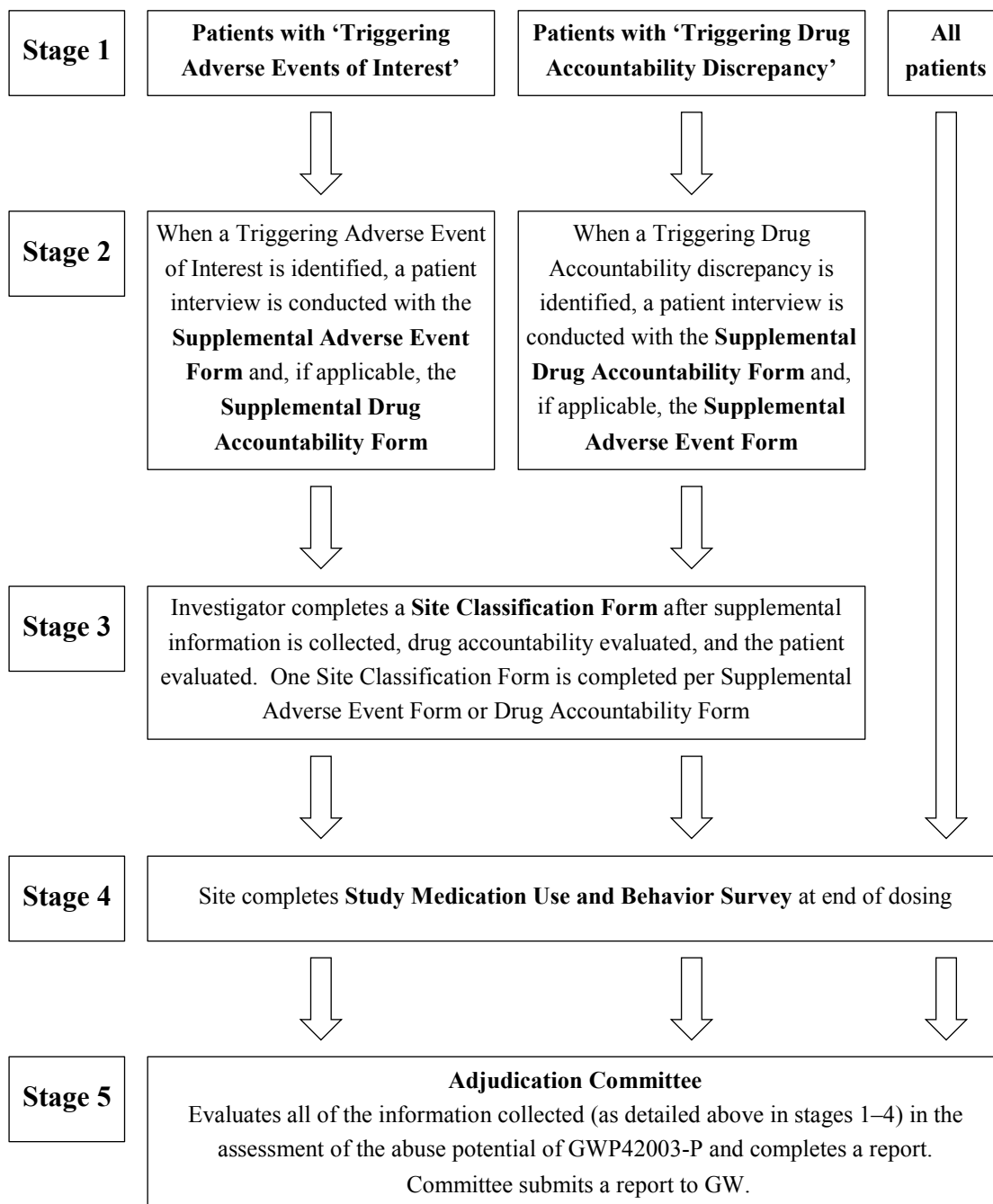
A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- All triggering AE information.
- Supplemental Adverse Event Form (if applicable).
- All triggering drug accountability discrepancies.
- Supplemental Drug Accountability Form (if applicable).
- Site Classification Form.
- Study Medication Use and Behavioral Survey.
- Additional information from site(s) as requested by the Committee.

The Adjudication Committee will assess all of the information. It will form a position on the classification of each event and will write a study-related report, detailing the conclusions and recommendations.

The overall process is summarized in [Figure 9-1](#).

