A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFTEY OF CANNABIDIOL (GWP42003-P) IN CHILDREN AND YOUNG ADULTS WITH DRAVET SYNDROME

Unique Protocol ID:	**GWEP1424**
NCT Number:	**NCT02224703**
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TITLE: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome

STUDY CODE: GWEP1424

EudraCT NUMBER: 2014-002939-34

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Confidentiality Statement

Investigator Agreement

I have read the attached protocol entitled "A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome", dated 06 September 2018 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: _____ Date: _____

Principal Investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print Name: PPD Date: 11 SEPT 2018.

Clinical Manager (DD Month YYYY)

Signature: _____

1 PROTOCOL SYNOPSIS

Study Title	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.
Clinical Study Type	Phase Three Study
Indication	Dravet syndrome (DS)
Primary Objective	To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the change during the treatment period of the study compared to baseline in convulsive seizure frequency. The dose response effect between two GWP42003-P Dose Levels (10 mg/kg/day and 20 mg/kg/day) and placebo will also be explored. Convulsive seizures are defined as tonic-clonic, tonic, clonic or atonic and non-convulsive seizures as myoclonic, partial or absence.
Secondary Objective(s)	• To assess changes from baseline in convulsive and non-convulsive seizure frequency, duration, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, quality of life, growth and development, and conduct behavioral and cognitive assessments in patients taking GWP42003-P as an adjunctive treatment, when compared with placebo. • To determine the pharmacokinetics (PKs) of cannabidiol (CBD) and its major metabolites following single and multiple doses of GWP42003-P and to assess the presence of Δ^9-tetrahydrocannabinol (THC) and its major metabolites in plasma and the presence of THC, CBD and their major metabolites in urine after multiple doses of GWP42003-P. • To determine effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), where available. • To assess the safety of both GWP42003-P doses when compared with placebo.
Study Design	This study is a randomized, double-blind, 14-week comparison of two Dose Levels of GWP42003-P (10 mg/kg/day and 20 mg/kg/day) versus placebo. The treatment period will consist of a two-week titration period followed by a 12-week maintenance period. The treatment period will be followed by a 10-day taper period and a four-week follow-up period. The study will aim to determine the efficacy, safety and tolerability of two Dose Levels of GWP42003-P

	compared with placebo. Following study completion, all patients will be invited to continue to receive GWP42003-P in an open label extension (OLE) study (under a separate protocol).
Primary Endpoint	The primary endpoint is the change in total convulsive seizure frequency during the treatment period (Day 1 to the end of the evaluable period) compared to baseline in patients taking GWP42003-P compared with placebo.
Secondary Endpoint(s)	The following endpoints will be compared between treatment groups over the 14-week, double-blind treatment period: • Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline. • Number of patients considered treatment responders, defined as those with a ≥25%, ≥50% or ≥75% reduction in convulsive seizures from baseline (overall and four-weekly). • Number of patients who are convulsive seizure free. • Change in non-convulsive seizure frequency. • Change in total seizure frequency. • Change in subtypes of seizures. • Changes from baseline in number of episodes of *status epilepticus*. • Changes from baseline in duration of seizure subtypes as assessed by the Caregiver Global Impression of Change in Seizure Duration (CGICSD). • Changes from baseline in usage of rescue medication. • Changes from baseline in number of inpatient hospitalizations due to epilepsy. • Changes from baseline in Sleep Disruption 0–10 Numerical Rating Scale (0–10 NRS) score. • Changes from baseline in Epworth Daytime Sleepiness Scale (EDSS) score. • Changes from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score. • Changes from baseline in the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) score. • Change from baseline in cognitive function as measured with a cognitive assessment battery. • Change from baseline in growth and development by

	measurement of height, weight, insulin-like growth factor-1 (IGF-1) levels and Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty). • Changes from baseline in the Caregiver Global Impression of Change (CGIC) score. **PK:** • The plasma concentrations of CBD and its major metabolites will be determined following single and multiple doses of GWP42003-P. The following PK parameters will be calculated from sparse sampling: – The concentration at each time interval (C_t) of CBD and its metabolites. – Area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable concentration. • Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available. • The plasma concentrations of THC and its major metabolites will be determined at a single time point (Visit 8, two to three hours post-dose) following multiple doses of GWP42003-P. • The concentrations of THC, CBD, and their major metabolites will be determined in urine after multiple doses of GWP42003-P. The safety profile of GWP42003-P compared with placebo will also be assessed at each Dose Level by measuring: • Adverse events (AEs). • Vital signs. • Physical examination parameters. • 12-lead Electrocardiogram (ECG). • Clinical laboratory parameters. • Columbia-Suicide Severity Rating Scale (C-SSRS) score. • Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale (PCWS) score, as appropriate. • Abuse liability. • Effects on menstruation cycles (in females).
Sample Size	A total of 186 patients will be randomized to one of four treatment groups (GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The randomization will be stratified by age group (2–5 years, 6–12 years

	and 13–18 years). The placebo groups will be pooled for the analyses of efficacy. For a Wilcoxon–Mann–Whitney test comparing two distributions with a two-sided significance level of 0.05, a sample size of 62 per group is required to obtain a power of at least 80%. This is based on a gamma distribution for the GWP42003-P groups with scale parameter of 65.614 and shape parameter of 1.0886, and a gamma distribution for the placebo group with scale parameter of 40.887 and shape parameter of 2.3059. Maximum likelihood estimates using the Newton-Raphson approximation were computed for the scale and shape parameters using data from study GWEP1332 Part B.
Summary of Patient Eligibility Criteria	**Inclusion:** Patients meeting the following criteria will be considered eligible for this study: • Patient and/or parent(s)/legal representative must be willing and able to give informed assent/consent for participation in the study (see Section 15.2). • Patient and their caregiver must be willing and able (in the investigator's opinion) to comply with all study requirements. • Patient must be male or female aged between two and 18 years (inclusive). • Patient must have a documented history of DS which is not completely controlled by current AEDs. • Patient must be experiencing **four or more** convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period. • Patient must be taking one or more AEDs at a dose which has/have been stable for at least four weeks. • All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for four weeks prior to screening and patient and caregiver are willing to maintain a stable regimen throughout the study. The ketogenic diet and VNS treatments are not counted as an AED. • Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant to be notified of participation in the study. • Patient has completed their Interactive Voice Response System (IVRS) telephone diary on at least 25 days of the baseline period; patients who are non-compliant will be deemed ineligible to continue.

	Exclusion: The patient may not enter the study if ANY of the following apply: • Patient has clinically significant unstable medical conditions other than epilepsy. • Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or randomization, other than epilepsy. • Patient has clinically significant abnormal laboratory values, in the investigator's opinion, at screening or randomization. • Patient has clinically relevant abnormalities in the ECG measured at screening or randomization. • Patient has any concurrent cardiovascular conditions which will, in the investigator's opinion, interfere with the ability to assess their ECGs. • Patient has a history or presence of alcohol or substance abuse within the last two years prior to the study or daily consumption of five or more alcohol-containing beverages. • 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 is unwilling to abstain from using recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) during the study. • Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure due to postural changes. • Patient has ingested alcohol in the 24-hour period prior to the first study visit and/or is unwilling to abstain from drinking alcohol throughout the treatment period. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMPs (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 or planning pregnancy during the course of the study and for three months thereafter. • Patient has been part of a clinical trial involving another IMP in the previous six months. • 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 affect the patient's ability to participate in the study. • Patient has significantly impaired hepatic function at screening (Visit 1) or randomization (Visit 2), defined as **any** of the following: – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN). – ALT or AST >3 × ULN **and** (total bilirubin [TBL] >2 × ULN **or** international normalized ratio [INR] >1.5). – ALT or AST >3 × 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. • 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. • Patient is unwilling to abstain from donation of blood during the study. • There are plans for the patient to travel outside their country of residence during the study. • Patient has previously been randomized into this study. • Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS at screening.
Criteria for Withdrawal	The patient must be withdrawn from the study if any of the following apply: • 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/assent. • Withdrawal of parent(s)/legal representative consent. • Lost to follow-up. • ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). • ALT or AST >8 × ULN. • ALT or AST >5 × ULN for more than two weeks. • ALT >3 × ULN or AST >3 × ULN **and** (TBL >2 × ULN **or** INR >1.5). 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.
Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration	GWP42003-P oral solution (100 mg/mL CBD in sesame oil with anhydrous ethanol, added sweetener [sucralose] and strawberry flavoring). Placebo oral solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. Dosage: Patients will titrate the IMP to the target Dose Level (10 mg/kg/day or 20 mg/kg/day). Patients will then remain at this Dose Level for the duration of the treatment period of the study. IMP will be taken twice daily (morning and evening).
Control Group	The control group will receive placebo matching the assigned IMP Dose Level.
Procedures	During Visit 1 (Day −28), the following assessments will be made: demographics, medical history (including seizure frequency over the last six months, *SCN1A* mutation status, history of epilepsy-specific genetic testing and all prior AEDs taken), vital signs, postural blood pressure, physical examination (including height and body weight), ECG, C-SSRS (Children's Baseline), and visit procedure-related

	AEs. If the mutation status of *SCN1A* is unknown, a blood sample will be taken for *SCN1A* analysis (this can be taken at any visit during the study). Clinical laboratory samples (urine [where possible] and blood) will be taken for hematology, biochemistry, urinalysis, a urine Δ^9-tetrahydrocannabinol (THC) screen and a serum pregnancy test (if appropriate). Patients or their caregivers will also be asked for information regarding concomitant medications and/or changes to medication (including AEDs). Eligible patients will then begin the 28 (+3)-day baseline period. Patients or their caregivers will be issued with IVRS details and will be instructed on how to use it to record daily seizure information. Patients or their caregivers will also be given a paper diary to record usage of IMP, rescue medication, concomitant AEDs and AEs, and will be instructed on how to do so. At each subsequent clinic visit (Visits 2, 3, 4, 6 and 8), the following assessments will be made: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC (assessment not completed at Visit 2), cognitive assessment battery by participating sites (Visits 2 and 8 only), QOLCE (Visits 2 and 8 only), C-SSRS (Children's Since Last Visit), the Vineland-II and the CGICSD (assessment at Visit 8 only). For those patients who weigh ≥20 kg, blood samples will be taken for PK determination of CBD (Visit 2 and 8) and THC (Visit 8 only, at a single time point), and provided the risk/benefit outcome is favorable in the investigator's opinion, for measurement of concomitant AED plasma concentrations (all patients; Visits 2, 4, 6 and 8). A urine sample (complete void) will be collected for measurement of THC, CBD and their major metabolites at Visit 8. Clinical laboratory samples (urine [where possible] and blood) will be taken for hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen from Visit 2 onwards. After 28 (+3) days, patients will return to the clinic at Visit 2 (Day 1). Patients will be instructed to record the dosing time of their concomitant AEDs in the diary. In addition to the above assessments, postural blood pressure, details on normal menstruation cycles (for females), Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) and the CWS/PCWS will be assessed; samples will also be taken for the determination of THC levels, IGF-1 levels and pregnancy (if appropriate). The investigator

	will assess the patient's daily number of convulsive seizures from the patient's IVRS data. Patients who have experienced four or more convulsive seizures (i.e., tonic-clonic, tonic, clonic or atonic seizures) during the first 28 days of the baseline period and who meet all of the other inclusion and none of the exclusion criteria will be eligible to continue in the study. If a patient does not meet the eligibility criteria within this period, consideration will be given to rescreen at a later date. Eligible patients will then be randomized to receive GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent at a 2:2:1:1 ratio using the IVRS. At Visit 2, caregivers will be asked to write a brief description of the patient's overall condition and to assess the average duration of seizure subtypes as a memory aid for the CGIC and CGICSD respectively. These will be referred to at relevant subsequent visits or withdrawal. Patients will then receive sufficient IMP, as assigned by the IVRS, every 28 to 42 days for the 14-week treatment period. Patients or their caregivers will be instructed on using the IVRS's reporting diary, as well as how to complete the paper diary. Blood samples will be collected pre-dose to determine plasma concentrations of CBD and its major metabolites (only patients who weigh ≥20 kg) and, provided the risk/benefit outcome is favorable in the investigator's opinion, concomitant AEDs (all patients). Patients will then be given their first dose of IMP while in the clinic. Vital signs and ECG will be re-assessed two to three hours post-dose. For CBD PK, patients who weigh ≥20 kg will have two further blood samples taken for PK analyses: at two to three hours post-dose and four to six hours post-dose. There must be a minimum period of at least two hours between each of the three PK time-points. Patients will titrate to the target Dose Level using the regimen provided via the IVRS. If an unacceptable AE develops at any time during titration, dosing should initially be suspended or amended, as appropriate, until the event has resolved or is well tolerated. After titration, patients should continue on a stable dosing regimen at the dose they achieved at the end of the titration period. If that dose becomes poorly tolerated during the post-titration period, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study. However, where possible, the patient should be encouraged to return to the target dose. Patients will return to the clinic for further visits at Visit 3 (Day 15±3), Visit 4 (Day 29±3), Visit 6 (Day 57±3) and Visit 8 (Day

