TITLE: An open label extension study to investigate the safety of cannabidiol (GWP42003-P; CBD) in children and adults with inadequately controlled Dravet or Lennox-Gastaut Syndromes.

STUDY CODE: GWEP1415

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Confidentiality Statement

Investigator Agreement

I have read the attached protocol entitled "An open label extension study to investigate the safety of cannabidiol (GWP42003-P; CBD) in children and adults with inadequately controlled Dravet or Lennox-Gastaut Syndromes", dated 25 April 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 Clinical Trials 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.

Center No: _____

Print Name: _____ Date: _____

Principal Investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print Name: [redacted] Date: [redacted]

Clini[redacted]nager (DD Month YYYY)

Signature: [redacted]

1 PROTOCOL SYNOPSIS

Study Title	An open label extension study to investigate the safety of cannabidiol (GWP42003-P; CBD) in children and adults with inadequately controlled Dravet or Lennox-Gastaut Syndromes.
Clinical Study Type	Phase 3 Study.
Indication	Dravet Syndrome (DS) or Lennox-Gastaut Syndrome (LGS).
Primary Objective	To evaluate the long-term safety and tolerability of GWP42003-P, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS.
Secondary Objective(s)	**All Patients:** To evaluate the effect of GWP42003-P, as adjunctive treatment, on: • Quality of life. • Adaptive behavior. • Need for hospitalizations due to epilepsy. • Usage of rescue medication. • Maintenance of seizure frequency reduction and freedom from seizures during the open label extension (OLE) study. • Frequency of total and subtypes of seizures. • Change in duration of subtypes of seizures. • Number of episodes of *status epilepticus*. • Cognitive function. • Growth and development. • Menstruation cycles (in females). • Signals indicating drug abuse liability of GWP42003-P. **DS Patients Only:** To evaluate the effect of GWP42003-P, as adjunctive treatment, on: • Total convulsive seizure frequency. • Total non-convulsive seizure frequency. • Number of patients convulsive seizure-free. • Responder rate (defined in terms of percentage reduction in total convulsive seizure frequency). **LGS Patients Only:** To evaluate the effect of GWP42003-P, as adjunctive treatment, on: • Drop seizure frequency.

	• Non-drop seizure frequency. • Number of patients drop seizure-free. • Responder rate (defined in terms of percentage reduction in drop seizure frequency).
Study Design	This is a multi-center, OLE study for patients with DS or LGS who have completed the double-blind, placebo-controlled, clinical studies with GWP42003-P (Core Studies). The study consists of a titration period and a maintenance period, followed by a 10-day taper period. **Titration Period:** All patients will titrate up to 10–20 mg/kg/day GWP42003-P using a recommended titration schedule. It is advised that the Investigator considers monitoring hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL] and international normalized ratio [INR] levels) during the titration period for patients taking concomitant antiepileptic drugs (AEDs) that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10–20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW Research Ltd (GW) medical monitor. **Maintenance Period:** Patients will continue dosing at doses up to 10–20 mg/kg/day. However, Investigators may decrease the dose if a patient experiences intolerance, or increase the dose if required for better seizure control, until the optimal dose is found. The Investigator may schedule additional clinic visits to facilitate dose adjustments, e.g., when increasing doses above 20 mg/kg/day. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. The maximum dose patients can receive will be 30 mg/kg/day (51 mg/kg/day is the maximum dose safely used in the USA Intermediate Expanded Access Investigational New Drug Program [EAP] to date, with a mean dose of 24 mg/kg/day [$n = 59$]). Dose increases above 20 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg every 5–7 days. If seizure freedom is achieved with use of GWP42003-P during the study, the Investigator can consider reducing the dose of concomitant AEDs after consultation with the GW medical monitor. **Study Completion:** The maximum duration of this OLE study will be 4 years (208 weeks after Visit 1). • A patient with at least 2 years' participation in the OLE

	(≥ 104 weeks after Visit 1) will complete the OLE phase when GWP42003-P is approved in their indication and is commercially available. Patients will complete an unscheduled 'End of treatment' visit to transition from OLE to commercial product. The timing will vary per patient and is projected to begin in February 2019. • A patient with less than 2 years' participation in the OLE when GWP42003-P is approved in their indication and is commercially available will continue the OLE phase until reaching a maximum of 2 years' (104 weeks after Visit 1) OLE treatment, at which point an unscheduled 'End of Treatment' visit will be conducted. The unscheduled 'End of Treatment' visit will be conducted no earlier than 730 days after Visit 1. • A patient who does not continue treatment with GWP42003-P will commence the 10-day taper period (down-titrating 10% per day for 10 days) and complete an 'End of Taper Period' visit followed by a Follow-up visit (which can be by telephone) 4 weeks later. **Interim Analysis:** At least one interim analysis will be conducted to support New Drug Application and Marketing Authorization Application filings. Further interim analyses may be conducted as required.
Primary Endpoint	The safety of GWP42003-P will be assessed by the adverse event (AE) profile and by evaluating changes in the following, relative to the pre-randomization baseline of the Core Study: • Vital signs. • Physical examination (including height and body weight). • 12-lead electrocardiogram (ECG). • Columbia-Suicide Severity Rating Scale (C-SSRS) score. • Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale (PCWS) score, as appropriate. • Clinical laboratory parameters. The CWS will be administered to patients aged 18 and older while the PCWS will be administered to patients aged 4–17 (inclusive). The Children's C-SSRS will be used for patients aged 6–18 (inclusive) while the C-SSRS will be used for patients aged 19 and older.
Secondary Endpoint(s)	**All Patients:** • Change in quality of life as measured with Quality of Life in Childhood Epilepsy (QOLCE) if 18 years of age or younger, or Quality of Life in Epilepsy (QOLIE) if 19 years of age or older, relative to the pre-randomization baseline of the Core

	Study, if assessed during the Core Study. • Change in Subject/Caregiver Global Impression of Change (S/CGIC), relative to the pre-randomization baseline of the Core Study. • Change in adaptive behavior as measured with the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II), relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study. • Change in the number of inpatient epilepsy-related hospitalizations (number of hospitalizations due to epilepsy in each 28-day period), relative to the pre-randomization baseline of the Core Study. • Change in the use of rescue medication (number of days used in each 28-day period), relative to the pre-randomization baseline of the Core Study. • Maintenance of seizure frequency reduction and freedom from seizures during the OLE study. • Percentage change in the frequency of total seizures, relative to the pre-randomization baseline of the Core Study. • Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in total seizures, relative to the pre-randomization baseline of the Core Study. • Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in total seizures, relative to the pre-randomization baseline of the Core Study. • Percentage change in the frequencies of subtypes of seizures, relative to the pre-randomization baseline of the Core Study. • Changes in duration of seizure subtypes as assessed by the Subject/Caregiver Global Impression of Change in Seizure Duration (S/CGICSD), relative to the pre-randomization baseline of the Core Study. • Change in the number of episodes of *status epilepticus*, relative to the pre-randomization baseline of the Core Study. • Change in cognitive function as measured with a cognitive assessment battery, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study. • Change in growth and development for patients less than 18 years of age 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), relative to the pre-randomization baseline of the Core

	Study. • Effects on menstruation cycles (in females). • Drug abuse liability, as measured by AEs of abuse potential, drug accountability and Study Medication Use and Behavior Survey in patients aged 12 and older. **DS Patients Only:** • Percentage change in total convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study. • Percentage change in total non-convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study. • Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in convulsive seizures, relative to the pre-randomization baseline of the Core Study. • Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in convulsive seizures, relative to the pre-randomization baseline of the Core Study. **LGS Patients Only:** • Percentage change in the number of drop seizures, relative to the pre-randomization baseline of the Core Study. • Percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study. • Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures, relative to the pre-randomization baseline of the Core Study. • Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in drop seizures, relative to the pre-randomization baseline of the Core Study.
Sample Size	All patients who wish to continue on Investigational Medicinal Product (IMP) from the populations included in the double-blind Phase 2 and Phase 3 studies in DS and LGS. Approximately 680 patients will be enrolled.
Summary of Patient Eligibility Criteria	**Inclusion (ALL must be fulfilled):** • Patient has completed the treatment phase of their Core Study. • Patient and/or parent(s)/legal representative must be willing and able to give informed consent/assent for participation in the study. • Patient and their caregiver must be willing and able (in the Investigator's opinion) to comply with all study requirements.

	• 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. **Exclusion (if ANY apply):** • Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex®) within the 3 months prior to study entry, not including IMP received during the Core study. • 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. • Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS at Visit 1. • Patient has been part of a clinical trial involving an IMP during the inter-study period. • Patient has previously been enrolled and dosed in this study. • 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 3 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 3 months thereafter. • 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. • 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. • Patient has significantly impaired hepatic function at the 'End of Treatment' visit of their Core Study or at Visit 1 if

	re-assessed, defined as **any** of the following: – ALT or AST > 5 × upper limit of normal (ULN). – ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** 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%). If the Core Study 'End of Treatment'/'End of Taper Period' visit assessments or Visit 1 re-assessments (as applicable) raise any safety concerns, the Investigator should consider whether it will be appropriate for the patient to continue to participate in the OLE study, or if the patient should be withdrawn.
Criteria for Withdrawal	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 **and** (TBL > 2 × ULN **or** INR > 1.5). • ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • ALT or AST > 8 × ULN. • ALT or AST > 5 × ULN for more than 2 weeks. Note: Prior to withdrawal for the transaminase elevations noted above, the Investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma glutamyl transferase and alkaline phosphatase. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial.** 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 4 or 5 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). Dosage: Patients will titrate up to 10–20 mg/kg/day GWP42003-P. Patients will then remain at this dose until the 'End of Treatment' visit, with the option for doses to be increased (up to 30 mg/kg/day, maximum) or decreased, if deemed necessary by the Investigator. Following the 'End of Treatment'/Withdrawal visit, doses of IMP will be down-titrated at home (10% per day for 10 days) until the 'End of Taper Period' visit. IMP will be taken twice daily (morning and evening).
Control Group	Not applicable.
Procedures	**Visit 1 (Day 1):** Every effort should be made for this visit to take place on the same day as the 'End of Treatment' visit or up to 7 (+ 3) days after the 'End of Treatment' visit of the Core Study. If this is not possible then patients can still enter the OLE study by passing the screening procedures at Visit 1. All patients will be instructed to begin titration of OLE IMP in the evening of Visit 1 (Day 1). Patients with no gap in IMP dosing between the Core Study and the OLE (including tapered dose) will take their final dose of Core Study IMP in the morning of Visit 1. Any OLE procedures that were not assessed during the Core Study should first be assessed at Visit 1, with the exception of the cognitive assessment battery. **For patients enrolling immediately from the Core Study into the OLE (same day):** The following data collected at the 'End of Treatment' visit of the Core Study will also be considered as Visit 1 data: vital signs, 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), ECG, clinical laboratory samples (including serum IGF-1 levels [patients less than 18 years of age] and pregnancy test [if appropriate]), Interactive Voice Response System (IVRS) and paper diary information from the previous study (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, concomitant medications and/or changes to medication, C-SSRS, QOLCE/QOLIE, Vineland-II, cognitive assessment battery (participating centers only), S/CGIC and S/CGICSD. A pregnancy test (if appropriate) must be conducted using a urine dipstick to confirm eligibility.