Figure 9-1 **Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization Tabulation and Analysis which can Illuminate an Abuse Potential Signal**



9.2 Study Procedures by Visit

Patients and their caregivers will be invited to participate in the study and will be issued with the patient information and informed consent or the personal legal representative information and informed consent (refer to [Section 9.1.2](#) and [Section 15.2](#)). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/legal representatives who provide written informed consent at Visit 1 will be screened for entry into the study.

9.2.1 Double Blind Phase

9.2.1.1 Visit 1 (Day -14 to -7, Screening)

The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, THC testing, urinalysis and a pregnancy test (using a serum sample, if appropriate). The laboratory results should be available within 3-5 working days after Visit 1. If the results show a patient is ineligible, the patient will not be enrolled into the study. The C-SSRS will be administered.

Patients who satisfy all inclusion and none of the exclusion criteria specified in [Section 6](#) will be assigned a unique patient number and then begin the baseline period. Patients or their caregivers will be given a paper diary to record daily seizure information, rescue medication, concomitant AEDs and AEs; and will be instructed on how to do so. The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.

9.2.1.2 Visit 2

9.2.1.2.1 Visit 2 (Day 1) – Enrollment (+ 3 days)

This visit will occur 7–14 days after Visit 1.

The following observations will be made at Visit 2: concomitant medications, (including AEDs), physical examination (including body weight), ECG, vital signs and review of patient diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing and urinalysis. Blood samples will also be taken for genetic testing if additional consent has been obtained. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit, and confirm the outcome of the visit prior to enrollment.

Following enrollment patients will begin the PK sampling process. Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV and TPM. A baseline PK sample will be taken before the patient takes their morning dose of CLB. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of any AEDs must be taken after the 12 hour PK blood sample. Patients will either remain in clinic overnight throughout this PK sampling process or return to the clinic on Day 2 ahead of additional sample collection.

9.2.1.2.2 Visit 2 (Day 2) - Enrollment

This is the second part of the two day enrollment visit. The final PK sample will be collected 24 hours after the Day 1 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 2: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.

GWP42003-P/placebo will be dispensed and both the morning dose of CLB and of GWP42003-P/placebo will be taken in clinic. Following administration of GWP42003-P/placebo, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions. Patients and/or their caregivers will be provided with individual dosing schedules as described in [Section 8.1.2](#). Each patient will then receive their GWP42003-P/placebo for the 10 day titration period followed by the 21 day maintenance period. Patients, or their caregivers, will be instructed on how to record the diary information.

9.2.1.3 Visit 3 (Day 12 +3 days)

This visit will occur 11 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at Visit 3 (Day 12): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, AEs and review of patient diary completion.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered.

9.2.1.4 Visit 4

9.2.1.4.1 Visit 4 (Day 33) (\pm 3 days)

This visit will occur 32 days after Visit 2, Day 1 (enrollment). Patients will return all used and unused GWP42003-P/placebo. The following observations will be made at

Visit 4 (Day 33): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of patient diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry, alcohol testing, and urinalysis. The C-SSRS will be administered.

Blood samples will be taken for analysis of plasma concentrations of CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites. A baseline PK sample will be taken before the patient takes their morning dose of CLB, followed immediately by their dose of GWP42003-P/placebo. Further samples will then be taken at the following times relative to the CLB dose: 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours and 12 hours. The evening dose of GWP42003-P/placebo and any AEDs must be taken after the 12 hour PK blood sample. Patients are expected to remain in clinic throughout this PK sampling.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.1.4.2 Visit 4 (Day 34)

This is the second part of the two day visit. The final PK sample will be collected 24 hours after the Day 33 morning CLB dose.

Following completion of the PK sampling process the following observations will be made on Day 34: concomitant medications (including AEDs), physical examination (including body weight), vital signs and AEs.

At the end of the blinded phase of the study on Day 34, providing the investigator and patient both agree, patients will be invited to continue taking GWP42003-P and to enter the OLE.

Patients who enter the OLE will be dispensed GWP42003-P on Day 34 and the first dose will be taken in clinic. Following administration of GWP42003-P, patients must remain in clinic for at least 30 minutes to monitor for any adverse reactions. At the point of entry to the OLE, patients will be transitioned to the OLE treatment over a 10 day period in order to maintain blinding.

Patients who do not enter the OLE will begin a 10 day taper period during which they will taper off their daily dose of GWP42003-P/placebo. The daily dose will be reduced by 10% of the maintenance dose per day and treatment will end on Day 42.