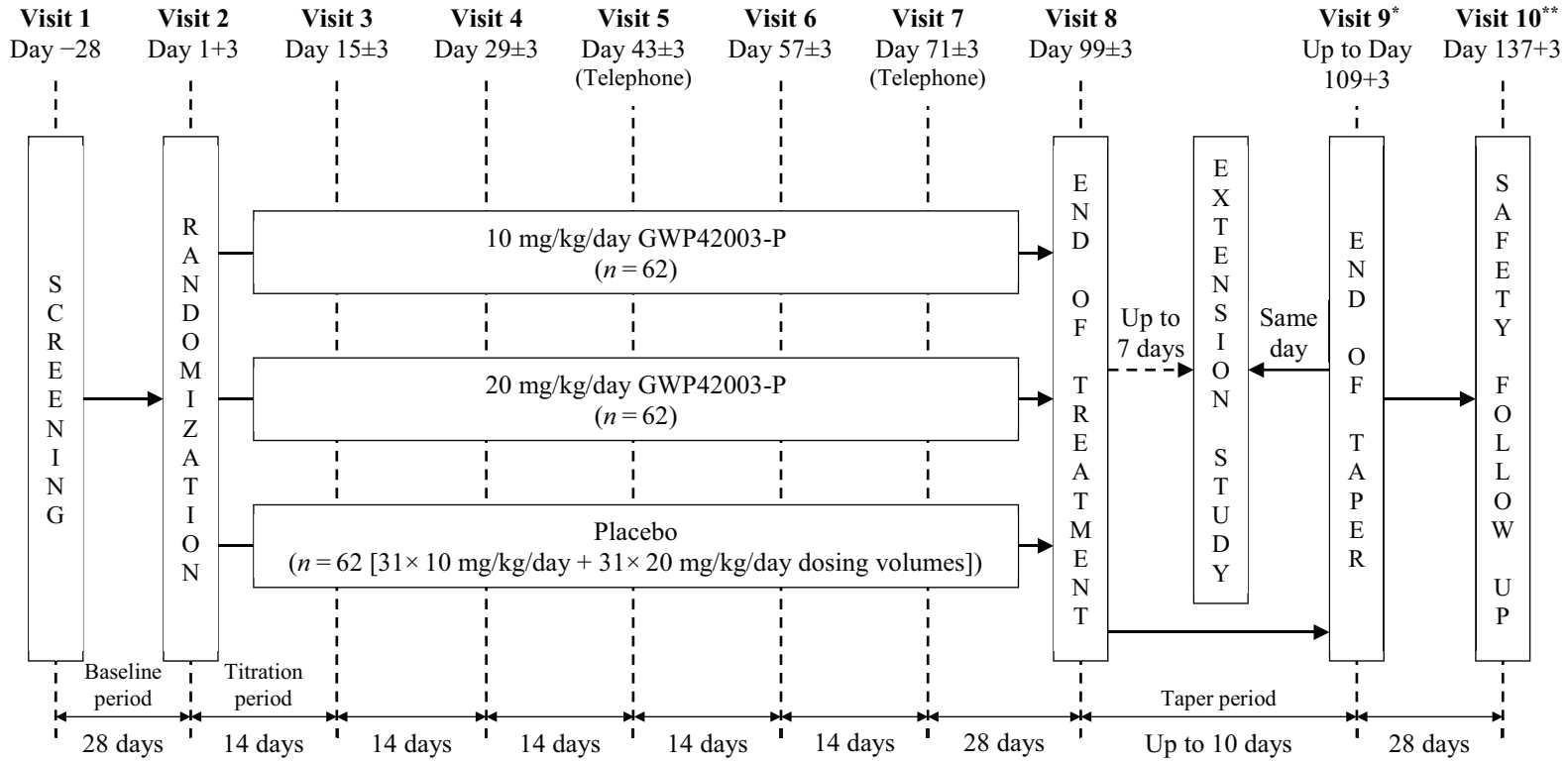
	99±3). At Visits 4, 6 and 8 / the Withdrawal visit, blood samples will be taken prior to administration of IMP for measurement of concomitant AED plasma concentrations, provided the risk/benefit outcome is favorable in the investigator's opinion. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary. Adherence to the titration regimen and compliance will be assessed for safety reasons. Additional safety assessments will be made by telephone at Visit 5 (Day 43±3) and at Visit 7 (Day 71±3). During these calls, patients or their caregivers will be asked for information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to their medication (including AEDs). Visit 8 is the 'End of Treatment'/Withdrawal visit. Patients will have blood samples collected for measurement of concomitant AED plasma concentrations (all patients, provided the risk/benefit outcome is favorable in the investigator's opinion) and PK analyses of CBD, and its major metabolites (only patients who weigh ≥20 kg) at the same time intervals as Visit 2. Patients (≥20 kg in weight) will have blood samples collected for measurement of THC and its major metabolites in plasma at a single time point only (two to three hours after dosing). Patients will also be asked to provide a urine sample for the measurement of CBD, THC, and their major metabolites (complete void) at the time of the first blood sample and the exact urine volume recorded. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary and to record their meal times the day before and the day of Visit 2 and Visit 8. Samples will be taken for determination of THC levels, IGF-1 levels and pregnancy (if appropriate). The Caregiver Impression of IMP Palatability, CGIC, CGICSD, effects on menstruation cycles (for females) and Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will also be assessed. At participating sites the Cognitive Assessment Battery will be repeated at this time (ideally before any other study procedures but can be completed on a separate day, if necessary, within three days of the visit). At Visit 8, patients who have completed all of the scheduled study visits will be offered the option to enter an OLE study. Entry is to be on the same day as Visit 8 (Day 99) or within seven days of Visit 8. Patients not entering the OLE study at this visit will commence a taper period (down-titrating 10% per day for 10 days), and additional IMP will be dispensed, if required. Patients who withdraw early should also begin the taper period following the Withdrawal visit (unless continued dosing is not possible due to an AE). The IVRS will generate the patient's daily IMP dosing volumes for the 10-day

	taper period, during which time IVRS and diary information will continue to be recorded. The taper period may be interrupted if the patient wishes to enter the OLE study within the seven days of Visit 8. Following completion or cessation of the taper period, patients will return to the clinic for Visit 9 ('End of Taper Period' Visit) where the following assessments will be made: vital signs, physical examination (including height and body weight), C-SSRS (Children's Last Visit) and CWS/PCWS. In addition, the following assessments will be made for patients who opt not to enter the OLE study and for those who withdraw early and taper IMP (including withdrawal during the taper period): ECG and clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). For patients who complete treatment but opt not to enter the OLE study, Visit 9 should occur 10 (+3) days after Visit 8 (i.e., on Day 109[+3]). For patients who withdraw early and taper IMP, this visit should occur 10 (+3) days after the Withdrawal visit. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date. For patients who delay entry into the OLE study, Visit 9 should occur on the day the patient enters the OLE study and within seven days of Visit 8 (i.e., up to Day 106), to allow the patient to enter the OLE study within this timeframe. A safety follow-up visit (Visit 10) is required for patients who do not enter the OLE study or who withdraw from the study early. This visit should occur four weeks after Visit 9 (i.e., on Day 137+3), or date of final dosing, and can be conducted by telephone. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). For patients not entering the OLE study, or who withdraw from the study early, safety telephone calls will be made weekly (±3 days) from Visit 9, or date of final dosing, until Visit 10. Patients who enter the OLE study on Day 99 will not complete Visits 9 or 10. **Monitoring of Drug Abuse Liability (for patients 12 years of age and older):** 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 discussion of the event(s) with the patient/caregiver. 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 bottles. Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (Visit 8/Withdrawal visit or Visit 9, as applicable) and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator. 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.
Statistical Considerations	The following endpoints will be described and compared between treatment groups, using appropriate statistical methods, over the 14-week, double-blind treatment period: • Change in total convulsive seizure frequency. • Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline. • Number of patients considered treatment responders, defined as those with a ≥25%, ≥50% or ≥75% reduction in convulsive seizures from baseline (overall and four-weekly). • Number of patients who are convulsive seizure free. • Change in non-convulsive seizure frequency. • Change in total seizure frequency. • Change in subtypes of seizures. • Changes from baseline in number of episodes of *status epilepticus*. • Changes from baseline in duration of seizure subtypes as assessed by the CGICSD. • Change from baseline in use of rescue medication. • Changes from baseline in number of inpatient hospitalizations due to epilepsy. • Changes from baseline in Sleep Disruption 0–10 NRS score.

	• Changes from baseline in EDSS score. • Changes from baseline in QOLCE score. • Change from baseline in cognitive assessment battery. • Changes from baseline in Vineland-II score. • Change from baseline in growth and development by measurement of height, weight, IGF-1 levels and Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty). • Changes from baseline in the CGIC score. • Plasma and urine concentrations of CBD and its major metabolites together with any estimates of PK parameters. • Plasma and urine concentrations of THC and its major metabolites together with any estimates of PK parameters. • Changes in plasma AED levels. There are three treatments, so multiple significance testing will occur when making comparisons between the treatments; the major comparisons of interest are those between each of the GWP42003-P Dose Levels and placebo and, in particular, the 20 mg/kg/day Dose Level and placebo. A step down procedure will be used to control the type I error. The comparison of 20 mg/kg/day GWP42003-P and placebo will be tested first and only if this is statistically significant at the 5% level will the comparison of 10 mg/kg/day GWP42003-P and placebo be tested. All statistical tests will be two-tailed and carried out at the 5% level of significance. All safety data will be summarized using appropriate statistical methods.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

Figure 1-1 Study Design and Treatment Schema



* For patients not entering the OLE study at Visit 8 or for those who withdraw early and taper IMP. Patients who complete treatment but opt not to enter the OLE study, or who withdraw from the study early, must have weekly (±3 days) safety telephone calls from Visit 9 (or date of final dosing) until Visit 10.

** For patients not entering the OLE or who withdraw from the study early; can be conducted by telephone.

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List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic drugs
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
$AUC_{(0–t)}$	Area under the plasma concentration curve from time zero to the last measurable concentration
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CGICSD	Caregiver Global Impression of Change in Seizure Duration
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
C_t	Concentration at each time interval
CWS	Cannabis Withdrawal Scale
DS	Dravet syndrome
EC	Ethics Committee
ECG	12-lead Electrocardiogram
EDSS	Epworth Daytime Sleepiness Scale
EEG	Electroencephalogram
ESC	Epilepsy Study Consortium
EU	European Union
GCP	Good Clinical Practice
G-tube	Gastrostomy tube
GW	GW Research Ltd
GWP	GW Pharma Ltd
IB	Investigator Brochure

ICH GCP	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice
IGF-1	Insulin-like Growth Factor-1
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
MAR	Missing at Random
MI	Multiple Imputation
MNAR	Missing Not at Random
N-G tube	Nasogastric tube
NOCB	Next Observation Carried Backward
0–10 NRS	0–10 Numerical Rating Scale
OLE	Open label extension
PCWS	Pediatric Cannabinoid Withdrawal Scale
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PVD	Pharmacovigilance Department
QOLCE	Quality of Life in Childhood Epilepsy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCN1A	Voltage-gated sodium channel α1 subunit gene
SMEI	Severe Myoclonic Epilepsy in Infancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
THC	Δ^9-tetrahydrocannabinol
ULN	Upper limit of normal

Vineland-II	Vineland Adaptive Behavior Scales, Second Edition
VNS	Vagus Nerve Stimulation

Definition of Terms

Term	Definition
Baseline	The 28 (+3)-day period from screening (Visit 1 [Day −28]) to randomization (Visit 2 [Day 1+3]).
Convulsive seizures	Tonic-clonic, tonic, clonic or atonic seizures.
Countable partial seizures	Partial/focal seizures with a motor or behavioral component that allows such seizures to be easily identified and hence counted.
Day 1	The day a patient first receives investigational medicinal product or placebo.
End of treatment	Completion of the treatment period (Visit 8 [Day 99]) or withdrawal.
End of study	Last patient's last visit / last contact; whichever occurs last.
IMP	Investigational Medicinal Product (Study Medication). Used to describe both investigational active product and reference therapy (placebo).
INR	International Normalized Ratio 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.
Status epilepticus	Any seizure lasting for 30 minutes or longer.
Sub-types of seizures	Seizure sub-types can be atonic, tonic, clonic, tonic-clonic, myoclonic, absence (typical and atypical), countable partial and other partial.

2 OBJECTIVES

2.1 Primary

To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the change during the treatment period of the study compared to baseline in convulsive seizure frequency. The dose response effect between two GWP42003-P Dose Levels (10 mg/kg/day and 20 mg/kg/day) and placebo will also be explored. Convulsive seizures are defined as tonic-clonic, tonic, clonic or atonic and non-convulsive seizures as myoclonic, partial or absence.

2.2 Secondary

- To assess changes from baseline in convulsive and non-convulsive seizure frequency, duration, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, quality of life, growth and development, and conduct behavioral and cognitive assessments in patients taking GWP42003-P as an adjunctive treatment, when compared with placebo.
- To determine the pharmacokinetics (PKs) of cannabidiol (CBD) and its major metabolites following single and multiple doses of GWP42003-P and to assess the presence of Δ^9-tetrahydrocannabinol (THC) and its major metabolites in plasma and the presence of THC, CBD and their major metabolites in urine after multiple doses of GWP42003-P.
- To determine effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), where available.
- To assess the safety of both GWP42003-P doses when compared with placebo.

3 BACKGROUND AND RATIONALE

3.1 Disease

Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy in Infancy (SMEI), is a rare form of severe epilepsy with onset in early childhood. It has an incidence of less than one per 40,000 and accounts for 1.4% of epilepsies in children aged <15 years[1,2,3]. DS is characterized by a variety of treatment-resistant seizures (febrile and afebrile, generalized and unilateral, clonic or tonic-clonic) that occur in the first year of life and has a poor cognitive prognosis. Onset usually occurs between four and eight months of age and manifests typically as a prolonged (>15 min) clonic, generalized or unilateral convulsive seizure, often triggered by fever, that can evolve into status epilepticus[4,5,6]. After a typical period of two weeks to two months, further febrile seizures occur and afebrile seizures also appear. In addition to convulsive seizures, other seizure types appear between the ages of one and four years, including myoclonic seizures, focal seizures, atypical absences and obtundation statuses (in which consciousness is impaired). Significant developmental delay becomes apparent from the second year onwards and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common. Beyond five years of age, convulsive seizures decrease but persist and occur mainly in sleep. Myoclonic and absence seizures tend to disappear and focal seizures either persist or decrease. Although psychomotor development and behavior tend to improve over time, cognitive impairment persists throughout the patient's lifetime[4,5,6].