	Hepatic function must be confirmed before OLE dosing commences. In order to confirm normal hepatic function, an additional blood sample must be taken to analyze ALT, AST, TBL and INR at a local laboratory. **For patients enrolling from the taper period of the Core Study (1–7 [+ 3] days post 'End of Treatment' visit):** At Visit 1, patients should have their Core Study 'End of Taper Period' assessments made. These data, along with all other data collected at the 'End of Treatment' visit of the Core Study, will also be considered as Visit 1 data. A pregnancy test (if appropriate) must be conducted using a urine dipstick to confirm eligibility. Hepatic function must be confirmed before OLE dosing commences. In order to confirm normal hepatic function, an additional blood sample may be taken to analyze ALT, AST, TBL and INR at a local laboratory. **For patients with any gap in IMP dosing between the Core Study and the OLE:** At Visit 1, all aforementioned procedures must be re-assessed, with the exception of the cognitive assessment battery. A pregnancy test (if appropriate) must be conducted using a urine dipstick to confirm eligibility. Hepatic function must be confirmed before OLE dosing commences. In order to confirm normal hepatic function, an additional blood sample must be taken to analyze ALT, AST, TBL and INR at a local laboratory. All patients or their caregivers will receive a 2-week supply of GWP42003-P together with a titration schedule. If an unacceptable AE develops at any time during titration, dosing should initially be suspended or amended, at the Investigator's discretion, as appropriate, until the event has resolved or is well tolerated. It is advised that the Investigator considers monitoring hepatic function (ALT, AST, TBL and INR levels) during the titration period for patients taking AEDs that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10–20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW medical monitor. Patients or their caregivers will be given a paper diary to record information regarding AEs, usage of rescue medication, concomitant AEDs and IMP dosing during the time they are on treatment. In addition, patients/caregivers will be instructed to complete a weekly seizure reporting diary until the 'End of

	Treatment'/Withdrawal visit using the IVRS. **Visit 2 (Day 15 ± 3), Visit 3 (Day 29 ± 3):** The following assessments will be made: vital signs, physical examination (including height and body weight) and ECG. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the titration/dosing regimen. A 2-week supply of IMP will be issued to the patient/caregiver on Day 15. An 8-week supply of IMP will be issued to the patient/caregiver on Day 29. A safety telephone call must be made every 4 weeks (± 7 days) after Visit 3 to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. **Visit 4 (Day 85 ± 3):** The following assessments will be made: vital signs, physical examination (including height and body weight) and ECG. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen. A 12-week supply of IMP will be issued to the patient/caregiver. Following Visit 4, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. **Visit 5 (24 weeks ±7 days) and Visit 6 (36 weeks ± 7 days):** The following assessments will be made: vital signs, physical examination (including height and body weight), ECG, C-SSRS, Vineland-II, QOLCE/QOLIE, S/CGIC and S/CGICSD. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes

	to medication. The Investigator must assess adherence to the dosing regimen. Patients/caregivers will receive a 12-week supply of IMP at Visits 5 and 6. Between Visits 5 and 6, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. **Visit 7 (48 weeks ± 7 days):** The following assessments will be made: vital signs, physical examination (including height and body weight), effects on 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), ECG, C-SSRS, Vineland-II, cognitive assessment battery (participating centers only), QOLCE/QOLIE, S/CGIC and S/CGICSD. Clinical laboratory samples (urine [where possible] and blood) will be taken for determination of serum IGF-1 levels (for patients less than 18 years of age), pregnancy (if appropriate, using a serum sample), hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen. The cognitive assessment battery will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within 3 days of the visit) and will only be administered to patients who underwent cognitive testing during their Core Study. A 14-week supply of IMP will be issued to the patient/caregiver. Following Visit 7, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. At least 1 dispensing appointment will be scheduled to occur between Visits 7 and 8. The dispensing appointment date(s) will be calculated from Visit 7. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments.

	Visit 8 (76 weeks ± 7 days): The same assessments and review procedures will be made as at Visits 2, 3, 4, 5 and 6. A 14-week supply of IMP will be issued to the patient/caregiver. Following Visit 8, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. At least 1 dispensing appointment will be scheduled to occur between Visits 8 and 9. The dispensing appointment date(s) will be calculated from Visit 8. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments. **Visit 9 (104 weeks ± 7 days):** The same assessments and review procedures will be made as at Visit 7. A 14-week supply of IMP will be issued to the patient/caregiver. Following Visit 9, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. At least 1 dispensing appointment will be scheduled to occur between Visits 9 and 10. The dispensing appointment date(s) will be calculated from Visit 9. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments. **Visit 10 (132 weeks ± 7 days):** The same assessments and review procedures will be made as at Visits 2, 3, 4, 5, 6 and 8. A 14-week supply of IMP will be issued to the patient/caregiver. Following Visit 10, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. 1In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. At least 1 dispensing appointment will be scheduled to occur between Visit 10 and Visit 11. The dispensing appointment date(s) will be calculated from Visit 10. At each dispensing

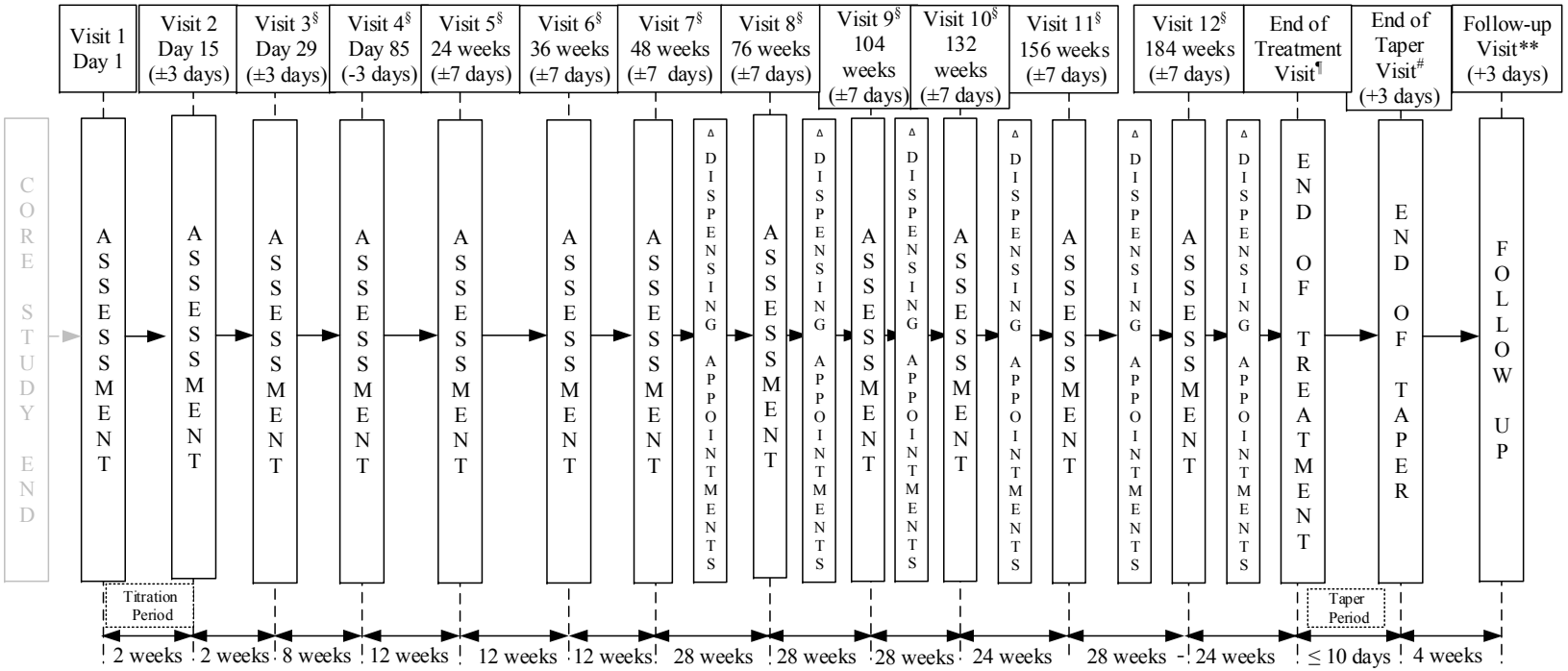
	appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments. **Visit 11 (156 weeks ± 7 days):** The same assessments and review procedures will be made as at Visit 7 and Visit 9. A 14-week supply of IMP will be issued to the patient/caregiver. Following Visit 11, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, weekly safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. At least 1 dispensing appointment will be scheduled to occur between Visits 11 and 12. The dispensing appointment date(s) will be calculated from Visit 11. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments. **Visit 12 (184 weeks ± 7 days):** The same assessments and review procedures will be made as at Visits 2, 3, 4, 5, 6, 8 and 10. A 14-week supply of IMP will be issued to the patient/caregiver. Following Visit 12, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. At least 1 dispensing appointment will be scheduled to occur between Visit 12 and 'End of Treatment' visit. The dispensing appointment date(s) will be calculated from Visit 12. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments. **<u>End of Treatment/Withdrawal, End of Taper and Follow-up Visits</u>** **End of Treatment/Withdrawal Visit:** This visit will take place after a maximum of 4 years' (208 weeks after Visit 1) treatment (as detailed below), or following early withdrawal from the study. • A patient with at least 2 years' participation in the OLE (≥ 104 weeks after Visit 1) will complete the OLE phase when GWP42003-P is approved in their indication and is

	commercially available. Patients will complete an unscheduled 'End of Treatment' visit to transition from OLE to commercial product. The timing will vary per patient and is projected to begin in February 2019. • A patient with less than 2 years' participation in the OLE when GWP42003-P is approved in their indication and is commercially available will continue the OLE phase until reaching a maximum of 2 years' OLE treatment, at which point an unscheduled 'End of Treatment' visit will be conducted. The unscheduled 'End of Treatment' visit will be conducted no earlier than 730 days after Visit 1. • Patients who do not continue treatment with GWP42003-P will be scheduled for an 'End of Taper' visit. The following assessments will be made: vital signs, physical examination (including height and body weight), effects on 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), ECG, C-SSRS, Vineland-II, cognitive assessment battery (participating centers only), QOLCE/QOLIE, S/CGIC and S/CGICSD. Clinical laboratory samples (urine [where possible] and blood) will be taken for determination of serum IGF-1 levels (for patients less than 18 years of age), pregnancy (if appropriate, using a serum sample), hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen. The cognitive assessment battery will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within 3 days of the visit) and will only be administered to patients who underwent cognitive testing during their Core Study. Patients who do not immediately continue to use GWP42003-P will then commence a taper period (down-titrating 10% per day for 10 days). 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 diary information will continue to be recorded in the paper diary. Following the 'End of Treatment'/Withdrawal visit, the IVRS seizure reporting diary should only be completed on the day before the 'End of Taper Period' visit and on the day before the Follow-up visit.

	End of Taper Period Visit: This visit will take place 10 (+ 3) days after the 'End of Treatment' visit or Withdrawal visit for patients who withdraw early or who do not transition to commercial product. 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. The following assessments will be made: vital signs, physical examination (including height and body weight), CWS/PCWS and C-SSRS. In addition, the following assessments will be made for patients who do not transition to commercial product or 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen. Following the 'End of Taper Period' visit (or date of final dosing), the IVRS seizure reporting diary should only be completed on the day before the Follow-up visit. **Post-Taper Safety Telephone Call:** A safety telephone call must be made 2 weeks (± 3 days) after the 'End of Taper Period' visit or date of final dosing. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The CWS/PCWS will be administered as well. Following this call, the IVRS seizure reporting diary should only be completed on the day before the Follow-up visit. **Follow-up Visit:** For patients who withdraw or complete, but do not wish to continue to use GWP42003-P, a safety follow-up visit will be performed 4 weeks (+ 3 days) after the patient's last dose (including final taper period dose). This visit can be conducted over the telephone. During this visit/call, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The CWS/PCWS will be administered as well. **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, 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 ('End of Treatment'/Withdrawal visit or 'End of Taper Period' visit, 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	All data collected during this study will be summarized across time, using appropriate statistical methods. Where baseline data are available from the Core Studies (seizure information, C-SSRS, quality of life assessments, Vineland-II, cognitive assessment battery, other measures of safety [vital signs, clinical laboratory samples]), changes from baseline will also be presented. Summaries will be presented overall as well as for the different etiologies (DS and LGS) separately. Descriptive statistical methods will be used throughout. There will be no formal hypothesis testing.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

Figure 1-1 Study Design and Treatment Schema



* All patients will be instructed to begin titration of OLE IMP in the evening of Visit 1 (Day 1). Patients with no gap in IMP dosing between the Core Study and the OLE (including tapered dose) will take their final dose of Core Study IMP in the morning of Visit 1.

§ Between visits, safety telephone calls must be made every 4 weeks (± 7 days). In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. All safety telephone calls will assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

Δ IMP dispensing appointments will take place between all visits after Visit 7, 14 weeks following the previous visit.

¶ 'End of Treatment' visit will occur after a maximum of 4 years' treatment (208 weeks after Visit 1), following early withdrawal from the study, or following an unscheduled 'End of Treatment' visit conducted no earlier than 730 days after Visit 1.