9.2.1.5 Visit 5 (Patients not entering Open Label Extension) (Day 43 + 3 days)

This visit will occur 42 days after Visit 2, Day 1 (enrollment) for those patients who do not enter the OLE.

All GWP42003-P/placebo (used and unused) will be collected and a check of the returned GWP42003-P/placebo against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver. Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected.

9.2.1.6 Visit 6 - Safety Follow up Call (Day 71) (\pm 3 days)

This visit is required for patients who do not enter the OLE study on Day 34, or who withdraw from the study early. This visit should occur four weeks after Visit 5, (\pm 3 days) or withdrawal from treatment, and can be conducted over the telephone. The following observations will be made on Day 71: concomitant medications (including AEDs) and AEs.

9.2.2 Open Label Extension

Patients who enter the OLE will be dispensed IMP at Visit 4 (Day 34) and will have regular clinic visits for a maximum of one year or earlier (if marketing authorization is granted or the patient withdraws). The visit schedule is calculated relative to Visit 4 (Day 34).

9.2.2.1 Visit 5 (Open Label Extension) - Two Weeks (\pm 3 days)

This visit will occur two weeks after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 5 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

The GWP42003-P dose may be adjusted up or down by the investigator from the maintenance dose of 20 mg/kg/day achieved at the end of the 10-day transition period, up to a maximum of 30 mg/kg/day in the OLE period.

9.2.2.2 Visit 6 (Open Label Extension) - One Month (\pm 3 days)

This visit will occur one month (one month is considered as 28 days) after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 6 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.3 Visit 7 (Open Label Extension) - Two Months (\pm 3 days)

This visit will occur two months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 7 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.4 Visit 8 (Open Label Extension) - Three Months (\pm 7 days)

This visit will occur three months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 8 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.5 Visit 9 (Open Label Extension) - Six Months (\pm 7 days)

This visit will occur six months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 9 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.6 Visit 10 (Open Label Extension) - Nine Months (\pm 7 days)

This visit will occur nine months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 10 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

9.2.2.7 Visit 11 (Open Label Extension End of Treatment) - Twelve Months (\pm 7 days)

This visit will occur twelve months after Visit 4 (Day 34). Patients will return all used and unused IMP. The following observations will be made at Visit 11 (OLE): concomitant medications (including AEDs), physical examination (including body weight), ECG, vital signs, review of seizure diary and AEs.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis. The C-SSRS will be administered. The investigator must record the patient's attendance at the visit and the outcome.

The investigator must assess adherence to the dosing regimen and recording of rescue medications by reviewing the patient's diary.

Starting at Visit 11, patients will begin to taper down their IMP dose. The dose will be reduced by 10% of their OLE maintenance dose per day.

9.2.2.8 Visit 12 (Open Label Extension End of Taper)

This visit will be ten days after Visit 11. All IMP (used and unused) will be collected and a check of the returned IMP against usage must be made. A physical examination (including body weight), ECG and vital signs will be assessed and the C-SSRS will be administered. The trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

Clinical laboratory samples (blood and urine) will be taken for hematology, biochemistry and urinalysis and a review of concomitant medications (including AEDs) and AEs will be completed. Patient diaries will be collected and reviewed.

9.2.2.9 Safety Follow Up Call (\pm 3 days)

This visit will occur one month after the OLE End of Taper and can be conducted over the telephone. The following observations will be made during the follow up call: concomitant medications (including AEDs) and AEs.

10. WITHDRAWAL

In accordance with the Declaration of Helsinki³¹, the FDA regulations relating to good clinical practice (GCP) and clinical trials^{32,33,34}, the EU Clinical Trials Directive (2001/20/EC)³⁵ and/or other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

The patient must be withdrawn from the study if any of the following apply:

- Administrative decision by the investigator, GW, or a Regulatory Authority.
- Pregnancy.
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- Withdrawal of patient consent.
- Withdrawal of legal representative consent.
- Lost to follow up.
- ALT > 3 \times ULN or AST > 3 \times ULN **and** (TBL > 2 \times ULN **or** INR > 1.5).
- ALT or AST > 3 \times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 \times ULN.
- ALT or AST > 5 \times ULN for more than two weeks.
- Any other IMP is taken as part of a clinical trial during the study.

- Significant change in QTcB (> 60 msec) from the previous ECG or absolute QTcB of > 500 msec.