Myoclonic seizures are a defining characteristic of DS and can be massive, predominantly involving axial muscles, or erratic/segmental, which are mainly limited to the distal limbs and face. Massive myoclonic seizures are often associated with electroencephalogram (EEG) paroxysms and can be variable in intensity, with outcomes ranging from falling (drop attack) to causing only small, saccadic movements of the head, shoulders or trunk[4,5,6]. Erratic myoclonic seizures do not have an EEG correlate and are typically mild in intensity, although they can affect fine motor coordination. Some patients with DS experience both massive and erratic myoclonic seizures, yet these seizures can be absent in some DS patients. Such cases are defined as "borderline" SMEI and may have different EEG features to typical SMEI, although the course and outcome of the disease remain the same[2,6,7].

Genetic analyses have revealed that more than 70% of patients with DS have mutations in the voltage-gated sodium channel α1 subunit gene (*SCN1A*)[8,9,10,11,12,13]. *SCN1A* encodes the pore-forming subunit of the $Na_V1.1$ voltage-gated sodium channel and there are currently more than 700 published *SCN1A* mutations, 90% of which occur in DS patients[14]. Approximately two-thirds of these mutations give rise to truncations while the remaining third are missense mutations that are predicted to severely impair channel function[6]. In addition, intragenic and whole gene deletions of *SCN1A* as well as deletions within the 5' promoter sequence have also been identified in DS patients that are otherwise *SCN1A*-mutation-negative[9,10,11,12,13]. Most *SCN1A* mutations in DS patients arise *de novo*, although approximately 5% of cases involve inheritance of familial *SCN1A* mutations from a mildly affected parent[15,16,17,18]. In familial cases of DS, the phenotype and severity of epilepsy can be clinically variable among family members carrying the same *SCN1A* mutation. This heterogeneity is proposed to be due to variable familial expression of *SCN1A* mutations, mediated either by *SCN1A* mosaicisms or by the genetic and environmental background[19,20,21,22]. Candidate modifier genes currently include *SCN9A* (encoding the pore-forming subunit of the $Na_V1.7$ voltage-gated sodium channel) and *CACNB4* (encoding the β4 auxiliary subunit of high-voltage activated calcium channels), variants of which have been found in DS patients with *SCN1A* mutations[23,24]. Mouse models in which *SCN1A* is either mutated or knocked out have demonstrated that the α1 subunit is critical for the excitability and *in vivo* function of inhibitory hippocampal and cortical interneurons[25,26]. Reduced firing of these inhibitory interneurons would compromise network inhibition and cause a hyperexcitable gain-of-function effect that may underlie the severe epilepsy seen in DS. Moreover, *SCN1A* mutant mice reproduce the characteristic temperature- and age-dependent seizures and EEG paroxysms observed in DS, although the phenotypic variability of DS patients with *SCN1A* mutations remains unexplained[27].

More than 20% of patients with DS have no detectable mutations in *SCN1A* and it is possible that many of these patients harbor mutations in regulatory elements located outside coding regions. Familial and *de novo* mutations of *PCDH19* (encoding protocadherin 19) have been reported in a subset of *SCN1A*-mutation-negative DS patients and it is estimated that *PCDH19* mutations could account for 5% of all DS cases[28,29]. Additional genes in which mutations cause DS include *GABRG2* (encoding the γ2 subunit of γ-aminobutyric acid -A receptors), *SCN1B* (encoding the β1 auxiliary

subunit of voltage-gated sodium channels) and *SCN2A* (encoding the pore-forming subunit of the $Na_V1.2$ voltage-gated sodium channel), although very few cases have been reported[30,31,32].

DS is one of the most pharmacoresistant forms of epilepsy, with all seizure types extremely refractory to conventional AEDs, especially during the first several years. Sodium valproate is often used to prevent the initial recurrent convulsive febrile seizures and benzodiazepines (e.g., diazepam, midazolam, clonazepam or clobazam) are frequently co-administered to limit the duration of long-lasting seizures. In most cases however, the relief provided by these agents is insufficient[33,34]. Certain AEDs can paradoxically worsen seizures in DS patients, namely lamotrigine, carbamazepine and vigabatrin, and the use of certain barbiturates at high doses is associated with a poor outcome[35,36,37]. Potassium bromide can be effective at controlling convulsive status epilepticus and was found to be the most efficacious AED in a Japanese cohort of DS patients[38]. A study of DS patients treated with potassium bromide as adjunctive therapy showed a reduction in seizures in 81% of patients in the first three months, with 30% becoming seizure-free[39]. However, this compound has no effect on focal and tonic seizures and any initial efficacy is often not maintained long-term[34,39].

To date, the only AED that has proved efficacious in the majority of DS patients in placebo-controlled, double-blind trials is stiripentol[40,41,42]. In these studies, stiripentol was administered as adjunctive therapy to sodium valproate and clobazam. At least two thirds of patients experienced a >50% reduction in seizure frequency in the stiripentol arms of these studies versus <10% of patients in the placebo arms[40,41]. A subsequent meta-analysis of these studies showed that stiripentol reduced the overall seizure rate by 70%[42]. Both the frequency and duration of seizures remained significantly reduced at a median of 2.9 years follow-up, with the greatest efficacy observed in infants[36]. Both short-term and long-term benefits of stiripentol as adjunctive therapy have also been demonstrated in an open-label study of Japanese DS patients, with responder rates of 61% and 48% at six weeks and six months, respectively[43]. Stiripentol is generally well tolerated and can improve seizure control in DS patients receiving pharmacotherapy other than valproate and/or clobazam[43,44].

Topiramate and levetiracetam are two further AEDs that have undergone preliminary trials as adjunctive therapy in DS patients. In three open-label studies, more than half of

patients receiving topiramate as add-on therapy achieved >50% reduction in seizure frequency, with 17% becoming seizure-free for at least four months in all cases[45,46,47]. Similar results were demonstrated in a single open-label trial of levetiracetam, with 64% of patients experiencing >50% reduction in tonic-clonic seizures at 12 weeks[48]. Although these new AEDs appear promising, larger randomized placebo-controlled studies are required to accurately assess their efficacy in the treatment of DS. Non-pharmacological treatments of DS that have demonstrated benefit as adjunctive therapy to AEDs include vagus nerve stimulation (VNS)[49,50] and the introduction of a ketogenic diet[51,52,53,54]. Despite the therapies listed above, DS remains one of the most pharmacoresistant epilepsy syndromes. Consequently, there is a clear need for new, efficacious pharmaceutical treatments.

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 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 0.15% (w/w) THC (for oral formulations). 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 CB_1 and CB_2 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 conduction of ion channels and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1[55] and the orphan receptor GPR55[56]. Importantly, CBD lacks detectable psychoactivity as found with THC. Further to this, CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-

inflammatory activity[57]. Very little data concerning adverse events (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 humans[58].

3.3 Rationale

Given the limitations of current synthetic AEDs, it has been hypothesized that CBD can be tested for efficacy in children with pharmacoresistant epilepsy[59]. 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 >80% reduction in seizure frequency[60]. The majority of children had been diagnosed with DS, two thirds of which experienced ≥50% reduction in seizure frequency with one patient (8.3%) achieving complete seizure freedom. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

The primary objective of this study is to evaluate the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the change during the treatment period of the study compared to baseline in convulsive seizure frequency, in children and young adults with DS. The dose response effect between two GWP42003-P Dose Levels (10 mg/kg/day and 20 mg/kg/day) and placebo will also be explored. Additional objectives include evaluating changes from baseline in non-convulsive seizure frequency, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, cognitive function, quality of life and adaptive behaviors in patients taking GWP42003-P in combination with AEDs compared with placebo. These endpoints are among those recommended by the European Medicines Agency guideline on clinical investigation of medicinal products in the treatment of epileptic disorders[61].

3.3.1 Selection of Study Dose

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[62], which, assuming an average weight of 70 kg, equates to 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[58], which, in a 70 kg human, equates to a daily dose of 21.4 mg/kg CBD.

GWP42003-P is currently being used by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies in two open Individual Expanded Access Investigational New Drug (IND) studies and five open Intermediate Expanded Access IND studies. In the ongoing Individual Expanded Access IND studies, the initial dosing has been cautious (100 mg [morning] + 150 mg [afternoon/evening]), progressively increasing to 400 mg CBD/day; doses up to 22 mg/kg per day have been well tolerated in an individual pediatric patient. The Sponsor is not aware of any safety issues arising from the dosing used in the Individual Expanded Access INDs. Treatment is expected to begin imminently in the Intermediate Expanded Access INDs. Based on the above, a daily maximum dose of 20 mg/kg CBD (given as two divided doses) was selected for the phase two/three study in patients with DS (GWEP1332). At the end of Part A of the GWEP1332 study a Data Safety Monitoring Committee recommended the target maximum dose of 20 mg/kg/day and titration schedule for all subsequent studies, including this study (GWEP1424; see APPENDIX 4). During the maintenance phase, investigators may decrease the dose if a patient experiences intolerance. Patients whose dose has been decreased can have their dose increased again, if the tolerability improves.

3.4 Clinical Hypothesis

Pre-clinical studies have shown CBD to have anti-seizure and antiepileptic activity in a range of models. Anecdotal evidence and some literature reports[60] suggest that CBD is an effective AED in children with DS as discussed in Section 3.3. The hypothesis underlying this study is that CBD has a positive risk/benefit outcome in the adjunctive treatment of DS.

4 EXPERIMENTAL PLAN

4.1 Study Design

This study is a randomized, double-blind, 14-week comparison of two Dose Levels of GWP42003-P (10 mg/kg/day and 20 mg/kg/day) versus placebo. The treatment period will consist of a two-week titration period followed by a 12-week maintenance period. The treatment period will be followed by a 10-day taper period and a four-week follow-up period. The study will aim to determine the efficacy, safety and tolerability of two Dose Levels of GWP42003-P compared with placebo.

Following study completion, all patients will be invited to continue to receive GWP42003-P in an open label extension (OLE) study (under a separate protocol).

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 is provided in Section 8 and Section 9, respectively.

4.1.1 Primary Endpoint

The primary endpoint is the change in total convulsive seizure frequency during the treatment period (Day 1 to the end of the evaluable period) compared to baseline in patients taking GWP42003-P compared with placebo.

4.1.2 Secondary Endpoint(s)

The following endpoints will be compared between treatment groups over the 14-week, double-blind treatment period:

- Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline.
- Number of patients considered treatment responders, defined as those with a ≥25%, ≥50% or ≥75% reduction in convulsive seizures from baseline (overall and four-weekly).
- Number of patients who are convulsive seizure free.
- Change in non-convulsive seizure frequency.
- Change in total seizure frequency.

- Change in subtypes of seizures.
- Changes from baseline in number of episodes of *status epilepticus*.
- Changes from baseline in duration of seizure subtypes as assessed by the Caregiver Global Impression of Change in Seizure Duration (CGICSD).
- Changes from baseline in usage of rescue medication.
- Changes from baseline in number of inpatient hospitalizations due to epilepsy.
- Changes from baseline in Sleep Disruption 0–10 Numerical Rating Scale (0–10 NRS) score.
- Changes from baseline in Epworth Daytime Sleepiness Scale (EDSS) score.
- Changes from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score.
- Change from baseline in cognitive function as measured with a cognitive assessment battery.
- Changes from baseline in the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) score.
- Change from baseline in growth and development by measurement of height, weight, insulin-like growth factor-1 (IGF-1) levels and Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).
- Changes from baseline in the Caregiver Global Impression of Change (CGIC) score.

PK:

- The plasma concentrations of CBD and its major metabolites will be determined following single and multiple doses of GWP42003-P. The following PK parameters will be calculated from sparse sampling:
  - The concentration at each time interval (C_t) of CBD and its metabolites.
  - Area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable concentration.

- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.
- The plasma concentrations of THC and its major metabolites will be determined at a single time point (Visit 8, two to three hours post-dose) following multiple doses of GWP42003-P.
- The concentrations of THC, CBD, and their major metabolites will be determined in urine after multiple doses of GWP42003-P.

The safety profile of GWP42003-P compared with placebo will also be assessed at each Dose Level by measuring:

- AEs.
- Vital signs.
- Physical examination parameters.
- 12-lead Electrocardiogram (ECG).
- Clinical laboratory parameters.
- Columbia-Suicide Severity Rating Scale (C-SSRS) score.
- Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale (PCWS) score, as appropriate.
- Abuse liability.
- Effects on menstruation cycles (in females).

4.2 Number of Centers

Approximately 30 centers are expected to participate in this study.

4.3 Number of Patients

If patients fail screening they will be replaced until the target numbers of patients are achieved.

A total of 186 patients will be randomized to one of four treatment groups (GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio.

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 Labeling

The IMP will be manufactured and packaged by GW Pharma Ltd (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 relevant visit considering the dose group and 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 and the IMP information held on the Interactive Voice Response System (IVRS). GWP will ensure that all IMP provided is fully labeled and packaged. Label text will comply with

European Union (EU) guidance on Good Manufacturing Practice, Annex 13 Labelling. 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, 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 via the IVRS 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 (against the IVRS Shipment Request) and the condition of the drug. Details of the IMP received will be recorded in the IMP accountability record (see Section 5.3.4). The site will acknowledge IMP receipt via the IVRS and will complete any receipt forms required. IMP will be dispensed and returned as detailed in Section 8.4 with further IMP shipments to be initiated by the IVRS. 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 an authorized GW or GWP representative and local officials or regulatory agency inspectors.