Following the 'End of Taper Period' visit (or date of final dosing), a safety telephone call must be made 2 weeks (± 3 days) later to collect seizure information, administer the CWS/PCWS and to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

** Can be conducted by telephone.

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List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CGICSD	Caregiver Global Impression of Change in Seizure Duration
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CWS	Cannabis Withdrawal Scale
DS	Dravet syndrome
DSMC	Data Safety Monitoring Committee
EAP	Intermediate Expanded Access Investigational New Drug Program
EC	Ethics Committee
ECG	12-lead Electrocardiogram
EEG	Electroencephalogram
EU	European Union
GCP	Good Clinical Practice
GW	GW Research Ltd
GWP	GW Pharma Ltd
IB	Investigator Brochure
ICH GCP	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice
IGF-1	Insulin-like growth factor-1
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LGS	Lennox-Gastaut syndrome

OLE	Open label extension
PCWS	Pediatric Cannabinoid Withdrawal Scale
PI	Principal Investigator
PVD	Pharmacovigilance Department
QOLCE	Quality of Life in Childhood Epilepsy
QOLIE	Quality of Life in Epilepsy
S/CGIC	Subject/Caregiver Global Impression of Change
S/CGICSD	Subject/Caregiver Global Impression of Change in Seizure Duration
SGIC	Subject Global Impression of Change
SGICSD	Subject Global Impression of Change in Seizure Duration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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
VPA	Valproic Acid

Definition of Terms

Term	Definition
Baseline	The 28-day period of the Core Study from screening to randomization.
Convulsive seizures	Tonic-clonic, tonic, clonic or atonic seizures.
Core Study	A double-blind, randomized, placebo-controlled, parallel group study of GWP42003-P in patients with DS or LGS.
Countable partial seizures	Partial/focal seizures with a motor or behavioral component that allow such seizures to be easily identified and hence counted.
Day 1	The day a patient first receives investigational medicinal product in this study.
Drop seizure	An attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or may have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.
Enrolled patient	Patient is considered enrolled in the study from the time of providing written informed consent/assent.
End of treatment	A maximum of 4 years' (208 weeks after Visit 1) treatment.
End of study	Last patient last visit or last contact, whichever occurs last.
IMP	Investigational Medicinal Product (Study Medication).
INR	International Normalized Ratio (INR) is a calculation made to standardize prothrombin time.
Investigator	Study Principal Investigator or a formally delegated study physician.
Non-convulsive seizures	Myoclonic, partial or absence seizures.
Non-drop seizures	Seizures that would not result in a fall or drop attack.
Status epilepticus	Any seizure lasting for 30 minutes or longer.
Subtypes of seizures	Protocol seizure subtypes can be atonic, tonic, clonic, tonic-clonic, myoclonic, absence, countable partial and other partial.

2 OBJECTIVES

2.1 Primary

To evaluate the long term safety and tolerability of GWP42003-P, as adjunctive treatment, in children and adults with inadequately controlled Dravet Syndrome (DS) or Lennox-Gastaut Syndrome (LGS).

2.2 Secondary

All Patients:

To evaluate the effect of GWP42003-P, as adjunctive treatment, on:

- Quality of life.
- Adaptive behavior.
- Need for hospitalizations due to epilepsy.
- Usage of rescue medication.
- Maintenance of seizure frequency reduction and freedom from seizures during the open label extension (OLE) study.
- Frequency of total and subtypes of seizures.
- Change in duration of subtypes of seizures.
- Number of episodes of *status epilepticus*.
- Cognitive function.
- Growth and development.
- Menstruation cycles (in females).
- Signals indicating drug abuse liability of GWP42003-P.

DS Patients Only:

To evaluate the effect of GWP42003-P, as adjunctive treatment, on:

- Total convulsive seizure frequency.
- Total non-convulsive seizure frequency.
- Number of patients convulsive seizure-free.
- Responder rate (defined in terms of percentage reduction in total convulsive seizure frequency).

LGS Patients Only:

To evaluate the effect of GWP42003-P, as adjunctive treatment, on:

- Drop seizure frequency.
- Non-drop seizure frequency.
- Number of patients drop seizure-free.

- Responder rate (defined in terms of percentage reduction in drop seizure frequency).

3 BACKGROUND AND RATIONALE

3.1 Disease

DS, also known as Severe Myoclonic Epilepsy in Infancy, and LGS are two rare forms of severe epilepsy with onset in early childhood. DS and LGS each have an incidence of around 1 in 40–50,000[1,2,3] and account for 1.4% and 4.3% of childhood epilepsies, respectively[4,5]. Both DS and LGS are considered epileptic encephalopathies in which the epileptic activity contributes to mental deterioration/stagnation and behavioral disorders with a high proportion of patients being drug-resistant. DS and LGS differ in seizure types, age of onset and electroencephalogram (EEG) features.

In DS, onset usually occurs between 4 and 8 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*[6,7,8]. After a typical period of 2 weeks to 2 months, further febrile seizures occur and afebrile seizures begin to appear. In addition to the above convulsive seizures, myoclonic seizures, tonic-clonic seizures, focal seizures, atypical absences and obtundation statuses (in which consciousness is impaired) appear between the ages of 1 and 4 years. Episodes of convulsive or non-convulsive *status epilepticus* may also occur. Despite the frequent occurrence of convulsive seizures, interictal EEG recordings are generally normal during the first 6 months following onset of DS. However, background EEG activity tends to slow as the disease develops and EEG spike-waves with ≥ 3 Hz frequency are often observed during massive myoclonic seizures[6,9]. Significant developmental delay becomes apparent from the second year onwards and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common[6,7,8].

The onset of LGS usually occurs between 3 and 5 years of age and is characterized by the presence of multiple seizure types (predominantly tonic, atonic and atypical absence seizures), slow (≤ 2.5 Hz) EEG spike-waves with abnormal background activity when awake and fast (10–20 Hz) polyspikes during sleep[10,11,12]. Other seizure types can occur in LGS, including generalized tonic-clonic, focal and myoclonic seizures. The diagnostic clinical and EEG features of LGS may not be present at the time of onset of LGS and it sometimes evolves from other early-onset epileptic encephalopathies. It is suggested that approximately 20% of LGS cases are preceded by West syndrome (peak onset 4–7 months), which itself can evolve from Ohtahara syndrome (onset within 1 month of birth)[12]. Due to this etiology, 20–60%

of LGS patients already have delayed cognitive development at onset of LGS[10]. In cryptogenic cases of LGS (25–30% of all cases) development appears normal prior to the onset of the first seizures, yet cognitive impairment is apparent in 75–95% of all LGS patients by 5 years post-onset[10]. As with DS, various behavioral and psychiatric comorbidities are often seen in LGS patients, including attention deficit/hyperactivity disorder, anxiety, aggressive behavior, psychosis and depression[10,12]. Generally, both LGS and DS are more prevalent in boys.

Genetic analyses have revealed that more than 70% of patients with DS have mutations in the voltage-gated sodium channel α1 subunit gene (*SCN1A*)[13,14,15,16,17,18]. *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[19]. 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[20,21,22,23]. 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. Additional genes in which mutations cause DS include *PCDH19*[24,25], *GABRG2*[26], *SCN1B*[27] and *SCN2A*[28], although very few cases have been reported. Genetic factors are regarded to be less important in LGS as approximately 75% of cases are symptomatic with underlying cerebral malformation, hypoxic–ischemic injury, tuberous sclerosis or metabolic disease[11,12]. However, a genetic predisposition has been hypothesized to underlie cryptogenic cases of LGS[29] and a variant of the mitochondrial *MTND1* gene has recently been associated with LGS evolving from West syndrome[30]. Furthermore, in a cohort of LGS and West syndrome patients, *de novo* mutations have recently been found in the genes *GABRB3* and *ALG13*, as well as in several genes regulated by the fragile X protein[31].

DS and LGS are two of the most pharmacoresistant forms of epilepsy, with all seizure types extremely refractory to conventional antiepileptic drugs (AEDs). Sodium valproate (valproic acid [VPA]) is often used to prevent the initial recurrent convulsive seizures and benzodiazepines (e.g., diazepam, midazolam, clonazepam or clobazam) are frequently co-administered to limit the duration of long-lasting seizures and frequency of drop attacks. In most cases however, the relief provided by these agents is insufficient[10,32,33]. Two randomized, double-blind, dose-ranging studies evaluated the safety and efficacy of clobazam as adjunctive therapy for drop seizures in LGS patients[34,35]. In the first study, which compared 2 doses of clobazam, two

thirds of patients in the high dose group (1.0 mg/kg/day, $n = 36$) experienced ≥ 75% reduction in weekly drop seizures after 4 weeks' stable dosing, compared with one quarter of patients in the low dose group (0.25 mg/kg/day, $n = 32$). Moreover, 22% of patients in the high dose group achieved drop seizure freedom compared with 6% of patients in the low dose group[34]. In the second study, which compared 3 doses of clobazam with placebo, 78% of patients in the high dose group (1.0 mg/kg/day, $n = 49$) achieved a ≥ 50% reduction in drop seizures after 12 weeks' stable dosing, compared with 32% of patients taking placebo ($n = 57$)[35]. Eligible patients from both of these trials were then given the opportunity to continue receiving clobazam as adjunctive treatment for LGS in an OLE study[36,37]. Of the patients who had a ≥ 50% reduction in drop seizures after 3 months' continuing treatment, 86% maintained this degree of drop seizure reduction at Year 3, and 47% were drop seizure free[37]. Following the results of the 2 randomized trials, clobazam (under the name Onfi) was later approved by the FDA in 2011 as add-on therapy for LGS patients aged 2 years and older.

Lamotrigine has been shown to reduce the frequency of all seizure types in LGS, with one third of patients receiving lamotrigine achieving a > 50% reduction at 16 weeks compared with 16% receiving placebo[38]. Similarly, more than half of LGS patients taking lamotrigine experienced a > 50% reduction in seizures at 12 weeks when compared with placebo in a 2-period, within-patient crossover study[39]. Lamotrigine can paradoxically worsen seizures in DS patients however[40] and all sodium channel blockers are best avoided in DS patients. Potassium bromide can be effective at controlling seizures in DS, with over half of patients achieving a > 50% reduction and 30% becoming seizure-free at 3 months[41]. However, this compound has no effect on focal and tonic seizures (hence it is not used in LGS) and any initial efficacy is often not maintained long term[33,41].

To date, the only AED that has proved efficacious in the treatment of DS in placebo-controlled, double-blind trials is stiripentol[42,43]. In these studies, stiripentol was administered as adjunctive therapy to VPA 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[42,43]. A subsequent meta-analysis of these studies showed that stiripentol reduced the overall seizure rate by 70%[44]. 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[41]. 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 6 weeks and 6 months, respectively[45]. Stiripentol is generally well tolerated and can improve seizure control in DS patients receiving pharmacotherapy other than VPA and/or clobazam[45,46].

Topiramate and levetiracetam are 2 further AEDs that have undergone preliminary trials as adjunctive therapy in DS and LGS patients. In 3 open label studies, more than half of DS patients receiving topiramate as add-on therapy achieved a > 50% reduction in seizure frequency, with 17% becoming seizure-free for at least 4 months in all cases[47,48,49]. In the only randomized placebo-controlled trial of adjunctive topiramate use in LGS to date, one third of patients taking topiramate achieved a > 50% reduction in drop attacks and tonic–clonic seizures at 11 weeks compared with 8% taking placebo[50]. As such, topiramate was approved by the FDA in 2001 as add-on therapy for LGS patients 2 years of age and older. Two subsequent long term open label studies showed that 55% and 40% of LGS patients experienced a 50% reduction in drop attacks at 6 and 16 months, respectively[51,52]. Open label trials of levetiracetam have demonstrated similar results, with approximately two thirds of DS and LGS patients experiencing a 50—100% reduction in tonic–clonic seizures at 12 weeks and 12 months, respectively[53,54]. However, tonic seizure frequency in LGS patients remained unchanged.

Following preliminary trials, felbamate and rufinamide have also been approved as add-on therapy for treatment of LGS. Felbamate was approved by the FDA for the treatment of LGS after a randomized controlled study demonstrated a 19% overall decrease in the total frequency of seizures in LGS patients receiving felbamate at 10 weeks compared with a 4% increase in the placebo group[55]. Similarly, rufinamide was granted FDA approval after a placebo-controlled, double-blind study showed there was a 33% overall reduction in all seizures experienced by LGS patients taking rufinamide at 12 weeks compared with a 12% reduction in patients taking placebo[56]. These newer AEDs therefore appear promising for the management of seizures in DS and LGS; however, larger randomized placebo-controlled studies are required to accurately assess their efficacy in the treatment of these syndromes.
Non-pharmacological treatments of DS and LGS have also demonstrated benefit as adjunctive therapy to AEDs, including vagus nerve stimulation[57,58,59] and the introduction of a ketogenic diet[60,61,62,63]. Despite the therapies listed above, DS and LGS remain 2 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 Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), although the amounts and proportions of the various phytocannabinoids in each plant vary by strain and can be adjusted by breeding.

The Investigational Medicinal Product (IMP), GWP42003-P, is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (≥ 98%) CBD that typically contains less than 0.15% (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 ion channel conductances and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1[64] and the orphan receptor GPR55[65]. Importantly, CBD generally lacks detectable psychoactivity as found with THC. CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity[66]. 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[67].

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[68]. 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[69]. 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 only child diagnosed with LGS achieved a > 80% reduction in seizure

frequency. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness and better mood.