Patients may also be withdrawn from the study for any of the following:

- Patient non-compliance.
- AE, which in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Any evidence of drug abuse or diversion.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

Should a patient request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients who withdraw should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator's clinical judgment. All assessments required at Visit 4 (if the withdrawal is during the blinded phase) or Visit 11 (if the withdrawal is during the OLE) should be conducted if possible. If the tapered dose is administered, patients should return for Visit 5 (if withdrawal is during the blinded phase) or Visit 12 (if the withdrawal is during the OLE) if possible. Wherever possible, the safety follow-up visit should be conducted 28 days from the date of the last dose of IMP. Patients withdrawing due to an AE should be followed up according to [Section 12.7](#). All information should be reported on the applicable CRF pages

11. URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or safety. If such measures are taken by the investigator they must notify GW immediately or at least within 24 hours of awareness. GW will report urgent safety measures to Competent Authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the Competent Authorities and IRB/EC within three days.

12. ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this study an AE is defined as:

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which is present following screening (Visit 1) throughout the study and up to the post treatment, safety follow-up visit (28 days after last dose of IMP), which may or may not be considered to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

Surgical/Investigational procedures are not AEs. The medical reason for the procedure is the AE. Elective hospitalizations for pre-study existing conditions or elective procedures are not AEs. The exception may be if the patient has an AE during hospitalization which prolongs their scheduled hospital stay in which case it would be considered a SAE (refer to [Section 12.2](#)).

If reporting a fatal event, the SAE term should be the underlying cause of the death (e.g., disease or medical condition leading to death).

12.1.2 Investigator

The term ‘investigator’ refers to the study PI or a formally delegated study physician.

12.2 Serious Adverse Events

During clinical investigations, AEs may occur which, if suspected to be IMP related, might be significant enough to lead to important changes in the way the IMP is developed (e.g., change in dose, population, monitoring need, consent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported promptly to Regulatory/Competent Authorities, applicable IRB/ECs and Investigators (expedited reporting) by GW.

An AE must only be classed as serious i.e., an SAE, when the event falls into one of the following criteria:

- Results in death.
- Is life-threatening.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/birth defect.
- Medically significant.**

* The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

** Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.3 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study must be reported to GW with any other supporting information and recorded in the AE section of the CRF. Any on-going SAEs should be followed up until resolution wherever possible. For all deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports and relevant medical reports should be sent to GW promptly.

All SAEs must be reported directly to GW PVD within 24 hours of discovery or notification of the event. All SAE information must be recorded on the SAE forms provided in the site files and faxed to GW PVD. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form, signed/dated and faxed to the GW PVD and the AE section of the CRF must be updated.

The investigator should continue to document all AEs which occur up to the last formal follow-up visit (Visit 13 for patients entering the OLE and Visit 6 for those patients that are not entering the OLE). If the investigator subsequently becomes aware of any deaths or a new IMP-related SAE after the last formal follow-up period of the study, these should still be reported to the GW PVD.

Any other problem discovered outside these time limits which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have participated in the study, then these should be treated as an SAE and reported to GW PVD. Such post study SAEs do not need to be recorded on the patient’s CRF if editing rights to the CRF have been removed.

Contact details for the GW PVD are provided at the front of the site files for all study centers, and upon the GW SAE Report form.

12.4 Pregnancy

Any patient, or patient's partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD within 24 hours of first awareness. Please use the GW Pregnancy Monitoring Forms provided.

Where possible the investigator should provide the outcome of the pregnancy.

The investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the investigator becomes aware of a new pregnancy outside this time limit then they should report it as above. GW PVD will follow up for all pregnancy outcomes.

12.5 Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the study medication must be reported as such. The expression "*reasonable causal relationship*" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the investigator for all AEs is used to capture the reasonable causal relationship of an event to the study medication:

"In your opinion is there a plausible relationship to the study medication?" The answer is "yes" or "no".

Events that start before the first dose of study medication (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of study medication, a new event record should be entered into the CRF.

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the investigator assess not only the possible role of the study medication but also competing etiological factors as the underlying cause. Factors for consideration may include:

- Medical history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.

- Withdrawal of study medication.
- Protocol-related procedure.