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

6 PATIENT ELIGIBILITY

Investigators will be required to maintain a log that includes limited information about all screened patients (initials, age, sex; as allowed per local regulations) and outcome of screening. After the screening visit, investigators will submit the patient's documented history of DS and seizures directly to the Epilepsy Study Consortium (ESC) for confirmation of diagnosis and verification of seizure types. The ESC may ask the investigator for additional information to assist in their decision. The ESC will provide written confirmation directly to the investigator.

6.1 Inclusion Criteria

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

6.1.1 Patient and/or parent(s)/legal representative must be willing and able to give informed assent/consent for participation in the study (see Section 15.2).

6.1.2 Patient and their caregiver must be willing and able (in the investigator's opinion) to comply with all study requirements.

6.1.3 Patient must be male or female aged between two and 18 years (inclusive).

6.1.4 Patient must have a documented history of DS which is not completely controlled by current AEDs.

6.1.5 Patient must be experiencing **four or more** convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period.

6.1.6 Patient must be taking one or more AEDs at a dose which has/have been stable for at least four weeks.

6.1.7 All medications or interventions for epilepsy (including ketogenic diet and VNS) must have been stable for four weeks prior to screening and patient and caregiver are willing to maintain a stable regimen throughout the study. The ketogenic diet and VNS treatments are not counted as an AED.

6.1.8 Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant to be notified of participation in the study.

6.1.9 Patient has completed their IVRS telephone diary on at least 25 days of the baseline period; patients who are non-compliant will be deemed ineligible to continue.

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 Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or randomization, other than epilepsy.

6.2.3 Patient has clinically significant abnormal laboratory values, in the investigator's opinion, at screening or randomization.

6.2.4 Patient has clinically relevant abnormalities in the ECG measured at screening or randomization.

6.2.5 Patient has any concurrent cardiovascular conditions which will, in the investigator's opinion, interfere with the ability to assess their ECGs.

6.2.6 Patient has a history or presence of alcohol or substance abuse within the last two years prior to the study or daily consumption of five or more alcohol-containing beverages.

6.2.7 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.

6.2.8 Patient is unwilling to abstain from using recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) during the study.

6.2.9 Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure due to postural changes.

6.2.10 Patient has ingested alcohol in the 24-hour period prior to the first study visit and/or is unwilling to abstain from drinking alcohol throughout the treatment period.

6.2.11 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMPs (e.g., sesame oil).

6.2.12 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.

6.2.13 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.

6.2.14 Patient has been part of a clinical trial involving another IMP in the previous six months.

6.2.15 Patient is taking felbamate and they have been taking it for less than one year prior to screening.

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 affect the patient's ability to participate in the study.

6.2.17 Patient has significantly impaired hepatic function at screening (Visit 1) or randomization (Visit 2), defined as **any** of the following:

i) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN).
ii) ALT or AST >3 × ULN **and** (total bilirubin [TBL] >2 × ULN **or** international normalized ratio [INR] >1.5).
iii) ALT or AST >3 × 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.

6.2.18 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 is unwilling to abstain from donation of blood during the study.

6.2.20 There are plans for the patient to travel outside their country of residence during the study.

6.2.21 Patient has previously been randomized into this study.

6.2.22 Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS at screening.

7 PATIENT ENROLLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center's Ethical Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent/assent forms and other patient information material. Patients will be considered enrolled in the study from the time of providing written informed consent/assent. All patients and/or parent(s)/legal representatives, where appropriate, must personally sign and date the consent/assent form prior to any procedures being performed (refer to Section 9.1.1 and Section 15.2).

7.1 Treatment Assignment

At the start of Visit 1, a screening number will be assigned to each patient using an IVRS. After completion of assessments and confirmation of eligibility at Visit 2, patients will be assigned a unique patient number (to be used for the remaining duration of the study) and randomly allocated to one of four treatment groups (GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio using the IVRS. GWP will provide all IMP in a packed and labeled state and the IVRS will identify the pack number to be dispensed to the patient at each visit, according to the treatment assigned in the randomization schedule.

7.2 Randomization

The allocation of IMP to treatment number will be done according to a randomization schedule produced by an independent statistician. The randomization schedule will be held centrally and not divulged to any other person involved in the study until the database has been locked and unblinding authorized by the relevant GW personnel. The randomization will be stratified by age group (2–5 years, 6–12 years and 13–18 years).

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.

Patients will be assigned to receive GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy.

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 will be swallowed and may be taken with other concomitant medications, as directed by the investigator.

If the patient has a gastrostomy tube (G-tube) or nasogastric tube (N-G tube) fitted and has difficulty swallowing then IMP may be dosed via G/N-G tube, following discussion with the GW medical monitor.

8.1.2 Dose Escalation, Dose Adjustments and Down-Titration

The titration regimen is shown in APPENDIX 4. All patients will be weighed during Visit 2 and the daily volumes of IMP solution to be taken during the two-week titration period and for the remainder of the maintenance period will be calculated via the IVRS and the dosing regimen provided to the patient and/or caregiver. Patients should achieve their target Dose Level before the end of the two-week titration period; however, the titration period will be considered two weeks long to ensure all patients have achieved stable dosing from Visit 3 onwards (maintenance period). 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 1) and their final maintenance dose of IMP at Visit 8 (Day 99). If an unacceptable AE develops at any time during the titration period, dosing should initially be suspended or amended, at the investigator's discretion, until the event has resolved or is well tolerated. During the maintenance period, patients should continue on a stable dosing regimen at the target Dose Level. If that dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period. However, where possible, the patient should be encouraged to return to the target Dose Level.

Patients who do not immediately enter the OLE study at Visit 8 will have their dose of IMP tapered gradually (10% each day) over a period of 10 days. However, the taper period may be interrupted if the patient wishes to enter the OLE study within seven days of Visit 8. Patients who withdraw early should also begin the taper period following the Withdrawal visit (unless continued dosing is not possible due to an AE). Patients participating in the taper period will return used and unused IMP to the clinic at Visit 9 ('End of Taper Period' visit).

8.2 Concomitant Therapy

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant AEDs must have been stable for at least four weeks prior to screening and must remain stable throughout the study period. If there are any clinical symptoms of concern, thought to be linked to interaction of IMP with other AEDs then this should be discussed with the GW medical monitor. Adjustments to AEDs are permitted in these cases of safety concern. Any changes to AEDs must be recorded in the CRF. Further information on drug interactions can be found in the Investigator Brochure (IB)[63].

The use of rescue medication is allowed when necessary. 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 screening 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/assent. 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 during the assessment of the evaluable period (see Section 13.6.1).

- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.
- 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.
- Felbamate if taken for less than one year prior to screening.

8.4 Compliance in Investigational Medicinal Product Administration

The IMP is dispensed to the patient at each of the following visits:

- Visit 2 (Day 1).
- Visit 4 (Day 29).
- Visit 6 (Day 57).
- Visit 8 (Day 99) (for patients not entering the OLE study on Day 99; if required).

Patients or their caregivers will confirm the daily dose has been administered using the IVRS and record the total volume of IMP administered on each treatment day using the paper diary. Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 4, 6, 8 and 9). The site will check the returned IMP against the usage recorded using the IVRS report and paper diary. 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.

Refer to Section 9.1.16.2.1 for the list of 'Triggering Drug Accountability Discrepancies' associated with monitoring of drug abuse liability.

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 site, or his/her designee, is responsible for ensuring that information on how to access the IVRS for an individual patient is available to the relevant staff in case of an emergency and unblinding is required. A patient's treatment assignment should 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 prior to doing so. 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 reason(s) 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

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. 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 (CPMP/ICH/286/95 mod)[64]. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence. Abstinence 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. Female patients of child bearing potential must test negative for pregnancy to be eligible for the study.

9.1.1 Informed Consent/Assent

The parent(s)/legal representative of minor patients must personally sign and date the EC/IRB approved consent form before any study specific procedures are performed or any patient related data is recorded for the study. In addition, in cases where the patient possesses adequate understanding, assent will be taken along with parent(s)/legal representative consent, using EC/IRB approved assent forms. Assent is defined as the minor's permission or affirmative agreement to participate in the study. The explicit wish of a minor, who is capable of forming an opinion and assessing the information provided, to refuse participation in, or to be withdrawn from, the clinical trial at any time must be considered by the investigator.

Adult patients with an adequate level of understanding must personally sign and date the EC/IRB approved informed consent form before any study specific procedures are performed or any patient related data are recorded for the study. For adult patients with

an insufficient level of understanding of what is proposed, only parent(s)/legal representative consent will be sought.

For patients who go from being a minor to an adult (as per the country or state's age-of-majority regulation) during the course of the study, a new informed consent will be signed if the participant possesses an adequate understanding to do so.

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

9.1.2 Demographics

The following information will be obtained for each patient: date of birth, sex and race (as allowed per local regulations).

9.1.3 Medical History

Relevant, significant medical history (including seizure frequency over the last six months, history of epilepsy-specific genetic testing and all prior AEDs taken) will be obtained and is defined as any condition or disease that:

- May affect the condition under study.
- Is ongoing on entry into the study.
- Has occurred within one year prior to screening (Visit 1).

The mutation status (positive or negative for mutation) of the *SCN1A* gene will be determined through the patient's medical records. If the mutation status of *SCN1A* is unknown, *SCN1A* analysis will be carried out during the study analysis (a blood sample can be taken at any clinic visit).

9.1.4 Inpatient Epilepsy-Related Hospitalizations

The number of inpatient hospitalizations that are, in the investigator's opinion, due to epilepsy will be recorded in the patient's CRF and through the Serious Adverse Event (SAE) reporting process.

9.1.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 14 days), including AEDs, will be recorded at Visit 1. AEDs used during the study should be

maintained at a stable dose. All AEDs used since initiation of treatment (at or prior to diagnosis) should be recorded. 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

Physical examinations will include height and body weight measurements.

9.1.7 Vital Signs

Vital sign measurements, taken in a sitting position at rest for five minutes, will be completed alongside the physical examination. Postural blood pressure should be measured after five minutes in supine position and, if possible, two minutes in standing position. Blood pressure 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 a supine position. 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 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). Analysis of all clinical blood samples, pregnancy tests (using serum at Visits 1, 2 and 8 and using a urine dipstick at Visit 2) and tests to detect the presence of THC will be conducted at a central clinical laboratory.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further urinalysis at the central laboratory (urinalysis, microscopy, culture and sensitivity, as applicable). Urine pregnancy tests (using a dipstick) will be performed at the study center. In cases where urine samples cannot be analyzed at site due to local regulations, a full set of urine samples should be sent to the central laboratory for analysis.

The THC results will be reported back to the study site to permit confirmation of eligibility and to be used as a measure of study compliance (i.e., to confirm that the patient did not take cannabis during the course of the study).

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 or Urine	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				
Insulin-like growth factor-1 (IGF-1)				
Potassium				
Prolactin				
Prothrombin time (plasma)				
Sodium				
Total bilirubin (TBL)				
Total protein				
Triglycerides				
Urea (blood urea nitrogen [BUN])				

Investigators at study sites will be notified of safety laboratory test results. 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 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 the patient 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 during the one-month period leading up to a planned blood draw.

9.1.10 Pharmacokinetic Analyses (Including Plasma Concentrations of Concomitant Antiepileptic Drugs)

Plasma concentrations of concomitant AEDs will be assessed at Visits 2, 4, 6 and 8 / the Withdrawal visit (if possible) for all patients, provided the risk/benefit outcome is favorable in the investigator's opinion. At each visit, blood samples will be taken prior to administration of IMP. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

The plasma concentrations of CBD and its major metabolites will be assessed at Visits 2 and 8 / the Withdrawal visit (if possible). The following PK parameters will be calculated from sparse sampling:

- The concentration at each time interval (C_t) of CBD and its metabolites.
- Area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable concentration.

The plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

The concentrations of THC and its major metabolites in plasma will be assessed at a single time point (Visit 8; two to three hours post-dose).

A urine sample (complete void) at the time of blood sample collection will be used to determine the concentrations of CBD, THC, and their major metabolites after multiple doses of GWP42003-P. The exact urine volume will be recorded and patients will be instructed to record their meal times the day before and the day of Visit 2 and Visit 8 in

the diary. Blood samples will be taken as follows, provided that the patient is 20 kg in weight or above:

- One sample pre-dose (i.e., prior to administration of IMP).
- One sample between two and three hours post-dose.
- One sample between four and six hours post-dose.

There must be a minimum period of at least two hours between each of the three blood sampling time-points.

At Visit 8 / the Withdrawal visit (if possible), blood samples must be taken at the same time intervals as at Visit 2. Analysis of all PK samples will be conducted at a central clinical laboratory using validated liquid chromatography-tandem mass spectrometry assays. 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 a month of and during the study and to inform the investigator if they suffered any blood loss.

9.1.11 Interactive Voice Response System

The IVRS will be used to collect patient reported diary data (refer to Section 9.1.13), to assign patients to treatment groups and to provide treatment allocation information in the event of patient unblinding. The IVRS will also be used to manage IMP supply.

A member of the study team must contact the IVRS at each clinic visit in order to:

- Obtain a patient's screening number (Visit 1).
- Randomize a patient and obtain their patient number (Visit 2).
- Obtain dispensing information (Visits 2, 4, 6 and 8).
- Provide completion/taper/premature termination information (Visit 8/Withdrawal visit or Visit 9, as applicable).

Training will be given to all sites prior to the start of the study.