The current study will provide free access to GWP42003-P for patients with DS or LGS who have completed the double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies). The study will also assess the long term safety and efficacy of GWP42003-P when taken as adjunctive therapy for DS and LGS.

3.3.1 Selection of Study Dose

Doses up to 800 mg CBD per day for up to 8 weeks have been well tolerated in adults in GW Research Ltd (GW) clinical study GWMD09112[70], 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 4 weeks in adults[67], which, in a 70 kg human, equates to a daily dose of 21.4 mg/kg CBD.

At the time of dose selection, GWP42003-P was being used by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies in a number of open Individual Expanded Access Investigational New Drug (IND) studies and open Intermediate Expanded Access IND studies. In the ongoing Individual Expanded Access IND studies, the initial dosing had been cautious (100 mg [morning] + 150 mg [afternoon/evening]), progressively increasing to 400 mg CBD/day; doses up to 22 mg/kg per day had been well tolerated in an individual pediatric patient. The Sponsor was not aware of any safety issues arising from the dosing used in the Individual Expanded Access INDs. Treatment has also begun in the Intermediate Expanded Access INDs. Based on the above, a daily maximum dose of 20 mg/kg CBD (given as 2 divided doses) was selected for the Phase 2 study in patients with DS (GWEP1332 Part A). At the end of Part A of the GWEP1332 study a Data Safety Monitoring Committee (DSMC) recommended the 20 mg/kg/day maximum dose and titration schedule for all subsequent studies, including this OLE (see APPENDIX 4). During the maintenance phase, Investigators may decrease the dose if a patient experiences intolerance, or increase the dose if required for better seizure control, until the optimal dose is found. The Investigator may schedule additional clinic visits during the maintenance period to facilitate dose adjustments, e.g., when increasing doses above 20 mg/kg/day. Patients whose dose has been decreased can have their dose increased again, if the tolerability improves.

The maximum dose patients can receive during the OLE maintenance phase will be 30 mg/kg/day. This was based on data from the Intermediate Expanded Access IND program (EAP), at the time of initiation of GWEP1415. The Sponsor reviews all safety information on an ongoing basis from the patients in all of the Expanded

Access INDs regarding GWP42003-P. Please refer to the Development Core Safety Information[71] for the most current safety data. At the initiation of GWEP1415, the maximum dose used to date in the EAP was 51 mg/kg/day, with a mean dose of 24 mg/kg/day and 64% of doses falling within the 20-30 mg/kg/day range.

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[69] suggest that CBD is an effective AED in children with DS or LGS 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 and LGS.

4 EXPERIMENTAL PLAN

4.1 Study Design

This is a multi-center, OLE study for patients with DS or LGS who have completed the double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies). The study consists of a titration period and a maintenance period, followed by a 10-day taper period.

Titration Period: All patients will titrate up to 10–20 mg/kg/day GWP42003-P using a recommended titration schedule (see APPENDIX 4). It is advised that the Investigator considers monitoring hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL] and international normalized ratio [INR] levels) during the titration period for patients taking concomitant AEDs that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10–20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW medical monitor.

Maintenance Period: Patients will continue dosing at 10–20 mg/kg/day. However, Investigators may decrease the dose if the patient experiences intolerance, or increase the dose if required for better seizure control, until the optimal dose is found. The Investigator may schedule additional clinic visits to facilitate dose adjustments e.g., when increasing doses above 20 mg/kg/day. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. The maximum dose patients can receive will be 30 mg/kg/day (51 mg/kg/day is the maximum dose safely used in the USA EAP to date with a mean dose of 24 mg/kg/day [$n = 59$]). Dose increases above 20 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg every 5–7 days. If seizure freedom is achieved with use of GWP42003-P during the study, the Investigator can consider reducing the dose of concomitant AEDs after consultation with the GW medical monitor.

Study Completion: The maximum duration of this OLE study will be 4 years (208 weeks after Visit 1).

- A patient with at least 2 years' participation in the OLE (≥ 104 weeks after Visit 1) will complete the OLE phase when GWP42003-P is approved in their indication and is commercially available. Patients will complete an

unscheduled 'End of treatment' visit to transition from OLE to commercial product. The timing will vary per patient and is projected to begin in February 2019.

- A patient with less than 2 years' participation in the OLE when GWP42003-P is approved in their indication and is commercially available will continue the OLE phase until reaching a maximum of 2 years' (104 weeks after Visit 1) OLE treatment, at which point an unscheduled 'End of Treatment' visit will be conducted. The unscheduled 'End of Treatment' visit will be conducted no earlier than 730 days after Visit 1.
- A patient who does not continue treatment with GWP42003-P will commence the 10-day taper period (down-titrating 10% per day for 10 days) and complete an 'End of Taper Period' visit followed by a Follow-up visit (which can be by telephone) 4 weeks later.

Interim Analysis: At least one interim analysis will be conducted to support New Drug Application and Marketing Authorization Application filings. Further interim analyses may be conducted as required.

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, and is summarized in APPENDIX 1.

4.1.1 Primary Endpoint

The safety of GWP42003-P will be assessed by the AE profile and by evaluating changes in the following, relative to the pre-randomization baseline of the Core Study:

- Vital signs.
- Physical examination (including height and body weight).
- 12-lead electrocardiogram (ECG).
- Columbia-Suicide Severity Rating Scale (C-SSRS) score.
- Cannabis Withdrawal Scale (CWS) score or Pediatric Cannabinoid Withdrawal Scale (PCWS) score, as appropriate.
- Clinical laboratory parameters.

The CWS will be administered to patients aged 18 and older while the PCWS will be administered to patients aged 4–17 (inclusive).

The Children's C-SSRS will be used for patients aged 6–18 (inclusive) and the C-SSRS will be used for patients aged 19 and older.

4.1.2 Secondary Endpoint(s)

All Patients:

- Change in quality of life as measured with Quality of Life in Childhood Epilepsy (QOLCE) if 18 years of age or younger, or Quality of Life in Epilepsy (QOLIE) if 19 years of age or older, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in Subject/Caregiver Global Impression of Change (S/CGIC), relative to the pre-randomization baseline of the Core Study.
- Change in adaptive behavior as measured with the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II), relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in the number of inpatient epilepsy-related hospitalizations (number of hospitalizations due to epilepsy in each 28-day period), relative to the pre-randomization baseline of the Core Study.
- Change in the use of rescue medication (number of days used in each 28-day period), relative to the pre-randomization baseline of the Core Study.
- Maintenance of seizure frequency reduction and freedom from seizures during the OLE study.
- Percentage change in the frequency of total seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in total seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in total seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the frequencies of subtypes of seizures, relative to the pre-randomization baseline of the Core Study.
- Changes in duration of seizure subtypes as assessed by the Subject/Caregiver Global Impression of Change in Seizure Duration (S/CGICSD), relative to the pre-randomization baseline of the Core Study.
- Change in the number of episodes of *status epilepticus*, relative to the pre-randomization baseline of the Core Study.
- Change in cognitive function as measured with a cognitive assessment battery, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in growth and development for patients less than 18 years of age 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), relative to the pre-randomization baseline of the Core Study.

- Effects on menstruation cycles (in females).
- Drug abuse liability, as measured by AEs of abuse potential, drug accountability and Study Medication Use and Behavior Survey in patients aged 12 and older.

DS Patients Only:

- Percentage change in total convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.
- Percentage change in total non-convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in convulsive seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in convulsive seizures, relative to the pre-randomization baseline of the Core Study.

LGS Patients Only:

- Percentage change in the number of drop seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in drop seizures, relative to the pre-randomization baseline of the Core Study.

4.2 Number of Centers

Approximately 70 centers are expected to participate in this study.

4.3 Number of Patients

All patients who wish to continue on IMP from the populations included in the double-blind Phase 2 and Phase 3 Core Studies in DS and LGS. Approximately 680 patients will be enrolled. Patients are considered enrolled in the study from the time of providing written informed consent/assent.

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 Packaging, Storage and Drug Accountability

5.2.1 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 visit considering the decided dose as per the Investigator's discretion and weight of each patient. An Interactive Voice Response System (IVRS) will be utilized, where a unique pack identification number will be used to identify each box and the medication it contains. The pack numbers will cross check with the batch numbers held at GWP. GWP will ensure that all IMP provided is fully labeled and packaged. Label text will comply with European Union (EU) guidance on Good Manufacturing Practice, Annex 13. In addition, any local country requirements in accordance with local Drug Law or Regulatory Requirement will be included in the final label text.

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

5.2.2 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.

Patients or their caregivers will be provided with instructions regarding IMP home storage requirements.

5.2.3 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 5.2.4). 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.

5.2.4 Investigational Medicinal Product Accountability

The Investigator has overall responsibility for the accountability of all used and unused IMP. A drug accountability record for the IMP 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, if appropriate.

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 enrolled patients (initials, date of birth, sex; as allowed per local regulations) and outcome of applicable screening.

6.1 Inclusion Criteria

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

6.1.1 Patient has completed the treatment phase of their Core Study.

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

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

6.1.4 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.

6.2 Exclusion Criteria

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

6.2.1 Patient is currently using or has in the past used recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex®) within the 3 months prior to study entry, not including IMP received during the Core study.

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

6.2.3 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.

6.2.4 Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS at Visit 1.

6.2.5 Patient has been part of a clinical trial involving an IMP during the inter-study period.

6.2.6 Patient has previously been enrolled and dosed in this study.

6.2.7 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 3 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.

6.2.8 Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for 3 months thereafter.

6.2.9 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.

6.2.10 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.

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

6.2.12 Patient has significantly impaired hepatic function at the 'End of Treatment' visit of their Core Study or at Visit 1 if re-assessed, defined as **any** of the following:

i) ALT or AST > 5 × upper limit of normal (ULN).

ii) ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** 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%).

If the Core Study 'End of Treatment'/'End of Taper Period' visit assessments or Visit 1 re-assessments (as applicable) raise any safety concerns, the Investigator should consider whether it will be appropriate for the patient to continue to participate in the OLE study, or if the patient should be withdrawn.

7 PATIENT ENROLLMENT

Before patients may be entered into the study, GW requires a copy of the relevant center's Ethics Committee (EC) or Institutional Review Board (IRB) written approval of the protocol, informed consent/assent form 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

As this is a single-group OLE study, all patients will receive GWP42003-P. Patients will not be informed of their allocated treatment group in the Core Study. Patients will retain the patient number allocated to them during the Core Study.

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The IMP will be presented as an oral solution containing 100 mg/mL CBD and excipients. For details regarding IMP formulation see Section 5.

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.

Dosing through gastrostomy/nasogastric tubes may be allowed after consultation with the GW medical monitor. Alteration in dosing frequency may also be considered after consultation 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 titrate up to a target dose of 10–20 mg/kg/day GWP42003-P.

Patients will be weighed at each study visit. During Visit 1, the daily volumes of IMP solution to be taken during the titration period will be calculated via the IVRS and the dosing regimen provided to the patient and/or caregiver. Patients should aim to achieve the target dose before the end of the 2-week titration period; however, Investigators may decrease the dose if a patient experiences intolerance, or increase the dose if required for better seizure control, until the optimal dose is found. The titration period will be considered 2 weeks long to ensure most patients have achieved stable dosing from Visit 2 onwards (maintenance period). The rate of titration should be adjusted based on the specific needs of an individual patient. It is advised that the Investigator considers monitoring hepatic function (ALT, AST, TBL and INR levels) during the titration period for patients taking AEDs that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10-20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW medical monitor. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

If an unacceptable AE develops at any time during titration, dosing should initially be suspended or amended, at the Investigator's discretion, as appropriate, until the event has resolved or is well tolerated. During the maintenance period, Investigators may decrease the dose if a patient experiences intolerance, or increase the dose if required for better seizure control, until the optimal dose is found. The Investigator may schedule additional clinic visits during the maintenance period to facilitate dose adjustments, e.g., when increasing doses above 20 mg/kg/day. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. Dose increases above 20 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg every 5–7 days. The maximum dose patients can receive will be 30 mg/kg/day.

For patients who do not immediately continue to use GWP42003-P following the 'End of Treatment' visit, IMP will be down-titrated at home (10% per day for 10 days). 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.

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. Concomitant AED plasma level monitoring may be conducted if deemed necessary. However, if drug-drug interactions are suspected or observed, the Investigator must contact the GW medical monitor to discuss best management, but the expectation is that decisions should be based on clinical symptoms and not plasma levels of AEDs. Further information on drug interactions can be found in the Investigator Brochure (IB)[71].