12.6 Reporting Procedures for All Adverse Events

All AEs* (including SAEs) occurring during the study will be reported on the running logs in the AE section of the CRF. This includes all events from the time following screening (Visit 1) to post study follow-up (Visit 13 for patients entering the OLE and Visit 6 for those patients that are not entering the OLE), whether or not attributed to IMP and observed by the investigator or patient.

*For the patient's expected seizure types, these do not routinely require documentation as AEs. However, any worsening, including change in the pattern or severity of seizures must be documented as an AE. Any AE which meets SAE criteria should still be reported as a SAE.

The following information will need to be provided for all AEs:

A) Adverse Event (Diagnosis or Syndrome if known, or Signs and Symptoms)

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded on the AE section of the CRF. Once a diagnosis has been determined the AE section of CRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the CRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated e.g., fever and malaise due to a respiratory tract infection.

B) Adverse Event Start Date and Stop Date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given then record as much information as possible (i.e., month and year or in exceptional circumstances just year). When the actual start date becomes known the CRF must be updated to replace the previously recorded date.

C) Outcome

The outcome of the event must be recorded accurately and classified into one for the following categories:

- Recovered.
- Recovered with sequelae.
- Continuing.
- Patient died.

D) Severity

When describing the severity of an AE the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, for example, a headache or constipation, the change in severity should not be recorded each time, instead only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore it should not be classed as serious.

E) Causality

See [Section 12.5](#) above.

F) Action Taken with Study Medication

This question refers to the action taken with the IMP due to an AE. The action with the IMP must be classed as:

- None.
- Dose reduced temporarily.
- Dose reduced.
- Study medication interrupted.
- Study medication stopped.

12.7 Follow up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the GW PVD for any AEs reported.

AEs considered related to the IMP by the investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable

AE, further details of withdrawal are presented in [Section 10](#). If either of these occurs, the patient must undergo an end of treatment assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

12.8 Potential Cases of Drug Induced Liver Injury

All investigational sites are required to submit to the GW PVD the laboratory results for any patient after randomization that meet the criteria for the selected laboratory parameters as follows:

- ALT or AST $> 3 \times \text{ULN}$ **and** (TBL $> 2 \times \text{ULN}$ **or** INR > 1.5).
- ALT or AST $> 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).
- ALT or AST $> 8 \times \text{ULN}$.
- ALT or AST $> 5 \times \text{ULN}$ for more than two weeks.

These reports must be sent to the GW PVD using the same fax number for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the patient's baseline laboratory results with all reports to GW PVD.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol defined criteria for withdrawal and important medical events. The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase and gamma-glutamyl transferase levels, detailed history and physical examination. Patients should be followed until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

Elevations in ALT or AST $> 3 \times \text{ULN}$ or TBL $> 2 \times \text{ULN}$ alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours' notice of abnormal results. If the participant cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.

12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees.

In accordance with the EU Clinical Trials Directive³⁵, relevant parts of the FDA Code of Federal Regulations and any national regulations, GW will inform investigators,

regulatory authorities and relevant IRB/ECs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through three sources:

- Investigator Brochure³⁶: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study on the IMP in human participants. The IB is updated annually.
- Development Core Safety Information: this document actually forms the Safety Section of the IB³⁶, or is updated as an appendix of the IB³⁶. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).
- Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the regulatory authorities, the relevant central IRB/ECs which have approved the study and investigators. As required, the investigator should notify their regional IRB/EC of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the USA, investigators are normally required to promptly report to their IRBs all unanticipated problems involving risks to human patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance³² the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human patients, and reported to the IRB, *only* if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

The FDA guidance³⁷ states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

GW will inform investigators (regulatory authorities and applicable IRB/EC's) of any safety issues or case reports that are considered to be unanticipated and provide such

reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the study does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

As a minimum, the recipient will be sent all of the above and relevant updates between the period from ethics approval and final database lock.

13. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be produced prior to the database lock and analysis of the study. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

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

13.2 Interim Analysis

An interim analysis will be conducted at the end of the Double Blind phase of the study and may also be considered during the OLE phase, if long term data is required to support New Drug Application/Marketing Authorization Application submissions.

13.3 Analysis Sets

13.3.1 Safety Set

All subjects who are treated and receive at least one dose of IMP will be included.

The Safety set is the primary analysis set for all safety endpoints.

13.3.2 Pharmacokinetic Analysis Set

All subjects who are treated and receive at least one dose of IMP and who provide some on-treatment data will be included.