9.1.12 Questionnaires and Assessments Completed at Scheduled Visits

Questionnaires should be completed by the caregiver. The same person should complete/answer the questionnaires/assessments in order to maintain consistency. The C-SSRS will be administered by a trained rater.

9.1.12.1 Sleep Disruption 0–10 Numerical Rating Scale

The patient's caregiver will be asked:

- "On a scale of '0 to 10', please indicate the number that best describes your child's sleep disruption in the last week."

The markers range from 0 = slept extremely well, to 10 = unable to sleep at all.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

9.1.12.2 Epworth Daytime Sleepiness Scale

The EDSS is a questionnaire that provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The EDSS contains eight questions that are rated on a four-point numerical scale (0–3). The total EDSS score is the sum of the eight item-scores and can range between 0 and 24. Higher total scores represent greater levels of daytime sleepiness.

The EDSS will be completed by the patient's caregiver.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

9.1.12.3 Caregiver Global Impression of Change

The CGIC comprises the following question to be rated on a seven-point scale:

- Since your child started treatment, please assess the status of your child's overall condition (comparing their condition now to their condition before treatment) using the scale below.

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

The caregiver will be asked to assess the status of the patient's overall condition at Visit 2 (i.e., prior to commencement of IMP) as a memory aid for subsequent visits.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

9.1.12.4 Caregiver Global Impression of Change in Seizure Duration

The CGICSD comprises the following question to be rated on a three-point scale for each seizure subtype:

- Since the patient started treatment, please assess the average duration of the patient's seizures (comparing their condition now to their condition before treatment) using the scale below.

The markers are: Average duration of seizures has decreased; Average duration of seizures has stayed the same; Average duration of seizures has increased.

The caregiver will be asked to assess the average duration of the patient's seizures at Visit 2 (i.e., prior to commencement of IMP) as a memory aid for subsequent visits. If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

9.1.12.5 Quality of Life in Childhood Epilepsy

The QOLCE questionnaire was designed specifically to measure quality of life in children with epilepsy and is composed of 16 subscales assessing seven domains of Health Related Quality of Life (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life). The QOLCE must be completed by a parent or caregiver who interacts with the child on a consistent, daily basis. It should take 20–30 minutes to complete.

9.1.12.6 Cognitive Assessment Battery

The cognitive assessment battery will be administered at Visit 2 before receiving study medication and repeated at Visit 8 or when the patient withdraws/completes treatment (ideally before any other study procedures but can be completed on a separate day, if necessary, within three days of the visit). The items are age specific and the age of the patient at entry will be the age used when choosing the items to be given. Children and adults are to complete the battery as able. It is expected that a number of patients will only be able to complete part of the battery and some may not be able to complete it at all. Parent and/or caregivers are to complete certain items. The battery items will only be administered to a sub-group of sites that have the expertise to conduct the assessments.

Each assessment will need to be conducted by an experienced psychometrician. A summary of the battery is shown below in Table 9.1.12.6-1 and Table 9.1.12.6-2.

Table 9.1.12.6-1 Neuropsychological Protocol for Epilepsy Patients Treated with Cannabidiol - Patient Measures

Function	Patient Measures	Age Range	Approximate Administration Time for Psychometrician
Intelligence **IQ**	WPPSI-4 Vocabulary, Matrix Reasoning	2;6 - 5;11 years	30 minutes
	WASI-2 Vocabulary, Matrix Reasoning (Including Wechsler: 'Digit Span' subtest from WISC-4 and WAIS-4; 'Coding' subtest from WISC-4 & WAIS-4; 'Bug Search' from WPPSI-4)	6 - adult	45 minutes
Attention/Executive **Trail Making**	Trail Making Test D-KEFS	9 - adult	5 minutes
Language **Naming** **Fluency**	Expressive One-Word Picture Vocabulary Test-4th Ed	2 - adult	5 minutes
	NEPSY-2 Word Generation	2 - 5 years	5 minutes
	F-A-S and Animals	6 - adult	5 minutes
Visual-Spatial **VMI**	Developmental Test of Visual Motor Integration-6	2 - adult	5 minutes
Fine Motor Speed **Pegs**	Purdue Pegboard	4 - adult	5 minutes

Table 9.1.12.6-2 Neuropsychological Protocol for Epilepsy Patients Treated with Cannabidiol - Parent Measures

Function	Parent Measures	Age Range	Approximate Administration Time for Parents
Executive	Behavior Rating Inventory of Executive Function (Parent and Teacher)	3 - 21 years	10 minutes
Attention	ADHD Checklist (Parent and Teacher)	All ages	5 minutes
Mood/Anxiety	BASC-2 (Parent and Teacher)	3 - 21 years	20 minutes
Free-form report	Behavior Report Form (Parent and Teacher)	All ages	5 minutes

9.1.12.7 Vineland Adaptive Behavior Scales (Second Edition)

The Vineland-II is an individually administered instrument for assessing adaptive behaviors. Communication, Daily Living Skills, Socialization, and Motor Skills will be assessed by the caregiver using a rating scale.

9.1.12.8 Columbia-Suicide Severity Rating Scale (Children's)

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. At screening (Visit 1), questions will be in relation to lifetime experiences (Children's Baseline). Questioning at all subsequent visits will be in relation to the last assessment (Children's Since Last Visit).

The C-SSRS is to be administered by the investigator or his/her qualified designee at every visit as indicated in the Schedule of Assessments (see APPENDIX 1); "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. The survey should be completed by the same assessor, where possible, throughout the study. Assessments will be conducted only if patients are of an appropriate age (six years of age and older) and capable of understanding and answering the questions, in the investigator's opinion.

9.1.12.9 Caregiver Impression of Investigational Medicinal Product Palatability

The caregiver will be asked the following question to be rated on a five-point scale:

- Overall, how acceptable did your child find the study medication?

The markers are: Liked it a lot; Liked it; Neither liked nor disliked it; Didn't like it; Didn't like it at all.

If the main caregiver is not available at the appropriate visit then this information can be captured over the telephone, ideally on the day of the visit or otherwise within three days.

9.1.12.10 Cannabis Withdrawal Scale (18 years) or Pediatric Cannabinoid Withdrawal Scale (4–17 years)

The CWS is a 19-item scale with each item (withdrawal symptom) measured on a 0–10 NRS (0 = Not at all; 5 = Moderately; 10 = Extremely). The patient or their caregiver is asked to record the extent to which each withdrawal symptom was experienced in the last 24 hours and also to rate the negative impact on normal daily activities (i.e., two separate scores are recorded for each item using the same 0–10 NRS). Scores are summed over the 19 items for each measure. The PCWS was developed from the 19-item validated CWS (adults) that assesses mood, behavioral and physical symptoms associated with cannabis, which was based on the Marijuana Withdrawal Checklist. The modified

10-item PCWS was developed from a low literacy version of the CWS. Symptoms specific to adult cannabis withdrawal have been removed and the wording has been amended to be comprehensible to children of the specified age range (aged four to 17). Ratings are based on a four-point scale where 0 = none, 1 = a little bit, 2 = quite a bit, and 3 = a lot. This rating scale has been compacted from the original 11-point Likert scale used for the CWS in order to simplify the range of options to consider for potential intellectually disabled children. The PCWS was designed with epileptic children in mind as a tool to assess the safety of cannabinoid medications with respect to the stimulation of cannabinoid withdrawal syndrome when medications are withdrawn. As there may be a wide range of intellectual or developmental difficulties in severely epileptic children, from no intellectual or developmental impairment to extreme, the PCWS has been designed to be administered by a treating clinician, either directly to the child, or to the parent or caregiver of the child, reflecting on the child's symptoms within the chosen timeframe.

The CWS/PCWS will be used at Visit 2, to establish a baseline score, and then again at Visit 9, the safety follow-up telephone call on day 123 (±3) and Visit 10 for any patient completing the study or withdrawing early (see APPENDIX 1). Patients entering the OLE on the day of Visit 8 will continue taking IMP; in this instance withdrawal will be evaluated at the end of their participation in the OLE. For patients who delay entry into the OLE study, Visit 9 should occur on the day the patient enters the OLE study (and within seven days of Visit 8) and will include CWS/PCWS.

Assessments will be conducted only if patients are of an appropriate age (four years of age and older).

9.1.12.11 Menstruation

Caregivers will be asked if the female patient is menstruating and details will be recorded as part of their medical history (Visit 2); any changes in normal cycles will be captured at Visit 8 / the Withdrawal visit.

9.1.12.12 Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent/assent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed using Tanner Staging[65] (see APPENDIX 2). The patients will undergo a discreet physical examination and be

assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only).

Patients will be examined at Visit 2 and Visit 8 / the Withdrawal visit. Once a patient reaches a score of V (i.e., 5) the examination need not be performed again.

9.1.13 Patient Diary

Seizure information will be collected through an IVRS telephone diary completed daily throughout the study. The patient or their caregiver will also complete a paper diary daily to record daily IMP dosing volumes, usage of rescue medication, concomitant AEDs and AEs throughout the study. Patients' meal times the day before and the day of Visit 2 and Visit 8 will also be recorded in the paper diary. Seizure counts over 99 for any specific seizure type may also be collected in a paper diary.

The number and type of convulsive and non-convulsive seizures as well as information on usage of rescue medication, concomitant AEDs and AEs will be collected each day from screening (Visit 1) until completion of dosing or withdrawal (Visit 8/Withdrawal visit or Visit 9, as applicable). Information on IMP intake will also be recorded each day from randomization (Visit 2) until completion of dosing or withdrawal (Visit 8/Withdrawal visit or Visit 9, as applicable).

9.1.14 Investigational Medicinal Product Accountability

IMP will be dispensed at each of the following visits:

- Visit 2 (Day 1).
- Visit 4 (Day 29).
- Visit 6 (Day 57).
- Visit 8 (Day 99) (for patients not entering the OLE study on Day 99; if required).

Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 4, 6, 8 and 9). The site will check the returned IMP against the usage recorded using the IVRS report and diary. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

Refer to Section 9.1.16.2.1 for the list of 'Triggering Drug Accountability Discrepancies' associated with monitoring of drug abuse liability.

9.1.15 Adverse Events

Any adverse changes in the patient's medical condition, following completion of the consent/assent 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.

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.

The number of 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 (for Patients 12 Years of Age and Older)

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 8/Withdrawal visit or Visit 9, as applicable) 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 (i.e., Visits 2, 4, 6 and 8): the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations reported within the IVRS report and paper diary.
- At any time that the site is informed by either the IVRS or 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 IVRS report and paper diary.
- Returned IMP supply with evidence of tampering.
- Greater than the target daily dose as recorded in the IVRS report and paper diary.

9.1.16.2.2 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 8/Withdrawal visit or Visit 9, as applicable). 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 12 years of age and older 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

Any triggering AE or triggering drug accountability must be notified to the GW PVD using the same fax number for SAE reporting within 24 hours of becoming aware of the event.

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.

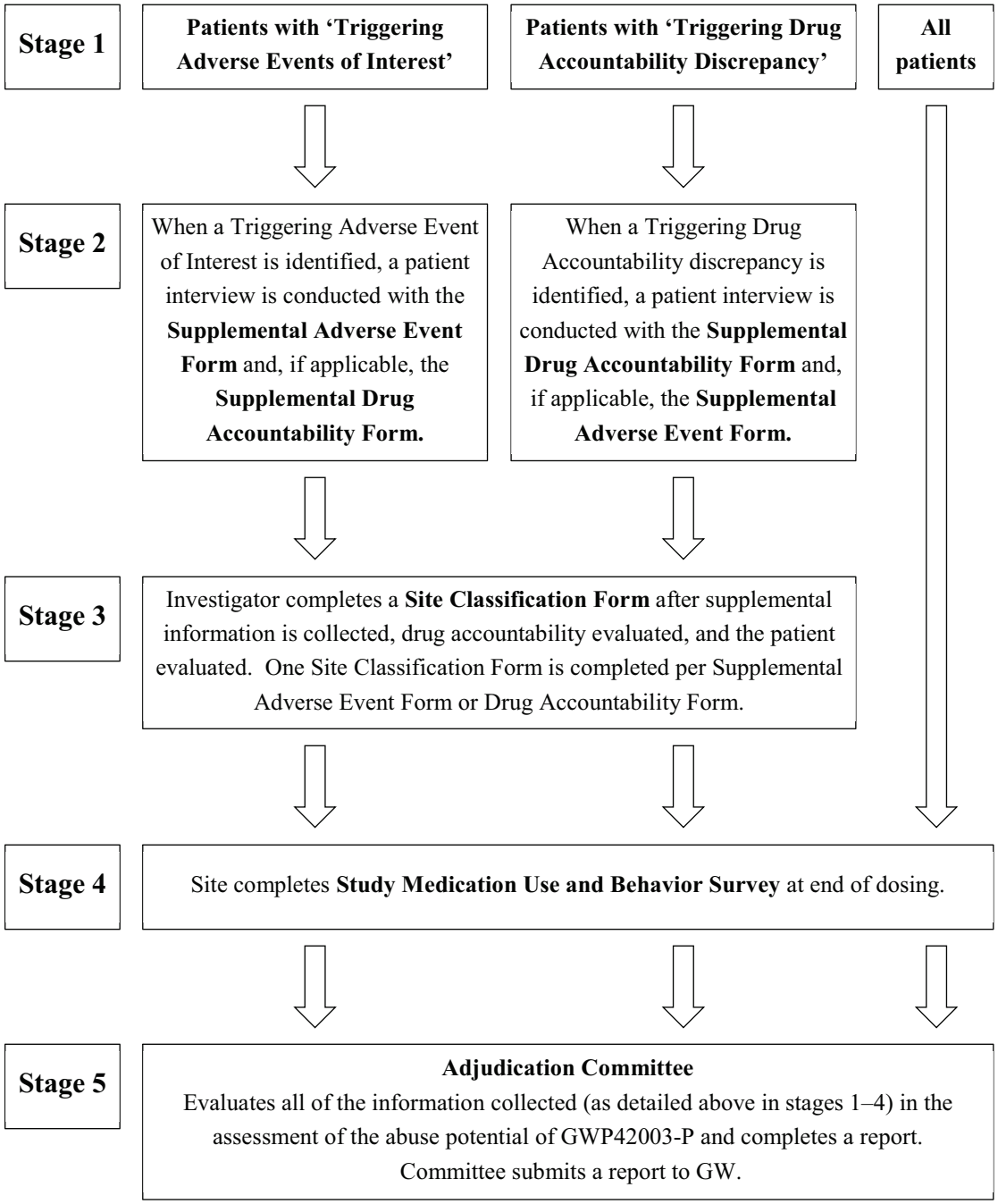
A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- 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 (for Patients 12 Years of Age and Older)**



9.2 Study Procedures by Visit

Patients and their parent(s)/legal representative will be invited to participate in the study and will be issued with the patient information and informed assent or the patient/parent(s)/legal representative information and informed consent (as applicable). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit 1 will be enrolled into the study.