It is advised that the Investigator considers monitoring hepatic function (ALT, AST, TBL and INR levels) during the titration period for patients taking AEDs that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10–20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW

medical monitor. If seizure freedom is achieved with use of GWP42003-P during the study, the Investigator can consider reducing the dose of concomitant AEDs after consultation with the GW medical monitor. Additional new AEDs are not allowed to be added but may be considered on a case-by-case basis after consultation with the GW medical monitor.

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).

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 enrollment 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).

- Recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex), other than the IMP, within the inter-study period or during the study.
- Any other IMP taken as part of a clinical trial within the inter-study period or during the study.

8.4 Compliance in Investigational Medicinal Product Administration

The IMP is dispensed to the patient at each study visit except the 'End of Taper Period' visit and the Follow-up visit. If necessary, additional IMP will be dispensed at dose-adjustment clinic visits scheduled by the Investigator. IMP will be dispensed at the 'End of Treatment'/Withdrawal visit only if required for the 10-day taper period. Patients or their caregivers will confirm the daily dose has been administered using the paper diary. Patients will be asked to return all IMP (used and unused) at each subsequent visit. 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 9.1.15.2.1 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 5.2.4.

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 3 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)[72]. 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 are 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, an informed consent form will be signed if the patient possesses adequate understanding to do so.

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

9.1.2 Demographics

The following demographic information collected for the Core Study will be used for the current study: date of birth, sex and race (as allowed per local regulations).

9.1.3 Medical History

Medical history collected for the Core Study will be used for the current study. New information about relevant, significant medical history discovered during/after the Core Study will be collected and is defined as any condition or disease that:

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

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 medication, including AEDs, recorded at the end of the Core Study ('End of Treatment', 'End of Taper Period' or Follow-up visit, as applicable) and medications, including AEDs, taken during the last 2 weeks of the inter-study period ("prior medications") will also be recorded for the current study and at each subsequent study visits. 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 enrollment, as defined in Section 8.3.

If seizure freedom is achieved with use of GWP42003-P during the study, the Investigator can consider reducing the dose of concomitant AEDs after consultation with the GW medical monitor.

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 5 minutes, will be completed alongside the physical examination. Blood pressure must be recorded using the same arm throughout the study.

9.1.8 12-Lead Electrocardiogram

An ECG will be performed, after 5 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). Analysis of all clinical blood samples and pregnancy tests (using serum at the 'End of Treatment'/Withdrawal visit) will be conducted at a central clinical laboratory. However, in order to confirm normal hepatic function before OLE dosing commences, an additional blood sample may be taken to analyze ALT, AST, TBL and INR at a local 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 at Visit 1. 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 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.

Throughout the study additional blood samples may be collected for measurement of plasma concentrations of concomitant AEDs. The decision on whether or not to assess plasma concentrations of concomitant AEDs will be left to the Investigator's clinical judgment. Analysis may be done at local or central laboratories and data

collected in the CRF. Central laboratory analysis results will not be released to the Investigator.

Table 9.1.9-1 Hematology, Biochemistry and Urinalysis

Biochemistry (serum)	Hematology (whole blood)	Urinalysis (urine)	Pregnancy Test
Alanine aminotransferase (ALT)	Hematocrit	Bilirubin	(Serum or Urine)
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 centers 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 Interactive Voice Response System

The IVRS will be used to collect patient reported diary data (refer to Section 9.1.12) and to manage IMP supply. A member of the study team must contact the IVRS at each clinic visit in order to obtain dispensing information and to provide completion/taper/premature termination information.

9.1.11 Questionnaires and Assessments Completed at Scheduled Visits

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

9.1.11.1 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. Vineland-II assessments will be performed for all patients irrespective of whether or not they completed the Vineland-II during their Core Study.

9.1.11.2 Quality of Life in Childhood Epilepsy (18 Years of Age and Younger) or Quality Life in Epilepsy (19 Years of Age and Older)

The QOLCE and the QOLIE are composed of 16 and 31 subscales, respectively, assessing 7 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 (and QOLIE, if completed by the caregiver) must be completed by a person who interacts with the patient on a consistent, daily basis. Quality of life assessments will be performed for all patients irrespective of whether or not they completed during their Core Study. The questionnaires should take 20–30 minutes to complete.

9.1.11.3 Subject/Caregiver Global Impression of Change

The S/CGIC, as appropriate, will be performed for all patients irrespective of whether or not it was completed during their Core Study. The patient or patient's caregiver will use the description of their/the patient's overall condition made during the Core Study (prior to commencement of IMP). If the memory aid is not available from the Core Study then the patient/caregiver will be asked to write a brief description from memory, if possible, at Visit 1 as an aid for subsequent visits. It is preferred that the same person performs this assessment at each visit.

The CGIC comprises the following question to be rated on a 7-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 SGIC comprises the following question to be rated on a 7-point scale:

- Since you started treatment, please assess the status of your overall condition (comparing your condition now to your 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.

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 3 days.

9.1.11.4 Subject/Caregiver Global Impression of Change in Seizure Duration

The S/CGICSD comprises a question to be rated on a 3-point scale for each seizure subtype:

CGICSD:

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

SGICSD:

- Since you started treatment, please assess the average duration of your seizures (comparing their condition now to their condition before treatment at the Baseline of the Core Study) 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 patient/caregiver would have been asked to assess and note the average duration of the patient's seizures at the Baseline of the Core Study as a memory aid for subsequent visits. If the memory aid is not available from the Baseline of the Core Study then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit 1.

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 3 days.

9.1.11.5 Columbia-Suicide Severity Rating Scale (Six Years of Age and Older)

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. Questioning will be in relation to the last assessment (Since Last Visit).

The C-SSRS is to be completed 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 anyone who has completed the C-SSRS training within the past 2 years. The survey should be completed by the same assessor, where possible, throughout the study. The Children's C-SSRS will be used for patients aged 6–18 (inclusive) while the C-SSRS will be used for patients aged 19 and older. For patients that become 6 years old during this OLE trial, the Children's Baseline C-SSRS (employing questions in relation to lifetime experience) should be completed at the next trial visit. Questioning at all subsequent visits will be in relation to the last assessment (Children's Since Last Visit).

9.1.11.6 Cognitive Assessment Battery

The items that comprise the cognitive assessment battery are age specific. The age of the patient at entry will be the age used when choosing the items to be administered. 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 any of it. Parents and/or caregivers are to complete certain items. The cognitive assessment battery items will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within 3 days of the visit). Each assessment will need to be conducted by an experienced

psychometrician. A summary of the battery is as shown below in Table 9.1.11.6-1 and Table 9.1.11.6-2. Items will only be administered to patients who underwent cognitive testing during their Core Study.

Table 9.1.11.6-1 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 9.1.11.6-2 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

9.1.11.7 Cannabis Withdrawal Scale (18 Years and Above) or Pediatric Cannabinoid Withdrawal Scale (4–17 Years)

The CWS is to be administered to patients 18 years of age and above. It 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., 2 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 is to be administered to patients aged 4 to 17 years of age (inclusive). It 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.

Ratings are based on a 4-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 or PCWS, as appropriate, would have been used at the Baseline of the Core Study to establish a baseline score for this current study, GWEP1415.

Assessments will be conducted only if patients are of an appropriate age (4 years of age and older).

9.1.11.8 Menstruation

For female patients, details of menstruation recorded during the Core Study (including whether the patient is menstruating and any changes in normal menstrual cycles) will continue to be assessed.

9.1.11.9 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 (see APPENDIX 3). The patients will undergo a discreet physical examination and assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only). Once a patient reaches a score of "V" (i.e., 5), the examination need not be performed again.

9.1.12 Patient Diary

Seizure information (number and type of seizures) will continue to be collected through an IVRS telephone diary, completed weekly until the 'End of Treatment'/Withdrawal visit. In addition, patients/caregivers will be instructed to complete the diary using IVRS at the following times:

- Once on the day before the 'End of Taper Period' visit.
- Once on the day before the Follow-up visit.

The patient or their caregiver will also continue to complete a paper diary daily to record daily usage of IMP, rescue medication, concomitant AEDs and AEs. Adequate training will be provided to the patient/caregiver in order to ensure data is being accurately collated via IVRS and paper diaries.

9.1.13 Investigational Medicinal Product Accountability

IMP will be dispensed at each visit except the 'End of Taper Period' visit and the Follow-up visit. IMP will also be dispensed between visits from Visit 7 through to the 'End of Treatment' visit. If necessary, additional IMP will be dispensed at dose-adjustment clinic visits scheduled by the Investigator. IMP will be dispensed at the 'End of Treatment'/Withdrawal visit only if required for the 10-day taper period. Patients/caregivers will be asked to return all IMP (used and unused) at each subsequent visit. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

Refer to Section 9.1.15.2.1 for the list of 'Triggering Drug Accountability Discrepancies' associated with monitoring of drug abuse liability.

9.1.14 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. Any AEs that are continuing from the Core Study will be carried over into the OLE study and transcribed in the CRF, only becoming classified as treatment emergent if they worsen. 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 9.1.15.1.1 for the list of 'Triggering AEs of Interest' associated with monitoring of drug abuse liability.

9.1.15 Monitoring of Drug Abuse Liability (for Patients 12 Years of Age and Older)

There are 2 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 ('End of Treatment'/Withdrawal visit or 'End of Taper Period' visit, 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.

9.1.15.1 Monitoring of Adverse Events

AE information will be collected according to Section 9.1.14.

9.1.15.1.1 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.

9.1.15.1.2 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.

9.1.15.2 Monitoring Drug Accountability Discrepancies

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

- At routine Drug Accountability collection times:
  the site personnel will collect the IMP clinical supplies and make sure the usage is in line with the expectations.
- 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.

9.1.15.2.1 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.
- Returned IMP supply with evidence of tampering.

- Greater than the target daily dose.

9.1.15.2.2 Supplemental Drug Accountability Form

This form consists of 8 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, not other concomitant medications).

9.1.15.3 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.

9.1.15.4 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 ('End of Treatment'/Withdrawal visit or 'End of Taper Period' visit, 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.

9.1.15.5 Adjudication Committee: Assessment of Abuse Potential of GWP42003-P

A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information collected on triggered cases.

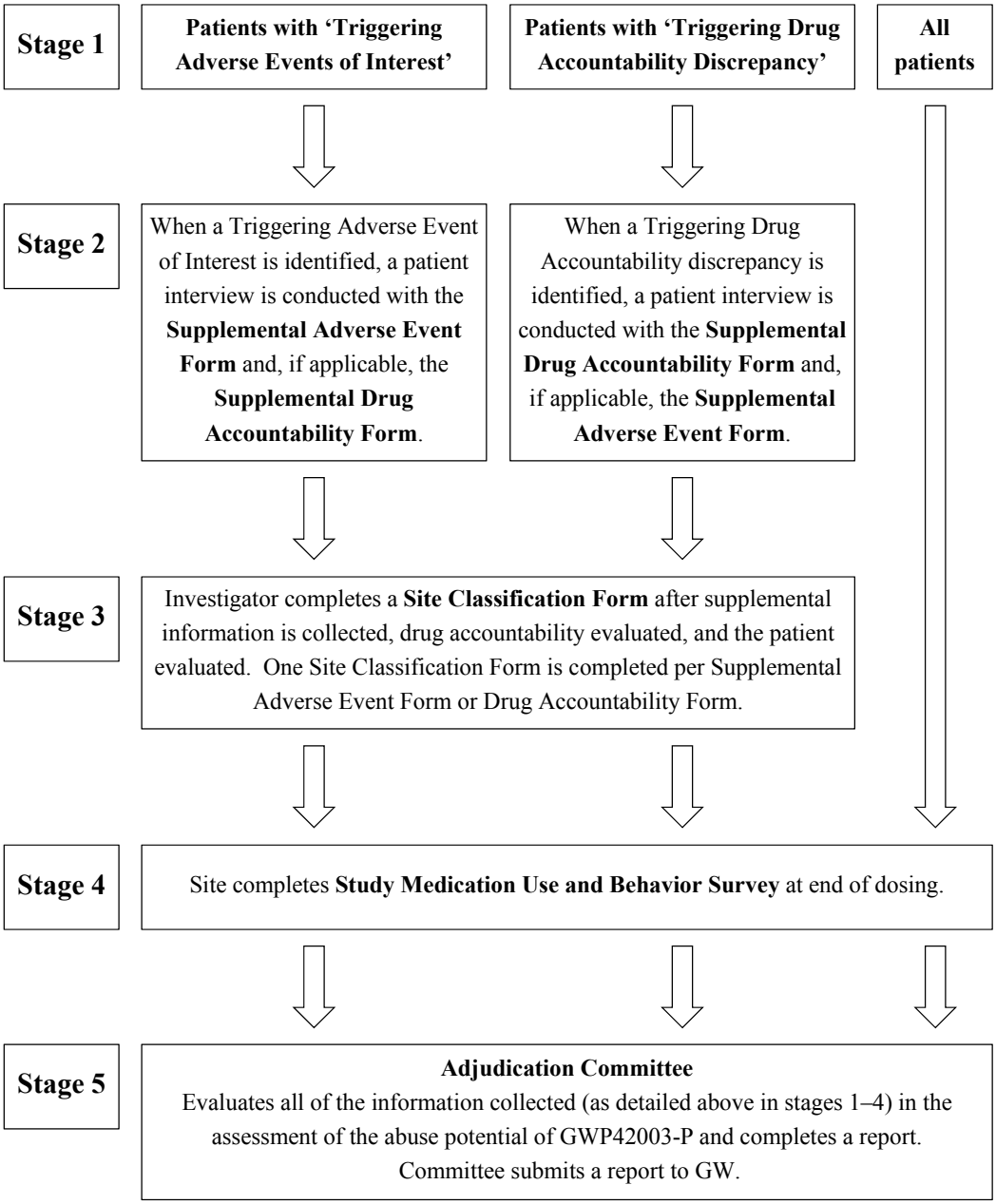
A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- 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 1)

Every effort should be made for this visit to take place on the same day as the 'End of Treatment' visit or up to 7 (+ 3) days after the 'End of Treatment' visit of the Core Study. If this is not possible then patients can still enter the OLE study by passing the screening procedures at Visit 1. All patients will be instructed to begin titration of OLE IMP in the evening of Visit 1 (Day 1) (APPENDIX 4). Patients with no gap in IMP dosing between the Core Study and the OLE (including tapered dose) will take their final dose of Core Study IMP in the morning of Visit 1.