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

13.3.3 Protocol Deviations

Any protocol deviations will be listed and reasons for exclusion from the analysis populations will be summarized

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (n), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category. Summaries will be presented for data recorded pre-treatment, during each 25 day dosing phase (placebo and GWP42003-P) and during the OLE phase separately.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, treated, completing the study and those prematurely terminated IMP) will be accounted for in the enrollment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Age, sex, race (as allowed per local regulations) and any other demographic or baseline characteristics will be summarized, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by system organ class, including details of the duration of epilepsy and the types of seizures currently experienced by the patients.

13.5.4 Concomitant Medication

Concomitant medications taken prior to and during the study will be summarized, by medication class and active ingredients. Summaries of medications taken during the IMP treatment phases and during OLE will be presented separately.

13.6 Endpoints and Statistical Methods

13.6.1 Primary Endpoint(s)

The primary endpoints of the study are the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

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

13.6.2 Secondary Endpoint(s)

The secondary endpoints of the study are the safety parameters (see [Section 13.6.4](#)) and the PK parameters (C_{\max} , t_{\max} , $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $t_{1/2}$) of the following analytes:

- THC
- THC major metabolites

13.6.3 Pharmacokinetics

Calculation of PK parameters will be based on actual blood sampling times [h] (relative to the corresponding administration time) rounded to two decimal digits with negative pre-dose times set to zero. Plasma concentrations of CLB, N-CLB, VPA, STP, LEV, TPM, CBD, CBD major metabolites, THC and THC major metabolites will be displayed graphically, summarized and listed. For descriptive statistics, values below the lower limit of quantification of the assay (LLOQ) will be excluded from any calculations. Descriptive statistics of concentrations will be calculated if at least half of the individual data points that have been measured are equal to or above the LLOQ.

For calculation of the PK parameters, the following rules will be applied:

At time zero and at time points in the lag-time between time zero and the first quantifiable concentration, concentrations below the LLOQ will be set to zero. All other concentrations below the LLOQ will not be used in calculations.

Variables derived from plasma concentrations:

- Concentration maximum (C_{\max}): Highest observed plasma concentration of the measured concentration-time profile. Dimension: [amount / volume].
- Terminal half-life $t_{1/2} = \ln(2)/\lambda_z$.
- The rate constant of the terminal phase λ_z will be determined by linear regression of log-transformed concentration data after the time of maximum concentration. A sequence of terminal elimination rate constants will be created by linear regression. Linear regressions are repeated using the last three points with a quantifiable concentration, the last four points, the last five points etc. For each regression, an adjusted R^2 is computed. The regression with the largest adjusted R^2 is selected to estimate the terminal half-life. Dimension: [time].
- Area under the concentration-time curve from administration until the last sampling point (t) equal or above the LLOQ $AUC_{(0-t)}$ will be calculated by the linear trapezoidal formula. Dimension: [time • amount / volume].
- Area under the concentration-time curve extrapolated to infinity: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_{\text{last}}/\lambda_z$ and C_{last} is the concentration observed at the last time point with a quantifiable concentration, λ_z refers to the terminal elimination rate constant. Dimension: [time • amount / volume].
- Time of maximum concentrations: T_{\max} will be taken as the time after administration at which C_{\max} occurs. Dimension: [time].
- PK parameters for each analyte will be summarized for the two treatment phases of the study separately, as appropriate.
- 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 group ratios of geometric means of C_{\max} , $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ will

be carried on logarithm scale using a linear mixed effect model with treatment (CLB or CLB+CBD) 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.

13.6.4 Safety

13.6.4.1 Treatment Compliance and Extent of Treatment Exposure

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

13.6.4.2 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities dictionary.

A treatment emergent AE is one that started, or worsened in severity or seriousness, following the first dose of IMP.

Descriptive presentations of treatment emergent AEs will be given by preferred term and system organ class for the safety analysis set. The number of patients reporting at least one AE will be provided. Summaries will be provided for each phase of the study separately.

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.

13.6.4.3 Clinical Laboratory Data

Clinical laboratory data at screening and at the end of the 31 day treatment phase and the change from baseline to end of treatment (OLE) will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of patients with values outside the normal range.

13.6.4.4 Columbia-Suicide Severity Rating Scale, Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data

The C-SSRS, vital signs, ECG and physical examination data will be summarized at screening, at the end of the 31 day treatment phase and during the OLE treatment period using appropriate summary statistics. Changes in the vital signs from baseline to end of each treatment phase will also be summarized.