9.2.1 Visit 1 (Day −28, Screening)

The following assessments will be made at Visit 1: demographics, medical history (including seizure frequency over the last six months, history of epilepsy-specific genetic testing and all prior AED medications), vital signs, postural blood pressure, physical examination (including height and body weight), ECG, C-SSRS (Children's Baseline) and visit procedure-related AEs. If the mutation status of *SCN1A* is unknown, a blood sample will be taken for *SCN1A* analysis (this can be taken at any visit during the study). Clinical laboratory samples (urine and blood) will be taken for hematology, biochemistry, urinalysis (where possible), a urine THC screen (required) and a pregnancy test (using a serum sample, as appropriate). Patients or their caregivers will also be asked for information regarding concomitant medications and/or changes to medication (including AEDs). Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will then begin the 28 (+3)-day baseline period.

The IVRS must be contacted by the site to register the screening visit and issue the screening number. If this does not occur, the patient will not be able to call into the telephone diary.

Patients or their caregivers will be issued with the IVRS details and will be instructed on how to use it to record daily seizure information. Patients or their caregivers will also be given a paper diary to record usage of IMP, rescue medication, concomitant AEDs, meal times the day prior to and on the day of Visit 2 and Visit 8, and AEs and will be instructed on how to do so.

The investigator should review the laboratory results as soon as these become available. If the results show a patient is ineligible, the patient must be withdrawn from the study. After the screening visit, investigators will submit the patient's documented history of DS and seizures directly to the ESC for confirmation of DS diagnosis and verification of seizure types (for full details see Section 14). The ESC may ask the investigator for

additional information to assist in their decision. The ESC will provide written confirmation directly to the investigator.

9.2.2 Visit 2 (Day 1, Randomization)

This visit will occur 28 days after Visit 1. A visit window of +3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary. They will also be asked to record their meal times the day before and the day of Visit 2.

The following assessments will be made at Visit 2: vital signs, postural blood pressure, physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) and ECG. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen, determination of serum IGF-1 levels and a pregnancy test, as appropriate (using both a serum sample and urine dipstick test). The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).

The investigator must assess the patient's daily number of convulsive seizures from the patient's IVRS data. Patients who have experienced four or more convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period, and who meet all of the other inclusion and none of the exclusion criteria specified in Section 6, will be eligible to continue in the study. If a patient does not meet the eligibility criteria within this period, consideration will be given to rescreen at a later date.

Eligible patients will then be randomized to receive GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent at a 2:2:1:1 ratio using the IVRS (see Section 7.1).

Following randomization, patients will remain at the clinic where the following assessments will be performed prior to the administration of study medication: EDSS, Sleep Disruption 0–10 NRS, QOLCE, C-SSRS (Children's Since Last Visit), cognitive assessment battery (at participating sites), CWS/PCWS and the Vineland-II. Caregivers will be asked to write a brief description of the patient's overall condition and assess the

average duration of seizure types as a memory aid for the CGIC and CGICSD respectively at relevant subsequent visits or withdrawal. Patients will then receive sufficient IMP and a dosing regimen as assigned by the IVRS for the following four weeks. Patients or their caregivers will be instructed on using the IVRS's daily reporting diary, as well as how to complete the paper diary.

Prior to the first dose of IMP, blood samples will be taken for analysis of plasma concentrations of CBD and its major metabolites (only patients who weigh ≥20 kg) and, provided the risk/benefit outcome is favorable in the investigator's opinion, concomitant AEDs (all patients). Patients will then be given their first dose of IMP while in the clinic. ECG and vital signs will be re-assessed 2–3 hours post-dose. Further blood samples will be taken for PK analyses as specified in Section 9.1.10.

The investigator should review the laboratory results as soon as these become available. If the results show a patient is ineligible, the patient must be withdrawn from the study.

9.2.3 Visit 3 (Day 15)

This visit will occur 14 days after randomization (Visit 2). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following assessments will be made at Visit 3: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC, C-SSRS (Children's Since Last Visit) and the Vineland-II. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the titration regimen.

9.2.4 Visit 4 (Day 29)

This visit will occur 28 days after randomization (Visit 2). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

The following assessments will be made at Visit 4: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC,

C-SSRS (Children's Since Last Visit) and the Vineland-II. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen.

Prior to the first daily dose of IMP, blood samples will be taken for analysis of plasma concentrations of concomitant AEDs, provided the risk/benefit outcome is favorable in the investigator's opinion.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The IVRS will be contacted for treatment pack assignment. Patients will receive sufficient IMP as assigned by the IVRS for the following four weeks.

9.2.5 Visit 5 (Day 43, Safety Telephone Call)

This visit will occur 42 days after randomization (Visit 2). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Visit 5 will be completed by telephone. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).

9.2.6 Visit 6 (Day 57)

This visit will occur 56 days after randomization (Visit 2). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

The following assessments will be made at Visit 6: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC, C-SSRS (Children's Since Last Visit) and the Vineland-II. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related

hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen.

Prior to the first daily dose of IMP, blood samples will be taken for analysis of plasma concentrations of concomitant AEDs, provided the risk/benefit outcome is favorable in the investigator's opinion.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The IVRS will be contacted for treatment pack assignment. Patients will receive sufficient IMP as assigned by the IVRS for the following six weeks.

9.2.7 Visit 7 (Day 71, Safety Telephone Call)

This visit will occur 70 days after randomization (Visit 2). A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

Visit 7 will be completed by telephone. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).

9.2.8 Visit 8 (Day 99, End of Treatment/Withdrawal Visit)

This visit will occur 98 days after randomization (Visit 2) or earlier if the patient withdraws from the study. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary. They will also be asked to record their meal times the day before and the day of Visit 8.

The following assessments will be made at Visit 8 / the Withdrawal visit: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC, CGICSD, QOLCE, C-SSRS (Children's Since Last Visit), cognitive assessment battery (at participating sites), details of menstruation (for females), Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) and the Vineland-II. The Caregiver Impression of IMP Palatability will also be assessed. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen (required), determination of serum IGF-1 levels and a pregnancy test (using a serum sample, as appropriate). The patient's IVRS report and paper diary will

be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen.

Prior to the final dose of maintenance IMP, blood samples will be taken to determine plasma concentrations of CBD and its major metabolites (only patients who weigh ≥20 kg) and, provided the risk/benefit outcome is favorable in the investigator's opinion, concomitant AEDs (all patients). The final maintenance dose of IMP will then be taken in the clinic. ECG and vital signs will be re-assessed two to three hours post-dose. Further blood samples will be taken for CBD PK analyses. The presence of THC in plasma will also be assessed at a single time point (two to three hours post-dose). A urine sample will be collected (complete void) at the time of first blood sample collection for both CBD and THC analysis, and the exact urine volume will be recorded. See Section 9.1.10.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the study. 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. If the tapered dose is administered, the IVRS will be contacted to generate the patient's daily IMP dosing volumes, confirm start of the 10-day taper period and for additional treatment pack assignment. Patients should continue to complete the IVRS and paper diary and should return for the 'End of Taper Period' visit, if possible.

Patients who have completed all of the scheduled study visits will be offered the option of entering an OLE study. Entry is to be on the same day as Visit 8 (Day 99) or within seven days of Visit 8.

For patients who enter the OLE study on Day 99, the IVRS will be contacted to confirm the patient's completion of this study and the paper diaries will be collected. For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

For patients not entering the OLE study on Day 99, the IVRS will be contacted to confirm start of the 10-day taper period and for additional treatment pack assignment (if required). The IVRS will generate the patient's daily IMP dosing volumes for the 10-day

taper period; patients will then receive sufficient IMP and a dosing regimen as assigned by the IVRS for the taper period. During this time IVRS and diary information will continue to be recorded. The taper period may be interrupted if the patient wishes to enter the OLE study within the seven-day timeframe.

9.2.9 Visit 9 (Day 100–106 or Day 109, End of Taper Period)

This visit is required only for those patients who do not enter the OLE study on the day of Visit 8 (i.e., Day 99±3) or for those who withdraw early and taper IMP. For patients who complete treatment but do not enter the OLE study, Visit 9 should occur 10 (+3) days after Visit 8 (i.e., on Day 109). For patients who withdraw early and taper IMP, this visit should occur 10 (+3) days after the Withdrawal visit. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

For patients who delay entry into the OLE study, Visit 9 should occur on the day the patient enters the OLE study and within seven days of Visit 8 (i.e., up to Day 106) to allow the patient to enter the OLE study within this timeframe.

The following assessments will be made at Visit 9: vital signs, physical examination (including height and body weight) and C-SSRS (Children's Since Last Visit). The CWS/PCWS will also be assessed. In addition, the following assessments will be made for patients who opt not to enter the OLE study and for those who withdraw early and taper IMP (including withdrawal during the taper period): ECG and clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the down-titration regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The IVRS will be contacted to confirm the patient's completion of the study and the paper diaries will be collected. For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

9.2.10 Visit 10 (Day 137, Safety Follow-Up)

This visit is required for patients who do not enter the OLE study or who withdraw from the study early. This visit should occur four weeks after Visit 9 (+3 days), or date of final dosing, and can be conducted by telephone.

The purpose of the follow-up is to ascertain the status of AEs continuing after cessation of IMP or any new AEs commencing after discontinuation. Epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs) must also be recorded. An assessment of withdrawal using the CWS/PCWS will also be administered.

All causally-related AEs that result in a patient's premature termination from the study or are present at the end of the study should be followed up until a satisfactory resolution occurs; that is, until the AE resolves or is considered clinically insignificant, or until an investigator is satisfied that the AE is not related to IMP and needs no further investigation.

9.2.11 Safety Telephone Calls

For patients not entering the OLE study, or who withdraw from the study early, safety telephone calls will be made weekly (±3 days) from Visit 9 (or date of final dosing) until Visit 10. Patients or their caregivers will be asked for information on ongoing and new AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The second safety telephone call (on Day 123 [±3]) will additionally include an assessment of withdrawal using the CWS (or PCWS as appropriate), for those patients aged four years or above.

10 WITHDRAWAL

In accordance with the Declaration of Helsinki[66], the FDA regulations relating to good clinical practice (GCP) and clinical trials[67,68,69], the EU Clinical Trials Directive (2001/20/EC)[70] 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/assent.
- Withdrawal of parent(s)/legal representative consent.
- Lost to follow-up.
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- ALT or AST >8 × ULN.
- ALT or AST >5 × ULN for more than two weeks.
- ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5).

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 8 / the Withdrawal visit should be conducted if possible. If the tapered dose is administered, patients should continue to complete the IVRS and paper diary and return for Visit 9, if possible. For patients who begin to taper IMP but subsequently withdraw, Visit 9 assessments (including ECG and clinical laboratory sampling) should be conducted, if possible; this visit should occur on the final day of dosing or as soon as possible after this date. Patients withdrawing due to an AE should be followed up according to Section 12.7 safety follow-up visit. All information should be reported on the applicable CRF pages (refer to Section 9.1). Wherever possible, the safety follow-up visit should be conducted 28 days from the date of the last dose of IMP (refer to Section 9.2.10).

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 provided 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) and the post treatment, safety follow-up visit (Visit 10), 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/assent 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., a 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.
- Is 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 observational period (Visit 10). If the investigator subsequently becomes aware of 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 IMP 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 IMP:

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

Events that start before the first dose of IMP (pre-treatment) should be considered as not causally related. Where a pre-treatment event worsens in severity following the first dose of IMP 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 IMP 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 IMP.
- 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 10), 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 of 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 × 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.
- ALT or AST >3 × ULN **and** (TBL >2 × ULN **or** INR >1.5).

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 in this way until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

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 detailed above, within 72 hours' notice of abnormal results. If the patient cannot return to the investigational site, 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 Directive[70], relevant parts of the FDA Code of Federal Regulations[71] 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 Reactions (SUSARs).

This information will be provided through three sources:

1) IB[63]: 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 patients. The IB is updated annually.
2) Development Core Safety Information: this document actually forms the Safety Section of the IB[63], or is updated as an appendix of the IB[63]. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).

3) 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 ethical committees 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 guidance[67] 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/assent, 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 guidance[71] 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/ECs) 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 ethical approval and final database lock.

13 STATISTICAL CONSIDERATIONS

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

13.1 Sample Size, Power and Significance Levels

A total of 186 patients will be randomized to one of four treatment groups (GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The randomization will be stratified by age group (2–5 years, 6–12 years and 13–18 years). The placebo groups will be pooled for the analyses of efficacy.