Any OLE procedures that were not assessed during the Core Study should first be assessed at Visit 1, with the exception of the cognitive assessment battery.

For patients enrolling immediately from the Core Study into the OLE (same day): The following data collected at the 'End of Treatment' visit of the Core Study will also be considered as Visit 1 data: vital signs, 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), ECG, clinical laboratory samples (including serum IGF-1 levels [patients less than 18 years of age] and pregnancy test [if appropriate]), IVRS and paper diary information from the previous study (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, concomitant medications and/or changes to medication, C-SSRS, QOLCE/QOLIE, Vineland-II, cognitive assessment battery (participating centers only), S/CGIC and S/CGICSD. A pregnancy test (if appropriate) must be conducted using a urine dipstick to confirm eligibility.

Hepatic function must be confirmed before OLE dosing commences. In order to confirm normal hepatic function, an additional blood sample must be taken to analyze ALT, AST, TBL and INR at a local laboratory.

For patients enrolling from the taper period of the Core Study (1–7 [+ 3] days post 'End of Treatment' visit): At Visit 1, patients should have their Core Study 'End of Taper Period' assessments made. These data, along with all other data collected at the 'End of Treatment' visit of the Core Study, will also be considered as Visit 1 data. A pregnancy test (if appropriate) must be conducted using a urine dipstick to confirm eligibility.

Hepatic function must be confirmed before OLE dosing commences. In order to confirm normal hepatic function, an additional blood sample may be taken to analyze ALT, AST, TBL and INR at a local laboratory.

For patients with any gap in IMP dosing between the Core Study and the OLE: At Visit 1, all aforementioned procedures must be re-assessed, with the exception of the cognitive assessment battery. A pregnancy test (if appropriate) must be conducted using a urine dipstick to confirm eligibility.

Eligibility will be assessed according to the entry criteria, as specified in Section 6. Hepatic function must be confirmed before OLE dosing commences. In order to confirm normal hepatic function an additional blood sample must be taken to analyze ALT, AST, TBL and INR at a local laboratory.

Eligible patients or their caregivers will receive sufficient IMP for 2 weeks' home dosing together with a titration schedule provided via the IVRS. If an unacceptable AE develops at any time during titration, dosing should initially be suspended or amended, at the Investigator's discretion, until the event has resolved or is well tolerated. It is advised that the Investigator considers monitoring hepatic function (ALT, AST, TBL and INR levels) during the titration period for patients taking AEDs that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10–20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW medical monitor.

Patients or their caregivers will be given a paper diary to record information regarding AEs, IMP, usage of rescue medication, concomitant AEDs and amount of IMP intake during the time they are on treatment. In addition, patients/caregivers will be instructed to complete a weekly seizure reporting diary until the 'End of Treatment'/Withdrawal visit using the IVRS.

The Investigator should review the laboratory results as soon as these become available. If the results raise any safety concerns, the Investigator should consider whether it will be appropriate for the patient to continue to participate in the extension study, or if the patient should be withdrawn.

In order to complete the S/CGIC, the patient/caregiver is to compare to the memory aid from the Baseline of the Core Study. If the memory aid is not available from the Baseline of the Core Study then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit 1.

In order to complete the S/CGICSD, the patient/caregiver would have been asked to assess and note the average duration of the patient's seizures at the Baseline of the Core Study as a memory aid for subsequent visits. If the memory aid is not available from the Baseline of the Core Study then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit 1.

9.2.2 Visit 2 (Day 15)

Visit 2 will take place 14 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.

The following assessments will be made at Visit 2: vital signs, physical examination (including height and body weight) and ECG. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the titration regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive a 2-week supply of IMP.

During titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

9.2.3 Visit 3 (Day 29)

Visit 3 will take place 14 days after Visit 2 (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.

The following assessments will be made at Visit 3: vital signs, physical examination (including height and body weight) and ECG. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive an 8-week supply of IMP.

A safety telephone call must be made 4 weeks (± 7 days) after Visit 3. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

9.2.4 Visit 4 (Day 85)

Visit 4 will take place 8 weeks after Visit 3 (84 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.

The following assessments will be made at Visit 4: vital signs, physical examination (including height and body weight) and ECG. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive a 12-week supply of IMP.

Following Visit 4, safety telephone calls must be made every 4 weeks (± 7 days). In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

9.2.5 Visit 5 and 6 (24-36 weeks)

Visit 5 will take place 12 weeks after Visit 4 (24 weeks after Visit 1). Visit 6 will then take place 12 weeks later (36 weeks after Visit 1). A visit window of ± 7 days

from the scheduled visit dates 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 visits 5 and 6: vital signs, physical examination (including height and body weight) and ECG, C-SSRS, Vineland-II, QOLCE/QOLIE, S/CGIC and S/CGICSD. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.

Patients/caregivers will then receive a 12-week supply of IMP at Visits 5 and 6.

Following Visits 5 and 6, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved.

9.2.6 Visit 7 (48 weeks)

Visit 7 will take place 12 weeks after Visit 6 (48 weeks after Visit 1). A visit window of ± 7 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: vital signs, physical examination (including height and body weight), effects on 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), ECG, C-SSRS, Vineland-II, cognitive assessment battery (participating centers only), QOLCE/QOLIE, S/CGIC and S/CGICSD. Clinical laboratory samples (urine [where possible] and blood) will be taken for determination of serum IGF-1 levels (for patients less than 18 years of age), pregnancy (if appropriate, using a serum sample), hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

The cognitive assessment battery will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within 3 days of the visit) and will only be administered to patients who underwent cognitive testing during their Core Study.

A 14-week supply of IMP will be issued to the patient/caregiver.

Following Visit 7, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved.

At least 1 dispensing appointment will be scheduled to occur between Visits 7 and 8. The dispensing appointment date(s) will be calculated from Visit 7. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments.

9.2.7 Visit 8 (76 weeks)

Visit 8 will take place 28 weeks after Visit 7 (76 weeks after Visit 1). A visit window of ± 7 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: vital signs, physical examination (including height and body weight), ECG, C-SSRS, Vineland-II, QOLCE/QOLIE, S/CGIC and S/CGICSD. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

A 14-week supply of IMP will be issued to the patient/caregiver.

Following Visit 8, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved.

At least 1 dispensing appointment will be scheduled to occur between Visit 8 and Visit 9. The dispensing appointment date(s) will be calculated from Visit 8. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments.

9.2.8 Visit 9 (104 weeks)

Visit 9 will take place 28 weeks after Visit 8 (104 weeks after Visit 1). A visit window of ± 7 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: vital signs, physical examination (including height and body weight), effects on 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), ECG, C-SSRS, Vineland-II, cognitive assessment battery (participating centers only), QOLCE/QOLIE, S/CGIC and S/CGICSD. Clinical laboratory samples (urine [where possible] and blood) will be taken for determination of serum IGF-1 levels (for patients less than 18 years of age), pregnancy (if appropriate, using a serum sample), hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

The cognitive assessment battery will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within 3 days of the visit) and will only be administered to patients who underwent cognitive testing during their Core Study.

A 14-week supply of IMP will be issued to the patient/caregiver.

Following Visit 9, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved.

At least 1 dispensing appointment will be scheduled to occur between Visits 9 and 10. The dispensing appointment date(s) will be calculated from Visit 9. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be

administered until the next scheduled appointment. Patients need not attend the dispensing appointments.

9.2.9 Visit 10 (132 weeks)

Visit 10 will take place 28 weeks after Visit 9 (132 weeks after Visit 1). A visit window of ± 7 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: vital signs, physical examination (including height and body weight), ECG, C-SSRS, Vineland-II, QOLCE/QOLIE, S/CGIC and S/CGICSD. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

A 14-week supply of IMP will be issued to the patient/caregiver.

Following Visit 10, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved.

At least 1 dispensing appointment will be scheduled to occur between Visit 10 and 'End of Treatment' visit. The dispensing appointment date(s) will be calculated from Visit 10. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments.

9.2.10 Visit 11 (156 weeks)

Visit 11 will take place 24 weeks after Visit 10 (156 weeks after Visit 1). A visit window of ± 7 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: vital signs, physical examination (including height and body weight), effects on 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), ECG, C-SSRS, Vineland-II, cognitive assessment battery (participating centers only), QOLCE/QOLIE, S/CGIC and

S/CGICSD. Clinical laboratory samples (urine [where possible] and blood) will be taken for determination of serum IGF-1 levels (for patients less than 18 years of age), pregnancy (if appropriate, using a serum sample), hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

The cognitive assessment battery will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within 3 days of the visit) and will only be administered to patients who underwent cognitive testing during their Core Study.

A 14-week supply of IMP will be issued to the patient/caregiver.

Following Visit 11, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved.

At least 1 dispensing appointment will be scheduled to occur between Visits 11 and 12. The dispensing appointment date(s) will be calculated from Visit 11. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments.

9.2.11 Visit 12 (184 weeks)

Visit 12 will take place 28 weeks after Visit 11 (184 weeks after Visit 1). A visit window of ± 7 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: vital signs, physical examination (including height and body weight), ECG, C-SSRS, Vineland-II, QOLCE/QOLIE, S/CGIC and S/CGICSD. 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

A 14-week supply of IMP will be issued to the patient/caregiver.

Following Visit 12, safety telephone calls must be made every 4 weeks (± 7 days) to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved.

At least 1 dispensing appointment will be scheduled to occur between Visit 12 and 'End of Treatment' visit. The dispensing appointment date(s) will be calculated from Visit 12. At each dispensing appointment caregivers will be dispensed with sufficient IMP to be administered until the next scheduled appointment. Patients need not attend the dispensing appointments.

9.2.12 End of Treatment/Withdrawal Visit

This visit will take place after a maximum of 4 years' (208 weeks after Visit 1) treatment (as detailed below), or following early withdrawal from the study.

- A patient with at least 2 years' participation in the OLE (≥ 104 weeks after Visit 1) will complete the OLE phase when GWP42003-P is approved in their indication and is commercially available. Patients will complete an unscheduled 'End of Treatment' visit to transition from OLE to commercial product. The timing will vary per patient and is projected to begin in February 2019.
- A patient with less than 2 years' participation in the OLE when GWP42003-P is approved in their indication and is commercially available will continue the OLE phase until reaching a maximum of 2 years' OLE treatment, at which point an unscheduled 'End of Treatment' visit will be conducted. The unscheduled 'End of Treatment' visit will be conducted no earlier than 730 days after Visit 1.
- Patients who do not continue treatment with GWP42003-P will be scheduled for an 'End of Taper' visit.

The following assessments will be made at the 'End of Treatment'/Withdrawal visit: vital signs, physical examination (including height and body weight), effects on 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), ECG, C-SSRS, Vineland-II, cognitive assessment battery (participating centers only), QOLCE/QOLIE, S/CGIC and S/CGICSD. Clinical laboratory samples (blood and urine [where possible]) will be taken for determination of serum IGF-1 levels (for patients less than 18 years of age), hematology,

biochemistry, a pregnancy test (if appropriate, using a serum sample) and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

The cognitive assessment battery items will only be administered at a sub-group of centers that have the expertise to conduct the assessments (ideally before any other study procedures but can be completed on a separate day, if necessary, within 3 days of the visit) and will only be administered to patients who underwent cognitive testing during their Core Study.