13.6.4.5 Seizure Data

Seizure data collected during the 31 day treatment phase and during the OLE phase of the study will be summarized using appropriate summary statistics.

14. DATA SAFETY MONITORING COMMITTEE

GW does not plan to use an independent data safety monitoring committee as part of this study.

15. REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the^{31,35} and the clinical trial regulations adopting European Commission Directives into national legislation^{38,39,40}.

15.2 Informed Consent

Initial master ICFs will be provided to the investigator to prepare the informed consent documents to be used at his or her center. The GW Clinical Manager will communicate updates to the templates by letter. The written informed consent documents should be prepared in the language(s) of the potential patient population.

Before a patient's participation in the trial, the investigator is responsible for obtaining written informed consent from the patient or legal representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol specific screening procedures or any IMPs are administered. The patient, or their legal representative, should have ample time for review to consider the information provided before giving written consent; more specific definitions of ample time may be in force if required by IRB/ECs or local regulations.

The acquisition of informed consent should be documented in the patient's medical records and the ICF should be signed and personally dated by the patient or legal representative (as applicable) and by the person who conducted the informed consent discussion. GW also requires a physician to be present for consent and to sign the consent forms as well. The original signed ICFs should be retained and a copy provided to the patient or legal representative.

15.3 Institutional Review Board/Ethics Committee

A copy of the protocol, proposed ICFs, other patient information material, any proposed advertising material and any further documentation requested, must be submitted to the IRB/EC for written approval. GW must receive a copy of the written approval of the protocol and ICFs before enrollment of patients into the study and shipment of IMP.

The investigator must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent documents. The investigator should notify the IRB/EC of deviations from the

protocol or SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The investigator will be responsible for obtaining on-going IRB/EC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/EC continuance of approval must be sent to GW.

15.4 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent for entry into the study:

- Signed and dated protocol signature page.
- Copy of approved ICFs and other patient information material.
- Copy of the IRB/EC approval of the protocol, ICFs and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/EC composition and/or written statement of the IRB/EC in compliance with the FDA regulations relating to GCP and clinical trials^{32,33,34,41}, the EU Clinical Trials Directive³⁵, or International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP)⁴² where the EU Directive does not apply.
- Signed laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed clinical trial agreement (including patient/investigator indemnity insurance and financial agreement).
- FDA 1572 form.
- Completed financial disclosure statements for the PI and all sub-investigators if relevant.

15.5 Participant Confidentiality

The investigator must ensure that the patient's anonymity is maintained. On the CRFs and within the databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials and race (if allowed per local regulations) and a patient study number only. Documents that are not for submission to GW, e.g., signed ICFs should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to good clinical practice and clinical trials^{32,33,34,41}, and the EU Clinical Trials Directive³⁵/ICH GCP Guidelines⁴², it is required that the investigator and institution permit authorized representatives of the company, the regulatory agencies and the IRB/EC direct access to review the patient's original medical records for verification of study related procedures and data. Direct

access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the patient that his/her study related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the company.

16. ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 Protocol Amendments and End of Study or Termination

Protocol amendments must be made only with the prior approval of GW. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent documents. The IRB/EC and Competent Authorities must be informed of all amendments and give approval for any substantial amendments prior to implementation. The investigator must send a copy of the approval letter from the IRB/EC to GW. Amendments for administrative changes can be submitted to the IRB/EC for information only.

Both GW and the investigator reserve the right to terminate the study, according to the clinical trial agreement. The investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to GW.

16.2 Study Documentation and Storage

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the GW delegation of authority and signature form.

Source documents are original documents, data and records from which the patient's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, electronic data captured by IVRS, microfiches, radiographs and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording; that is, there is no other written or electronic record of data. In the rare situations of this happening, then the source data from the CRF should be transcribed in the patient's notes with appropriate signature and date to provide a full audit trail. A Source Data Verification Plan, identifying the source for each data point at each site, will be agreed with each site prior to patient recruitment.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related, essential documentation (as outlined in ICH E6 Section 8.2⁴²), suitable for inspection at any time by representatives from GW and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, ICFs and supporting copies of source documentation.

- Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see [Section 15.4](#)) and all correspondence to and from the IRB/EC and GW.
- Proof of receipt, IMP accountability record, return of IMP for destruction, final IMP reconciliation statement and all drug related correspondence.