For a Wilcoxon–Mann–Whitney test comparing two distributions with a two-sided significance level of 0.05, a sample size of 62 per group is required to obtain a power of at least 80%. This is based on a gamma distribution for the GWP42003-P groups with scale parameter of 65.614 and shape parameter of 1.0886, and a gamma distribution for the placebo group with scale parameter of 40.887 and shape parameter of 2.3059.

Maximum likelihood estimates using the Newton–Raphson approximation were computed for the scale and shape parameters using data from study GWEP1332 Part B.

13.2 Interim Analysis

No interim analysis is planned for this study.

13.3 Analysis Sets

There will be up to three analysis sets:

Intention to Treat (ITT)

- All patients who are randomized, receive IMP in the study, and have post-baseline efficacy data will be included and analyzed according to their randomized treatment group.
- The ITT analysis set is the primary analysis set for all efficacy endpoints.

Per Protocol (PP)

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

- All patients who complete the study with no protocol deviations deemed to compromise the assessment of efficacy will be included and analyzed according to the treatment group they were randomized. The rules determining the PP analysis set will be fully defined prior to unblinding of the database.

Safety

All patients who received at least one dose of IMP in the study will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from this safety analysis set.

13.3.1 Protocol Deviations

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.

For clinic visit-based endpoints, baseline is defined as the last record or measure collected prior to the first dose of IMP.

For IVRS-based endpoints, baseline will include all available data prior to Day 1.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, randomized, 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, including history of epilepsy and epilepsy-specific genetic testing will be summarized by randomized treatment group, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by system organ class, including details of epilepsy.

13.5.4 Concomitant Medication

Concomitant medications (including all prior usage of AEDs, standard AED and rescue medication) taken prior to and during the study will be summarized separately, by medication class and active ingredients.

13.6 Endpoints and Statistical Methods

Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Since there is a single primary analysis endpoint, no formal adjustment of statistical significance for multiple testing on multiple endpoints is required, although such multiplicity should be allowed for when interpreting the results for secondary endpoints. However, there are three treatments, so multiple significance testing will occur when making comparisons between the treatments; the major comparisons of interest are those between each of the GWP42003-P Dose Levels and placebo and, in particular, the 20 mg/kg/day Dose Level and placebo. A step down procedure will be used to control the type I error. The comparison of 20 mg/kg/day GWP42003-P and placebo will be tested first and only if this is statistically significant at the 5% level will the comparison of 10 mg/kg/day GWP42003-P and placebo be tested.

13.6.1 Evaluable Period

The start of the evaluable period of the study (Day 1) is defined as the first day the patient took IMP, as recorded in the IVRS, or the day of randomization if this date is unknown.

The end of the evaluable period is defined as the earliest of:

i) Day 99 of treatment for the IVRS reported efficacy data and the day of Visit 8 for the CRF-based efficacy data;

ii) The last day on which study IMP was taken (as stated on the study outcome CRF) for the IVRS reported efficacy data and the day after this for the CRF-based efficacy data;

iii) The day before a relevant change in prohibited or AED medications was made.

13.6.2 Primary Endpoint(s)

The primary endpoint is the change in total convulsive seizure frequency during the treatment period of the study (Day 1 to the end of the evaluable period) compared to baseline in patients taking GWP42003-P compared with placebo.

Data will be analyzed using negative binomial regression on the sum of the convulsive seizure counts during the treatment period. However, convulsive seizure frequency (average per 28 days) and percentage change in seizure frequency will be presented using summary statistics. A mixed effect model with repeated measures will be performed modelling the observed number of convulsive seizures in the baseline period and treatment period implemented within the framework of general linear models using the negative binomial response distribution. The model will include stratified age group (2–5 years, 6–12 years and 13–18 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect. The log transformed number of days in which seizures were reported will be included as an offset. The time variable corresponds to an indicator for the baseline period and treatment period. The estimated ratio of least squares means for treatment period to baseline period and 95% confidence intervals (CIs) will be presented for each treatment arm. In addition, the estimated ratio of each GWP42003-P group to placebo and 95% CIs will be presented along with the p-value testing the null hypothesis that this ratio is 1. The comparison of 10 mg/kg/day GWP42003-P and placebo will be presented, but significance testing will only be performed if the comparison of 20 mg/kg/day GWP42003-P and placebo is statistically significant at the 5% level.

A step down procedure will be used to control the type I error as per Section 13.6.

If a patient withdraws from the study, then the primary analysis variable will be calculated from the available data, during the treatment period, prior to the patient withdrawing.

13.6.2.1 Sensitivity Analysis for the Primary Endpoint(s)

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

- Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P group and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.

- A rank analysis of covariance (ANCOVA) on percentage change from baseline in convulsive seizure frequency during the treatment period.
  - The ranks of the percentage change from baseline and the baseline convulsive seizure frequency will be calculated. The rank of the percentage change from baseline will then be analyzed using an ANCOVA model with the rank of the baseline convulsive seizure frequency and age group (2–5 years, 6–12 years and 13–18 years) as covariates and treatment group as a fixed factor. The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.
- ANCOVA of log transformed convulsive seizure frequency during the treatment period.
  - The convulsive seizure frequency during the treatment period and the baseline convulsive seizure frequency will be log transformed prior to analysis. The log transformed convulsive seizure frequency during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline convulsive seizure frequency and age group as covariates and treatment group as a fixed factor. The back transformed estimated treatment ratio, together with the 95% CIs and p-value will be presented.
  - If there are any patients with no seizures post-baseline, then one will be added to the convulsive seizure frequency for all patients prior to log transformation.
- ANCOVA on percentage change from baseline in convulsive seizure frequency during the treatment period including baseline and age group as covariates and treatment group as a fixed factor. The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.
- Primary endpoint analysis repeated using the maintenance period (Day 15 to the end of the evaluable period) rather than the treatment period.
- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the mean from the non-missing data for each patient to impute missing data arising from unreported days in IVRS.
  - Any intermittent missing data for the number of convulsive seizures arising from unreported days in IVRS will be imputed using the worst (highest

number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period based on non-missing data:

Number of seizures ÷ Number of reported days in IVRS

- Wilcoxon rank-sum test on percentage change from baseline in number of convulsive seizures (average per 28 days) during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption.
  - MNAR will be assumed for missing values resulting from two scenarios; discontinuation due to AEs, and discontinuation due to any reason in the GWP42003-P dose groups and Missing at Random (MAR) for others, including other patients discontinued in the GWP42003-P dose groups and patients in the placebo group.
  - MI will be performed on the convulsive seizure frequency, based on time-points corresponding to each 14 calendar days of the treatment period. Intermittent missing values for intermediate 14-day time-points before the last 14-day time-point will be imputed using the MCMC method in SAS PROC MI with an IMPUTE=MONOTONE statement for 100 times for each treatment group separately. Then, monotone missing data assumed under the MAR assumption at time-point *t* (i.e., patients in the placebo group and patients in the GWP42003-P groups who did not discontinue due to AEs or for any reason) will be imputed using the MI procedure with the 'MONOTONE REG' option, for each treatment group separately. The imputation model will include baseline convulsive seizure frequency and each 14-day time-point up to time-point *t* (in chronological order). With the data imputed from above, monotone missing data of patients in the GWP42003-P groups under the MNAR assumption will be imputed. At each 14-day time-point *t*, the input dataset for the MI procedure will include all placebo patients and those patients from the GWP42003-P groups that have values missing under MNAR at that time-point. The imputation model will include convulsive seizure frequency at baseline and each 14-day time point up to time-point *t* (in chronological order) and will be performed for each GWP42003-P group separately.

Full details for this sensitivity analysis will be provided in the SAP.

13.6.3 Secondary Endpoint(s)

The following endpoints will be compared between treatment groups over the 14-week, double-blind treatment period:

- Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline.
- Number of patients considered treatment responders, defined as those with a ≥25%, ≥50% or ≥75% reduction in convulsive seizures from baseline (overall and four-weekly).
- Number of patients who are convulsive seizure free.
- Change in non-convulsive seizure frequency.
- Change in total seizure frequency.
- Change in subtypes of seizures.
- Changes from baseline in number of episodes of *status epilepticus*.
- Changes from baseline in duration of seizure subtypes as assessed by the CGICSD.
- Changes from baseline in usage of rescue medication.
- Changes from baseline in number of inpatient hospitalizations due to epilepsy.
- Changes from baseline in Sleep Disruption 0–10 NRS score.
- Changes from baseline in EDSS score.
- Changes from baseline in the QOLCE score.
- Change from baseline in cognitive function as measured with the cognitive assessment battery.
- Changes from baseline in the Vineland-II score.
- Change from baseline in growth and development by measurement of height, weight, IGF-1 levels and Tanner Staging (for patients aged 10–17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

- Changes from baseline in the CGIC score.

The number of patients experiencing at least a 25%, 50% and 75% reduction in convulsive seizures and the number of patients seizure free will be summarized and analyzed using the difference in proportions and the odds ratios comparing the treatment groups will be presented together with 95% CIs.

For number of hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, QOLCE, cognitive function and behavior assessments, the data will be summarized at baseline, over the treatment period, and at each time point (or 28-day period, as appropriate) during the maintenance period. Changes from baseline to the average over the treatment period (or at the end of study) will be analyzed using ANCOVA (or appropriate non-parametric methods if data are found to be not normally distributed). The model will include baseline (where applicable) and age group as covariates and treatment group as a fixed factor. The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.

For changes in non-convulsive and total seizure frequency and changes in frequency of other seizure types the data will be summarized at baseline, over the treatment period, and at each time point (or 28-day period, as appropriate) during the maintenance period. Changes over the treatment period compared to baseline will be analyzed using the same analysis as the primary endpoint.

CGIC and CGICSD assessments recorded at the end of treatment will be analyzed with ordinal logistic regression using the proportional odds model.

Changes from baseline for IGF-1 levels will be summarized by treatment group and plotted against the Tanner Stages, weight, and height.

Tanner Stages will be evaluated and summarized descriptively at each time point in terms of frequency and proportions. Number (%) of patients with changes in Tanner Stages and the transition time between stages will be summarized by treatment group.

13.6.4 Handling of Missing Data

The primary efficacy analysis uses the ITT analysis set over the evaluable period. The primary analysis variable will be calculated from the available data, during the treatment period.

In order to explore the robustness of the primary analysis, further sensitivity analysis (in addition to that already detailed in Section 13.6.2.1) may be specified in the SAP.

13.6.5 Pharmacokinetics

Plasma concentrations of CBD and its major metabolites will be summarized after the first dose of IMP at Visit 2 and at Visit 8, together with any estimates of PK parameters. Urine concentrations of CBD and its major metabolites will be summarized at Visit 8. Plasma and urine concentrations of THC and its major metabolites will be summarized at Visit 8.

Where available, plasma concentrations of concomitant AEDs will also be summarized pre-treatment with IMP (Visit 2) and at Visits 4, 6 and 8.

13.6.6 Safety

In the presentation of safety data, data from the two cohorts of placebo patients (10 mg/kg/day and 20 mg/kg/day) will be presented separately and pooled together. This will allow the possibility to explore any effects of the volume of IMP on safety endpoints.

13.6.6.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.6.2 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. The number of patients reporting at least one AE will be provided.

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.

13.6.6.3 Clinical Laboratory Data

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

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

Vital signs, ECG, physical examination and C-SSRS data will be summarized for the safety analysis set, at screening, baseline and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs from baseline to end of treatment will also be summarized. CWS/PCWS and Study Medication Use and Behavior Survey data will be summarized for the safety analysis set using appropriate summary statistics. Details of menstruation cycles (in females) will be summarized and listed as appropriate.

14 DATA SAFETY MONITORING COMMITTEE

An independent ESC will monitor the DS diagnosis and verification of seizure subtypes of screened patients on an ongoing basis in order to ascertain the correct study population is randomized. Investigators will submit a documented history of DS, directly to the ESC, for confirmation of diagnosis and verification of seizures. The ESC will provide written documentation of the confirmation of diagnosis directly to the investigator, for inclusion in the patient file.

Details of the composition and standard operating procedures of the ESC will be detailed in a separate charter.

15 REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki[66], EU Clinical Trials Directive[70] and the clinical trial regulations adopting European Commission Directives into national legislation[72,73,74].

15.2 Informed Consent/Assent

Initial master informed consent and assent forms will be provided to the investigator to prepare the informed consent/assent 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/assent 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/assent from the patient and/or parent(s)/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 and parent(s)/legal representative should have ample time for review to consider the information provided before giving written consent/assent; more specific definitions of ample time may be in force if required by ECs/IRBs or local regulations.

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

15.3 Institutional Review Board/Ethics Committee

A copy of the protocol, proposed informed consent/assent 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/assent 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/assent 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/assent for entry into the study:

- Signed and dated protocol signature page.
- Copy of approved informed consent/assent forms and other patient information material.
- Copy of the IRB/EC approval of the protocol, informed consent/assent forms and other patient information material.
- Up to date curriculum 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[67,68,69,75], the EU Clinical Trials Directive[70], or International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP)[76] where the EU Clinical Trials 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 Patient 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 (if allowed per local regulations) and a patient study number only. Documents that are not for submission to GW, e.g., signed informed consent/assent forms, should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to GCP and clinical trials[67,68,69,75], and the EU Clinical Trials Directive[70]/ICH GCP Guidelines[76], 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/assent documents. The IRB/EC must be informed of all amendments and give approval for any substantial amendments. Amendments for administrational changes can be submitted to the IRB/EC for information only. The investigator must send a copy of the approval letter from the IRB/EC to GW.

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 center, will be agreed with each center 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 8.2[76]), 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/assent 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, 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 16[77]).

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 participant confidentiality is respected.