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 or who do not transition to commercial product, the IVRS will be contacted to confirm withdrawal from the study. For patients who immediately continue to use GWP42003-P following the 'End of Treatment' visit, 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 who do not immediately continue to use GWP42003-P following the 'End of Treatment' visit, IMP will be down-titrated at home (10% per day for 10 days). 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 diary information will continue to be recorded in the paper diary.

Following the 'End of Treatment'/Withdrawal visit, the IVRS seizure reporting diary should only be completed on the day before the 'End of Taper Period' visit and on the day before the Follow-up visit.

9.2.13 End of Taper Period Visit

This visit will take place 10 (+ 3) days after the 'End of Treatment' visit or Withdrawal visit for patients who withdraw early or who do not transition to commercial product. 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.

The following assessments will be made: vital signs, physical examination (including height and body weight), CWS/PCWS and C-SSRS. In addition, the following assessments will be made for patients who do not transition to commercial product or 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, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The Investigator must assess adherence to the dosing regimen.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. 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.

Following the 'End of Taper Period' visit (or date of final dosing), the IVRS seizure reporting diary should only be completed on the day before the Follow-up visit.

9.2.14 Post-Taper Safety Telephone Call

A safety telephone call must be made 2 weeks (± 3 days) after the 'End of Taper Period' visit or date of final dosing. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The CWS/PCWS will be administered as well.

Following this call, the IVRS seizure reporting diary should only be completed on the day before the Follow-up visit.

9.2.15 Follow-up Visit

This visit is required for patients who withdraw from the study or complete treatment but do not wish to continue to use GWP42003-P. The Follow-up visit will be performed 4 weeks (+ 3 days) after the patient's last dose of GWP42003-P (including final taper period dose) and can be conducted over the telephone. During this visit/call, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The CWS/PCWS will also be administered.

9.2.16 Safety Telephone Calls

From Visit 3 until the 'End of Treatment' visit, safety telephone calls must be made every 4 weeks (± 7 days). In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is

achieved. All safety telephone calls will assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

A post-taper safety telephone call must also be made (see Section 9.2.14).

10 WITHDRAWAL

In accordance with the Declaration of Helsinki[73], the FDA regulations relating to good clinical practice (GCP) and clinical trials[74,75,76], the EU Clinical Trials Directive 2001/20/EC[77] 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 **and** (TBL > 2 × ULN **or** INR > 1.5).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.

  Note: Prior to withdrawal for the transaminase elevations noted above, the Investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma glutamyl transferase and alkaline phosphatase. **Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial.**

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 4 or 5 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 the 'End of Treatment'/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 the 'End of Taper Period' visit, if possible. For patients who begin to taper IMP but subsequently withdraw, the 'End of Taper Period' 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 take place 4 weeks from the date of the last dose of IMP (refer to Section 9.2.15).

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 3 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 enrollment (Visit 1) and the post treatment, safety Follow-up visit, 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 principal Investigator (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.

- 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 (Follow-up visit). If the Investigator subsequently becomes aware of any 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".

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 and disease 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 enrollment (Visit 1) to post study follow-up (Follow-up visit), 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 centers 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 **and** (TBL > 2 × ULN **or** INR > 1.5).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.

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

Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined above are considered potential cases of drug-induced liver injury and will be considered as protocol defined criteria for withdrawal and important medical events. The Investigator will arrange for the patient to return to the investigational site as soon as possible (within 24-48 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase and gamma glutamyl transferase, 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; however, if the above transaminase elevation criteria are confirmed by the first set of follow-up laboratory tests, the patient must be withdrawn from the trial.

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[77], relevant parts of the FDA Code of Federal Regulations[78] and any national regulations, GW will inform Investigators, regulatory authorities and relevant IRB/ECs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through 3 sources:

1) IB[71]: 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[71], or is updated as an appendix of the IB[71]. 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 ECs 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[74] 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[78] 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 carrying out the database hard lock. Any deviations from the original SAP will be described in the final clinical study report.

13.1 Sample Size, Power and Significance Levels

As this is an open label safety study, there is no formal sample size calculation. All patients who wish to continue on IMP from the populations included in the double-blind Phase 2 and Phase 3 Core Studies in DS and LGS will be eligible for inclusion. Approximately 680 patients will be enrolled.

All data collected during this study will be summarized across time, using appropriate descriptive statistical methods. There will be no formal hypothesis testing.

13.2 Interim Analysis

At least one interim analysis will be conducted to support New Drug Application and Marketing Authorization Application filings. Further interim analyses may be conducted as required.

13.3 Analysis Sets

For this study, there will be only one analysis set:

Safety

All patients who receive at least one dose of IMP in the study will be included. 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 excluding any data from the analysis population 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 into each category. Summaries will be presented overall as well as for the different etiologies (DS and LGS) separately.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

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

13.5.2 Baseline and Demographic Characteristics

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

13.5.3 Medical History

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

13.5.4 Concomitant Medication

Concomitant medications taken 2 weeks prior to and during the study will be summarized separately, by medication class and active ingredients.

13.6 Endpoints and Statistical Methods

13.6.1 Evaluable Period

All data collected during this study will be summarized across time, using appropriate descriptive statistical methods. Where baseline data are available from the Core Studies (such as seizure frequencies, quality of life assessments, Vineland-II, other measures of safety [such as vital signs, clinical laboratory samples]), changes from pre-randomization baseline of the Core Study will also be presented. Treatment compliance and exposure to treatment will also be summarized.

13.6.2 Primary Endpoint(s)

The primary endpoint is the AE profile and other safety assessments reported during the study.

13.6.2.1 Adverse Events

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

A treatment emergent AE is one that started, worsened in severity or seriousness, following the first dose of IMP in this study. Any AEs that are continuing from the Core Study will be carried over into the OLE study and transcribed in the CRF, only becoming classified as treatment emergent if they worsen.

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

The following summaries will be produced:

- Pre-existing AEs.
- 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.

13.6.2.2 Clinical Laboratory Data

Clinical laboratory data from Central Laboratory obtained at baseline (Core Studies), screening (OLE Visit 1), during treatment and at the end of treatment and the change from baseline (Core Studies), during and at the 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 the normal range at each clinic visit.

In order only to confirm normal hepatic function before OLE dosing commences, an additional blood sample may be taken at Visit 1 to analyze ALT, AST, TBL and INR at a local laboratory. These data will only be used for eligibility determination.

13.6.2.3 Vital Signs, 12-lead Electrocardiogram, Physical Examination and Other Safety Data

Vital signs, ECG and physical examination data will be summarized at baseline (Core Studies), screening (OLE Visit 1) and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs from baseline (Core Studies) during and at the end of treatment will also be summarized. Study Medication Use and Behavior Survey data will be summarized using appropriate summary statistics.

13.6.2.4 Columbia-Suicide Severity Rating Scale Data

C-SSRS data will be summarized at baseline (Core Studies), screening (OLE Visit 1) and at each time point during the treatment period (including the taper period) using appropriate summary statistics. Changes from baseline (Core Studies) during and at the end of treatment will also be summarized.

13.6.2.5 Cannabis Withdrawal Scale and Pediatric Cannabinoid Withdrawal Scale Data

CWS/PCWS data will be summarized at baseline (Core Studies), the OLE end of taper period, 2 weeks after the OLE end of taper period and at OLE follow-up using appropriate summary statistics. Changes from baseline (Core Studies) following cessation of treatment will also be summarized.

13.6.3 Secondary Endpoint(s)

All Patients:

- Change in quality of life as measured with QOLCE if 18 years of age or younger, or QOLIE if 19 years of age or older, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in S/CGIC, relative to the pre-randomization baseline of the Core Study.
- Change in adaptive behavior as measured with the Vineland-II, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in the number of inpatient epilepsy-related hospitalizations (number of hospitalizations due to epilepsy in each 28-day period), relative to the pre-randomization baseline of the Core Study.
- Change in the use of rescue medication (number of days used in each 28-day period), relative to the pre-randomization baseline of the Core Study.
- Maintenance of seizure frequency reduction and freedom from seizures during the OLE study.
- Percentage change in the frequency of total seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in total seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in total seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the frequencies of subtypes of seizures, relative to the pre-randomization baseline of the Core Study.

- Changes in duration of seizure subtypes as assessed by the S/CGICSD, relative to the pre-randomization baseline of the Core Study.
- Change in the number of episodes of *status epilepticus*, relative to the pre-randomization baseline of the Core Study.
- Change in cognitive function as measured with a cognitive assessment battery, relative to the pre-randomization baseline of the Core Study, if assessed during the Core Study.
- Change in growth and development for patients less than 18 years of age 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), relative to the pre-randomization baseline of the Core Study.
- Effects on menstruation cycles (in females).
- Drug abuse liability, as measured by AEs of abuse potential, drug accountability and Study Medication Use and Behavior Survey in patients aged 12 and older.

DS Patients Only:

- Percentage change in total convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.
- Percentage change in total non-convulsive seizure frequency, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in convulsive seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in convulsive seizures, relative to the pre-randomization baseline of the Core Study.

LGS Patients Only:

- Percentage change in the number of drop seizures, relative to the pre-randomization baseline of the Core Study.
- Percentage change in the number of non-drop seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures, relative to the pre-randomization baseline of the Core Study.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in drop seizures, relative to the pre-randomization baseline of the Core Study.

These will be summarized across time, using appropriate statistical methods. Descriptive statistical methods will be used throughout. There will be no formal hypothesis testing.

14 DATA SAFETY MONITORING COMMITTEE

This study will not use a DSMC.

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[73], EU Clinical Trials Directive[77] and the clinical trial regulations adopting European Commission Directives into national legislation[79,80,81].

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 template 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[74,75,76,82], the EU Clinical Trials Directive[77], or International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP)[83] 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 and race (if allowed per local regulations) and a patient study number only. Documents that are not for submission to GW, e.g., signed informed consent/assent forms, should be kept in strict confidence by the Investigator.

In compliance with the FDA regulations relating to GCP and clinical trials[74,75,76,82], and the EU Clinical Trials Directive[77]/ICH GCP Guidelines[83], 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. A source data verification plan, identifying the source for each data point at each site, will be agreed with each site prior to patient recruitment. In the rare situations of data being recorded directly into the CRF in error, then the source data from the CRF should be transcribed into the patient's notes with appropriate signature and date to provide a full audit trail.

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[83]), 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 2 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 2 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[84]).

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

16.3 Study Monitoring and Data Collection

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

The GW study monitor, or designee, is responsible for inspecting the CRFs and available 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 5 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[74,75,76,82], the ICH GCP Guideline[83], 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 the 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[82].