In addition, all original source documents supporting entries on the CRFs, paper diary data and electronic data captured by IVRS must be maintained and be readily available.

Following completion or termination of a clinical study, GW will initiate proper archive of clinical study related documentation and electronic records generated by the investigator and/or GW. All clinical trial related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 25 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by GW (EU Directive 2005/28/EC Chapter 4 Trial Master File and Archiving Article 16⁴³).

GW will inform the investigators for each site in writing of the need for record retention. No study document should be destroyed without prior written agreement between GW and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify GW in writing of the new responsible person and/or the new location.

16.3 Study Monitoring and Data Collection

The GW representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study for example, CRFs and other pertinent data provided that patient confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting the CRFs and available diary data at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor should have access to patient medical records and other study related records needed to verify the entries on the CRFs.

The investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

The investigator is responsible for ensuring the data recorded in the CRFs are accurate and complete. The CRF should be completed within five working days after the patient's visit and before review by the study monitor. Queries generated by GW or its representative are to be answered within a similar period of time. Shorter periods of time may apply during specific situations such as interim analysis or final database cleaning.

All handwritten medical records should be filled out with a black or blue ball-point pen and must be legible. Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator. No correction fluid or tape may be used. The PI will sign and date the indicated places on the CRF. These signatures will indicate that the PI inspected or reviewed the data on the CRF, the data queries and the site notifications and agrees with the content.

To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations^{32,33,34,41}, the ICH GCP Guide⁴², and all other applicable regulatory requirements^{35,42}, to resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

GW's or the CRO's Clinical Data Management Department will correct the following issues in CRFs without any notification to site staff:

- Misspellings that do not change the meaning of the word, excluding AEs and medications.
- Date errors that occur at the end of the year and into the New Year.
- Temperature unit errors (Fahrenheit vs Centigrade).
- Weight unit errors (pounds vs kilograms) if a baseline weight has been established.
- Administrative data for example, event names for unscheduled visits or retests.
- Clarifying "other, specify" if data are provided for example, race, physical exam.

- If a YES or NO question for example, ‘Were there any AEs?’ is left blank yet AEs are listed on the CRF, YES will be entered in the blank.
- Correct CRF page numbers.

16.4 Quality Assurance

In accordance with the FDA regulations, EU Clinical Trials Directive/ICH GCP and the sponsor’s audit plans, representatives from GW’s Clinical Quality Assurance Department may select this study for audit. Inspection of site facilities for example, pharmacy, drug storage areas, laboratories and review of study related records will occur to evaluate the study conduct and compliance with the protocol, as per the EU Clinical Trials Directive/ICH GCP and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the study site in the event of any claim in respect of personal injury arising due to a patient’s participation in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical study patient would not otherwise have been exposed providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will co-ordinate this dissemination and may solicit input and assistance from the chief/PIs. A summary of the results of this study will be made available on <http://www.ClinicalTrials.gov>, as required by U.S. Law.

The raw data from this study may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analysis and are permitted to present such information along with methods and results of the clinical study at symposia, national or regional professional meetings, and to publish it in theses or dissertations.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this study, must be submitted to GW Medical Writing Department and, as applicable, GW Publication Committee for review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for

publication, public dissemination, or review by a publication committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

GW also reserve the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.7 Intellectual Property Rights

All Intellectual Property Rights owned by or licensed to either GW or the PIs, other than those arising from the clinical study, will remain their property. All Intellectual Property Rights arising out of the clinical study will vest in or be exclusively licensed to GW and as such, the PI should promptly disclose all knowledge to GW and refrain from using such knowledge without the prior written consent of GW.

16.8 Confidential Information

GW and the PI should ensure that only personnel directly concerned with the study should be party to confidential information and that any information coming to either party about the other during the course of the study should be kept strictly confidential and should not be disclosed to any third party or made use of without the prior written consent of the other.

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APPENDIX 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						
Enrollment		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			
Pregnancy test (if appropriate)	X							
Pharmacokinetic blood sampling**		X	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)
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 Behavior 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 Behavior Survey								X	

* For the purpose of scheduling, each month is considered as 4 weeks (28 days).

APPENDIX 2. STUDY PERSONNEL

Appendix 3.1 Investigator Details

At the time of protocol production, the participating investigators had not been confirmed. A list of all investigators will be maintained within the GW Master Files (electronically and added to the Trial Master File at the end of the study).

Appendix 3.2 Sponsor Contact Details

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