The GW study monitor, or designee, is responsible for inspecting the CRFs and available IVRS/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[67,68,69,75], the ICH GCP Guideline[76], and all other applicable regulatory requirements; 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 Electronic Data collected by Interactive Voice Response System

Source data for the assessments collected via the IVRS will be managed by the service provider in accordance with GCP and in adherence to a quality management system. All data will be stored in a secure (for example, redundant hardware, password control, limited physical access to servers), fully audit trailed environment with appropriate industry standard back-up and off-site storage practices.

Access for patients providing assessments and investigators will be authenticated and meet industry standards and comply with FDA 21 CFR part 11 (subpart B – Electronic Records) requirements[75].

After database lock all investigators will receive a certified copy of all the IVRS assessment data. This data will be in an agreed, read-only format with a covering letter explaining the content of the data, a quality statement from the IVRS provider and the investigator's responsibilities.

Regulatory and sponsor auditors will have the ability to review but not modify the IVRS data via an agreed means of access.

16.5 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.

16.6 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.

16.7 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.

16.8 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.

16.9 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	**1**	**2**	**3**	**4**	**5** (Tel.)	**6**	**7** (Tel.)	**8**[♣]	**9**[*]	**Safety Calls**	**10**[**]
Day Number (Visit window)	**−28**	**1 (+3)**	**15 (±3)**	**29 (±3)**	**43 (±3)**	**57 (±3)**	**71 (±3)**	**99 (±3)**	**100–106 or 109 (+3)**	**116, 123 & 130 (±3)**	**137 (+3)**
Informed consent/assent	X										
Eligibility Criteria	X	X									
Randomization		X									
Demographics	X										
Medical history	X										
Blood sample for *SCN1A* analysis[†]	X										
Vital signs	X	X[♠]	X	X		X		X	X		
Postural blood pressure	X	X									
Physical examination (including height and body weight)	X	X	X	X		X		X	X		
ECG	X	X[♠]	X	X		X		X	X[♦]		
Clinical laboratory blood sampling	X	X	X	X		X		X	X[♦]		
Clinical laboratory urine sampling (dipstick urinalysis)[§]	X	X	X	X		X		X	X[♦]		
Urine THC screen	X	X						X			
Pregnancy test (if appropriate)[¥]	X	X						X			
CBD Pharmacokinetic blood sampling[^]		X						X[◊]			
CBD Pharmacokinetic urine sampling[Ψ]								X			
THC Pharmacokinetic blood[^^^] and urine[Ψ] sampling								X			
AED blood sampling[^^]		X		X		X		X			
AEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Inpatient epilepsy-related hospitalizations		X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X		X		X	X		
Sleep Disruption 0–10 NRS		X	X	X		X		X			
EDSS		X	X	X		X		X			
Vineland-II		X	X	X		X		X			
CGIC[¶]		X[▲]	X	X		X		X			

Visit Number	**1**	**2**	**3**	**4**	**5** (Tel.)	**6**	**7** (Tel.)	**8**♣	**9***	**Safety Calls**	**10****
Day Number **(Visit window)**	**−28**	**1** (+3)	**15** (±3)	**29** (±3)	**43** (±3)	**57** (±3)	**71** (±3)	**99** (±3)	**100–106 or 109** (+3)	**116, 123 & 130** (±3)	**137** (+3)
CGICSD¶		X▲						X			
QOLCE		X						X			
Cognitive assessment battery∞		X						X			
Menstruation question (females)		X						X			
Tanner Staging and IGF-1 levels♥		X						X			
Caregiver Impression of IMP Palatability								X			
CWS/PCWS††		X							X	X£	X
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing, meal times the day prior to and the day of Pharmacokinetic sampling)		X	X	X		X		X	X		
IVRS Caregiver Training	X	X									
IMP dispensing		X		X		X		X			
Collection of IMP				X		X		X	X		
IMP compliance review			X	X		X		X	X		
Study Medication Use and Behavior Survey#								X			

♣ To be performed for all patients completing or withdrawing from the study. Patients who complete treatment but do not enter the OLE study on Day 99 will commence a 10-day IMP taper period, which may be interrupted at any time within seven days if the patient subsequently opts to participate in the OLE study. Patients who withdraw early should commence the 10-day IMP taper period, if possible.

* Only required for those patients who delay entry into or do not participate in the OLE study or for those who withdraw from the study early and taper IMP. Visit 9 should be within seven days of Visit 8 for patients delaying entry to the OLE study. For patients who complete treatment but do not participate in the OLE study, Visit 9 should be 10 (+3) days after Visit 8. For patients who withdraw early and taper IMP, this visit should occur 10 (+3) days after the Withdrawal visit. Patients who opt not to enter the OLE study or who withdraw early must have weekly (±3 days) safety telephone calls until Visit 10.

** For patients who do not enter the OLE study or who withdraw from the study early; can be conducted by telephone.

† Sample can be taken at any clinic visit during the study.

♠ Vital signs and ECG must be re-assessed 2–3 hours post dose.

♦ Only required for patients who opt not to enter the OLE study or who withdraw from the study early (including withdrawal during the taper period).

§ Urine sample taken if possible.

¥ Urine dipstick pregnancy test at Visit 2; serum sample test at Visits 1, 2 and Visit 8/Withdrawal visit.

^ For patients ≥20 kg: blood samples collected pre-dose and at 2–3 hours and 4–6 hours post-dose; there must be a minimum period of at least two hours between each of the three blood sampling time-points.

^^ For all patients, provided the risk/benefit outcome is favorable in the investigator's opinion. Blood samples taken prior to administration of IMP. Patients are to record the dosing time of their concomitant AEDs in the diary.

◊ Blood samples must be taken at the same time intervals as at Visit 2.

¶ Caregivers are to compare to the memory aid from Visit 2.

▲ Completion of memory aid; to be referred back to at subsequent assessments.

∞ Only completed at participating sites; Visit 8/Withdrawal visit assessment to be completed ideally before any other study procedures but can be completed on a separate day, if necessary, within three days of the visit.

♥ Tanner Staging to be assessed in all adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent/assent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty). IGF-1 level testing to be conducted in all patients.

†† PCWS to be used for patients aged 4–17 years; CWS to be used for patients aged 18 years.

£ To be performed on Day 123 (±3) only.

To be performed at final dosing visit (Visit 8/Withdrawal visit or Visit 9, as applicable) for patients 12 years of age and older.

Tel. Visit conducted by telephone.

^^^ For patients ≥20 kg: blood sample collected at 2–3 hours post-dose.

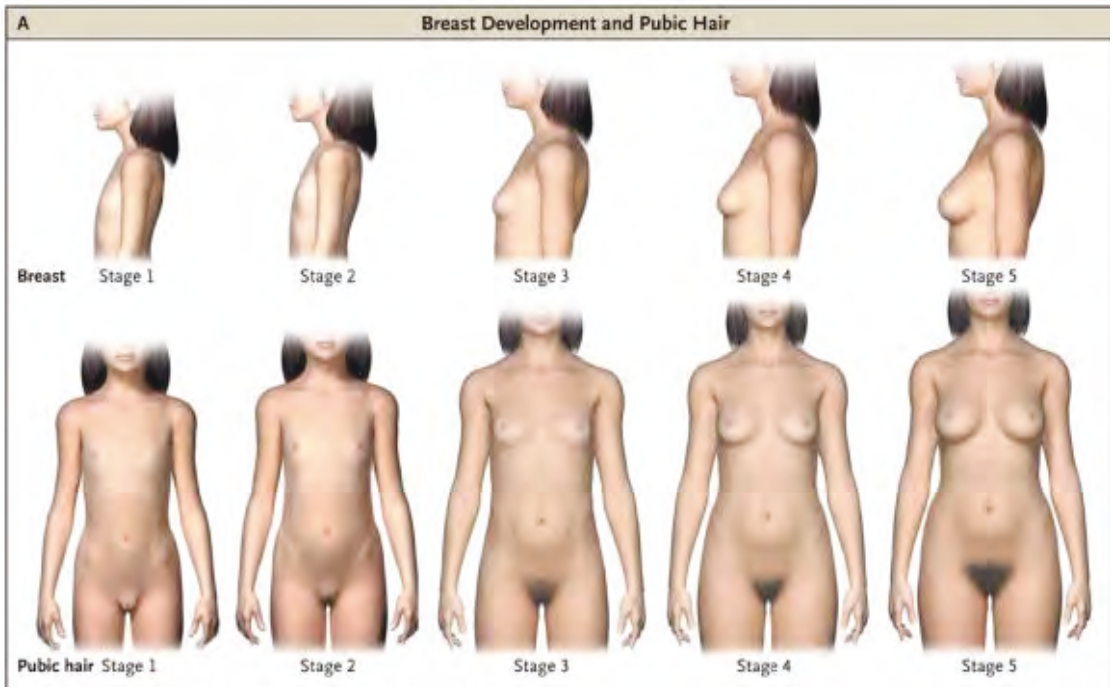
Ψ For patients ≥20 kg: urine sample (complete void prior to taking blood sample, recording the urine volume).

APPENDIX 2. TANNER STAGING

(Reproduced with permission from the New England Journal of Medicine[65].)

The following is to be completed for all female adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent/assent form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

Female Development & Pubic Hair



Please check the box next to the most appropriate stage; in the event that qualifying characteristics are not within the same stage, defer to the lesser stage as the overall Tanner Score.

Tanner Stage 1 (Prepubertal, typically 10 years and younger)

- No glandular tissue; areola follows the skin contours of the chest.
- No pubic hair at all.

Tanner Stage 2 (10–11.5 years)

- Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen.
- Small amount of long, downy hair with slight pigmentation on the labia majora.

Tanner Stage 3 (11.5–13 years)

- Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast.
- Hair becomes more coarse and curly and begins to extend laterally.

Tanner Stage 4 (13–15 years)

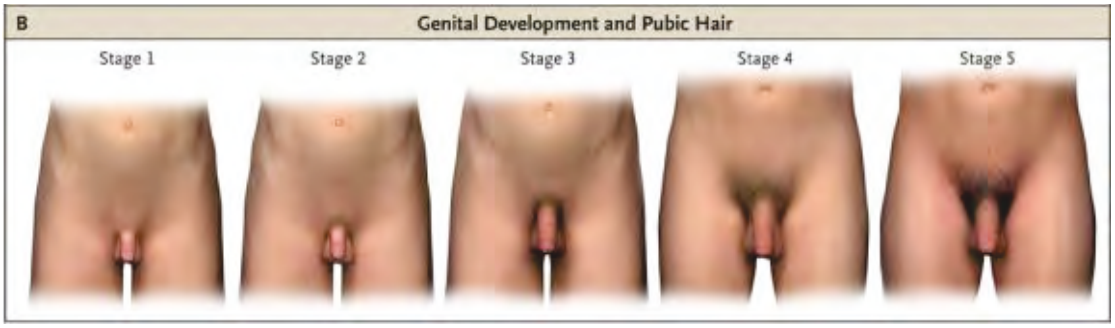
- Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast.
- Adult-like hair quality, extending across pubis but sparing medial thighs.

Tanner Stage 5 (15+ years)

- Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.
- Hair extends to medial surface of the thighs.

The following is to be completed for all male adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent/assent form, or earlier if clinically indicated by signs of precocious puberty).

Male Genital Development & Pubic Hair



Please check the box next to the most appropriate stage.

Tanner Stage 1 (Prepubertal, typically 9 years and younger)

- Testicular volume less than 1.5 mL; small penis of 3 cm or less.
- No pubic hair at all.

Tanner Stage 2 (9–11 years)

- Testicular volume between 1.6 and 6 mL; skin on scrotum thins, reddens and enlarges; penis length unchanged.
- Small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum.

Tanner Stage 3 (11–12.5 years)

- Testicular volume between 6 and 12 mL; scrotum enlarges further; penis begins to lengthen to about 6 cm.
- Hair becomes more coarse and curly and begins to extend laterally.

Tanner Stage 4 (12.5–14 years)

- Testicular volume between 12 and 20 mL; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference.
- Adult-like hair quality, extending across pubis but sparing medial thighs.

Tanner Stage 5 (14+ years)

- Testicular volume greater than 20 mL; adult scrotum and penis of 15 cm in length.
- Hair extends to medial surface of the thighs.

APPENDIX 3. 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 **USA Toll Free Fax:** PPD Tel: PPD
Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: PPD Fax: PPD
Medical Monitor	EU PPD Tel: PPD Mobile: PPD USA PPD Phone: PPD Cell: PPD
Clinical Project Manager/Clinical Operations Director:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: PPD Fax: PPD

Clinical Trials Supplies:

G-Pharm Ltd
Tel: PPD
Fax: PPD

APPENDIX 4. TITRATION REGIMEN

Dose Titration Regimen[1]		
Day	**10 mg/kg/day Dose Level**	**20 mg/kg/day Dose Level**
1	2.5 mg/kg	2.5 mg/kg
2	2.5 mg/kg	2.5 mg/kg
3	5.0 mg/kg	5.0 mg/kg
4	5.0 mg/kg	5.0 mg/kg
5	7.5 mg/kg	7.5 mg/kg
6	7.5 mg/kg	7.5 mg/kg
7	10.0 mg/kg	10.0 mg/kg
8	10.0 mg/kg	10.0 mg/kg
9	10.0 mg/kg	15.0 mg/kg
10	10.0 mg/kg	15.0 mg/kg
11	10.0 mg/kg	20.0 mg/kg
12	10.0 mg/kg	20.0 mg/kg
13	10.0 mg/kg	20.0 mg/kg
14	10.0 mg/kg	20.0 mg/kg

[1] IMP is to be taken twice daily; total daily doses are shown.