After database lock all Investigators will receive a certified copy of all the IVRS assessment data. These 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 6 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(s)	**1***	**2, 3, 4****	**5 & 6****	**7****	**Dispense**	**8****	**Dispense**	**9****	**Dispense**	**10****	**Dispense**	**11****	**Dispense**	**12****	**Dispense**	**End of Treatment**	**End of Taper**	**Safety Call**	**Follow-up** (Tel.)
Day/Week (Visit window)	**Day 1**	**Days 15, 29, 85 (± 3 days)**	**Weeks 24 & 36 (± 7 days)**	**Week 48 (± 7 days)**		**Week 76 (± 7 days)**		**Week 104 (± 7 days)**		**Week 132 (± 7 days)**		**Week 156 (± 7 days)**		**Week 184 (± 7 days)**		***	**Up to 10 days later (+ 3 days)**	**2 weeks after End of Taper (± 3 days)**	**4 weeks after End of Taper (+ 3 days)**
Informed consent/assent	X																		
Inclusion/ Exclusion Criteria	X																		
Demographics	X																		
Medical History	X																		
AEs	X	X	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	X	X	X
Concomitant medications	X	X	X	X		X		X		X		X		X		X	X	X	X
Physical examination (including height and body weight)	X	X	X	X		X		X		X		X		X		X	X		
Vital signs	X	X	X	X		X		X		X		X		X		X	X		
ECG	X	X	X	X		X		X		X		X		X		X	X♦		
Clinical laboratory	X	X	X	X		X		X		X		X		X		X	X♦		

Visit(s)	**1***	**2, 3, 4****	**5 & 6****	**7****	**Dispense**	**8****	**Dispense**	**9****	**Dispense**	**10****	**Dispense**	**11****	**Dispense**	**12****	**Dispense**	**End of Treatment**	**End of Taper**	**Safety Call**	**Follow-up** (Tel.)
Day/Week (Visit window)	**Day 1**	**Days 15, 29, 85 (± 3 days)**	**Weeks 24 & 36 (± 7 days)**	**Week 48 (± 7 days)**		**Week 76 (± 7 days)**		**Week 104 (± 7 days)**		**Week 132 (± 7 days)**		**Week 156 (± 7 days)**		**Week 184 (± 7 days)**		***	**Up to 10 days later (+ 3 days)**	**2 weeks after End of Taper (± 3 days)**	**4 weeks after End of Taper (+ 3 days)**
blood sampling																			
Clinical laboratory urine sampling (dipstick urinalysis)§	X	X	X	X		X		X		X		X		X		X	X♦		
Pregnancy test (if appropriate)§	X			X				X				X				X			
Vineland-II	X		X	X		X		X		X		X		X		X			
S/CGIC†	X		X	X		X		X		X		X		X		X			
S/CGICSD†	X		X	X		X		X		X		X		X		X			
QOLCE or QOLIE	X		X	X		X		X		X		X		X		X			
Cognitive assessment battery¶	X			X				X				X				X			
Menstruation question (females)	X			X				X				X				X			
Tanner Staging and IGF-1 levels♥	X			X				X				X				X			
C-SSRS‡	X		X	X		X		X		X		X		X		X	X		
CWS/PCWS																	X	X	X

Visit(s)	**1***	**2, 3, 4****	**5 & 6****	**7****	**Dispense**	**8****	**Dispense**	**9****	**Dispense**	**10****	**Dispense**	**11****	**Dispense**	**12****	**Dispense**	**End of Treatment**	**End of Taper**	**Safety Call**	**Follow-up** (Tel.)
Day/Week (Visit window)	**Day 1**	**Days 15, 29, 85 (± 3 days)**	**Weeks 24 & 36 (± 7 days)**	**Week 48 (± 7 days)**		**Week 76 (± 7 days)**		**Week 104 (± 7 days)**		**Week 132 (± 7 days)**		**Week 156 (± 7 days)**		**Week 184 (± 7 days)**		*****	**Up to 10 days later (+ 3 days)**	**2 weeks after End of Taper (± 3 days)**	**4 weeks after End of Taper (+ 3 days)**
Study Medication Use and Behavior Survey[#]																X			
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)[£]	X	X	X	X		X		X		X		X		X		X	X	X (seizure details)	X (seizure details)
IMP dispensing[£]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Return of IMP[£]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IMP compliance review[£]		X	X	X		X		X		X		X		X		X	X		

* All patients will be instructed to begin titration of OLE IMP in the evening of Visit 1 (Day 1). Patients with no gap in IMP dosing between the Core Study and the OLE (including tapered dose) will take their final dose of Core Study IMP in the morning of Visit 1. Any OLE procedures that were not assessed during the Core Study should first be assessed at Visit 1, with the exception of the cognitive assessment battery.
For patients enrolling immediately from the Core Study into the OLE (same day): All data collected at the 'End of Treatment' visit of the Core Study will also be considered as Visit 1 data. Hepatic function must be confirmed before OLE dosing commences. In order only to confirm normal hepatic function, an additional blood sample must be taken to analyze ALT, AST, TBL and INR at a local laboratory.
For patients enrolling from the taper period of the Core Study (1–7 [+ 3] days post 'End of Treatment' visit): Patients should have their Core Study 'End of Taper Period' assessments made; these data, along with all other data collected at the 'End of Treatment' visit of the Core Study, will be considered as Visit 1 data. Hepatic function must be confirmed before OLE dosing commences. In order only to confirm normal hepatic function, an additional blood sample

may be taken to analyze ALT, AST, TBL and INR at a local laboratory.
For patients with any gap in IMP dosing between the Core Study and the OLE: All procedures must be re-assessed, with the exception of the cognitive assessment battery. Hepatic function must be confirmed before OLE dosing commences. In order only to confirm normal hepatic function, an additional blood sample must be taken to analyze ALT, AST, TBL and INR at a local laboratory.

** From Visit 3 until the 'End of Treatment' visit, safety telephone calls must be made every 4 weeks (± 7 days). In addition, during titration of doses above 20 mg/kg/day, safety telephone calls must be made every 7 days (± 3 days) until stable dosing is achieved. All safety telephone calls will assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

*** 'End of Treatment' visit will occur after a maximum of 4 years' (208 weeks from Visit 1) treatment, when GWP42003-P is approved in their indication and is commercially available (as an unscheduled 'End of Treatment' visit as detailed below), or following the early withdrawal from the study. Patients who complete treatment but do not immediately continue to use GWP42003-P will commence a 10-day IMP taper period. Patients who withdraw early should commence the 10-day IMP taper period, if possible.

- A patient with at least 2 years' participation in the OLE (≥ 104 weeks after Visit 1) will complete the OLE phase when GWP42003-P is approved in their indication and is commercially available. Patients will complete an unscheduled 'End of Treatment' visit to transition from OLE to commercial product. The timing will vary per patient and is projected to begin in February 2019.
- A patient with less than 2 years' (104 weeks after Visit 1) participation in the OLE when GWP42003-P is approved in their indication and is commercially available will continue on the OLE phase until reaching a maximum of 2 years' OLE treatment, at which point an unscheduled 'End of Treatment' visit will be conducted. The unscheduled End of Treatment visit will be conducted no earlier than 730 days after Visit 1.
- Patients who do not continue treatment with GWP42003-P will be scheduled for an 'End of Taper' visit.

♦ Only required for patients who withdraw from the study early.

§ Urine sample taken if possible. Pregnancy test: Urine test at Visit 1, serum test at 'End of Treatment'/Withdrawal visit.

† Patient/Caregiver is to compare to the memory aid from the Baseline of the Core Study. If the memory aid is not available from the Baseline of the Core Study then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit 1.

¶ Only for patients who underwent cognitive testing during their Core Study. To be performed at the 'End of Treatment'/Withdrawal visit only. The cognitive assessment battery will only be administered at participating centers.

♥ 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 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 less than 18 years of age.

‡ For patients that become 6 years old during this OLE trial, the Children's Baseline C-SSRS (employing questions in relation to lifetime experience) should be completed at the next trial visit. Questioning at all subsequent visits will be in relation to the last assessment (Children's Since Last Visit).

To be performed at final dosing visit ('End of Treatment'/Withdrawal visit or 'End of Taper Period' visit, as applicable) for patients 12 years of age and older.

£ IVRS will be used to collect patient reported seizure information and to manage IMP supply. A member of the study team must contact the IVRS at each assessment/dispensing visit in order to obtain dispensing information and to provide completion/taper/premature termination information.

Tel. Visit can be conducted by telephone.

APPENDIX 2 STUDY PERSONNEL

Appendix 2.1 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 2.2 Sponsor Contact Details

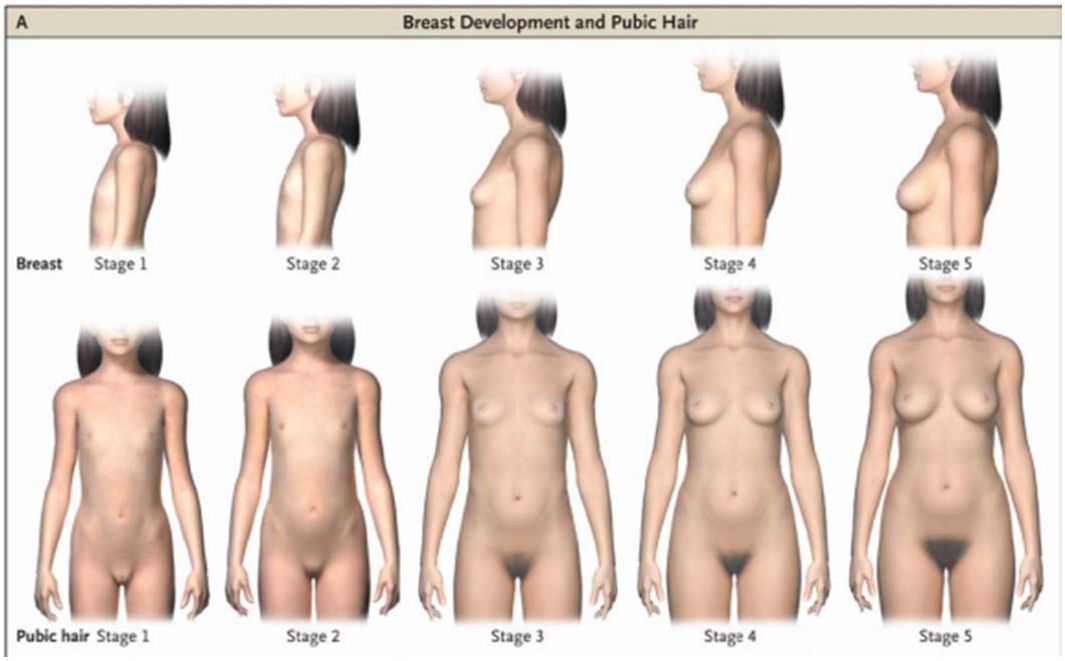
Pharmacovigilance Department — SAE Reporting:	**Fax:** [redacted] **USA Toll Free Fax:** [redacted] Tel: [redacted]
Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: +44 (0) 1233 266 800 Fax: +44 (0) 1223 235 667
Medical Monitor:	[redacted] Tel: [redacted] Cell: [redacted]
Clinical Project Manager/Clinical Operations Director:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: +44 (0)1223 266 800 Fax: +44 (0)1223 235 667
Clinical Trials Supplies:	GW Pharma Ltd Tel: [redacted] Fax: [redacted]

APPENDIX 3 TANNER STAGING

(Reproduced with permission from the New England Journal of Medicine[85].)

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)

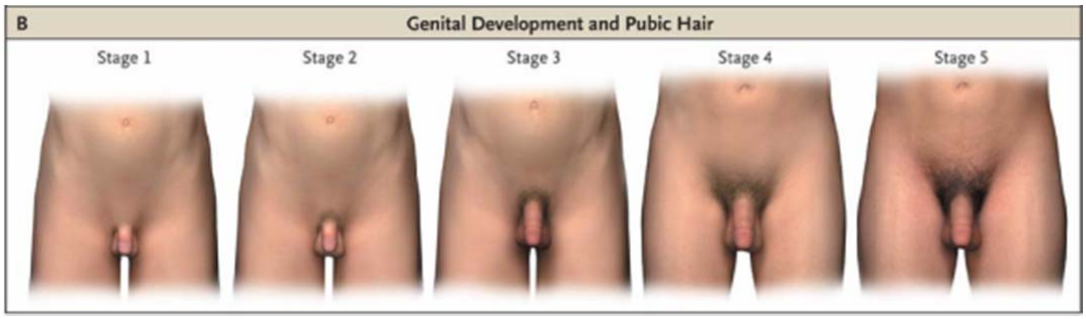
- Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast.
- Adult-like hair quality, extending across pubis but sparing medial thighs.

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 4 TITRATION REGIMEN

Dose Titration Regimen*		
Day	**OLE IMP Dosage**	**Total Daily OLE IMP Dose**
1	1.25 mg/kg (pm)	1.25 mg/kg
2	1.25 mg/kg bid (am/pm)	2.50 mg/kg
3	2.50 mg/kg bid (am/pm)	5.00 mg/kg
4	2.50 mg/kg bid (am/pm)	5.00 mg/kg
5	3.75 mg/kg bid (am/pm)	7.50 mg/kg
6	3.75 mg/kg bid (am/pm)	7.50 mg/kg
7	5.00 mg/kg bid (am/pm)	10.00 mg/kg
8	5.00 mg/kg bid (am/pm)	10.00 mg/kg
9	7.50 mg/kg bid (am/pm)	15.00 mg/kg
10	7.50 mg/kg bid (am/pm)	15.00 mg/kg
11	10.00 mg/kg bid (am/pm)	20.00 mg/kg
12	10.00 mg/kg bid (am/pm)	20.00 mg/kg
13	10.00 mg/kg bid (am/pm)	20.00 mg/kg
14	10.00 mg/kg bid (am/pm)	20.00 mg/kg

* It is advised that the Investigator considers monitoring hepatic function (ALT, AST, TBL and INR levels) during the titration period for patients taking AEDs that are known to be associated with hepatic injury or failure. To minimize any elevations in hepatic function markers the titration period can be extended and the dosage of a concomitant AED and/or GWP42003-P may be adjusted at the discretion of the Investigator. If there is intolerance during titration, the patient may be maintained on a dose below 10–20 mg/kg/day. A titration rate faster than recommended may be considered if there is an increase in seizures, following consultation with the GW medical monitor.

Emerging clinical data suggest that benefit may be seen in patients in the range of 10–20 mg/kg/day.