Study Title: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

Study Code: GWEP1521

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CLINICAL PROTOCOL

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Confidentiality Statement

Investigator Agreement

I have read the attached protocol entitled 'A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures', dated 23 April 2019, and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the U.S. Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical trials, the European Union (EU) Clinical Trials Directive (2001/20/EC), the EU Good Clinical Practice/GCP Directive (2005/28/EC) and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation Tripartite Guideline for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 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

PI

Date: 23-Apr-2019
(DD Month YYYY)

1 PROTOCOL SYNOPSIS

Study Title	A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures.
Clinical Study Type	Phase 3
Indication	Seizures* in patients with tuberous sclerosis complex (TSC). *Seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic-clonic, tonic, clonic or atonic) that are countable.
Primary Objective	**Blinded Phase:** To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with TSC. **Open-label Extension:** To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled seizures.
Secondary Objectives	**Blinded Phase:** • To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures. • To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo. • To evaluate the effects of GWP42003-P on quality of life compared with placebo. • To evaluate the safety and tolerability of GWP42003-P compared with placebo. **Open-label Extension:** • To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures. • To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old). • To evaluate the long term effects of GWP42003-P on quality of life. • To evaluate the long term safety and tolerability of

	GWP42003-P.
Exploratory Objectives	**Blinded Phase:** • To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo. • To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P. • To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), if applicable. **Open-label Extension:** • To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features.
Study Design	**This multicenter study consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.** **Blinded Phase:** The blinded phase of the study is a randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P versus placebo. Patients will complete a 1-week screening period and a 4-week baseline period before they are randomized to receive 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or equivalent volumes of placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded investigational medicinal product (IMP) for 12 weeks. Dose escalation for each patient is subject to the investigator's assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study. Clinic visits will occur for screening (Day −35), baseline (Day −28), randomization (Day 1) and, on Days 15 and 29 during titration and on Days 43, 57, 71 (telephone) and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 10 to Visit 12. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend

	instead. Patients will be required to perform daily interactive voice response system (IVRS) telephone calls to record seizure information. They will also complete a paper diary daily with information about their IMP and concomitant AED administration. Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE. Those patients opting not to enter the OLE will complete a 10-day taper period (down-titrating 10% per day for 10 days). **Open-label Extension Transition:** In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P: • Patients from the placebo group will titrate up to 25 mg/kg/day GWP42003-P. • Patients from the 25 mg/kg/day GWP42003-P group will continue to take 25 mg/kg/day GWP42003-P. • Patients from the 50 mg/kg/day GWP42003-P group will taper down (10% per day) to 25 mg/kg/day GWP42003-P. Safety telephone calls will be completed every two days throughout the OLE transition. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. **Open-label Extension:** The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The initial OLE period will last for a maximum of 1 year. Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found. Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg/day every two days. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. Safety telephone calls will be completed every two days throughout the OLE titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the

	Friday before or Monday after the weekend instead. If seizure freedom is achieved with use of GWP42003-P during the study, the investigator should consider reducing the dose of concomitant AEDs after six months of seizure freedom.
Primary Endpoint	**Blinded Phase:** The primary endpoint is the change in number of TSC-associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo. *Primary endpoint TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable. **Open-label Extension:** The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.
Secondary Endpoints	**Blinded Phase:** The following endpoints will be compared between treatment groups over the 16-week, double-blind treatment period (all changes relative to baseline): **Key:** • Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency*. • Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score. • Change in total seizures. **Other:** **Antiepileptic Efficacy Measures:** • Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure* frequency. • Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure* frequency. • Change in number of TSC-associated seizure*-free days. • Change in number of 'other' seizures (absence, myoclonic,

	focal sensory and infantile/epileptic spasms). **Growth and Development (in patients less than 18 years old):** • Change in serum insulin-like growth factor-1 (IGF-1) levels. • Change in Tanner Staging score (for patients aged 10–17 [inclusive]). **Quality of Life:** • Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score. • Change in Physician Global Impression of Change (PGIC) score. **Safety and Tolerability:** • AEs. • Clinical laboratory parameters. • 12-lead electrocardiogram (ECG). • Physical examination parameters (including height and weight). • Vital signs. • Columbia-Suicide Severity Rating Scale (C-SSRS; 19+ years) or C-SSRS Children's (6–18 years) score, where applicable. • Number of inpatient hospitalizations due to epilepsy. • Abuse liability. • Effects on menstruation cycles (in females). **<u>Open-label Extension:</u>** The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase: **Antiepileptic Efficacy Measures:** *TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable. **<u>Key:</u>** • Percentage change in number of TSC-associated seizures* (average per 28 days). • Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency*.

	• Change in CGIC or SGIC score. • Change in total seizures. **<u>Other:</u>** • Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure* frequency. • Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure* frequency. • Change in number of TSC-associated seizure*-free days. • Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms). **Growth and Development (patients less than 18 years):** • Change in serum IGF-1 levels. • Change in Tanner Staging score (for patients aged 10–17 [inclusive]). **Quality of Life:** • Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score. • Change in PGIC score. **Safety and Tolerability:** • Clinical laboratory parameters. • ECG. • Physical examination parameters (including height and weight). • Vital signs. • C-SSRS (19+ years) or C-SSRS Children's (6–18 years) score, where applicable. • Number of inpatient hospitalizations due to epilepsy. • Abuse liability. • Effects on menstruation cycles (in females).
Exploratory Endpoints	**Double-blind and Open-label Extension:** **Antiepileptic Efficacy Measures:** • Change in composite focal seizure score (frequency × severity). • Change in number of seizures by subtype. • Change in use of rescue medication.

	• Change in the number of episodes of *status epilepticus* (convulsive and non-convulsive). • Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD). **TAND:** <u>Cognitive and Behavioral Function:</u> • Changes in Vineland Adaptive Behavior Scales, Second Edition (Vineland-II). • Changes in Wechsler Scales (pre-school, primary, children, adult). • Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL). <u>Autistic Features:</u> • Change in Social Communication Questionnaire (SCQ) score. **PK (Double-blind only):** • The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable time-point will be calculated. • Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.
Sample Size	**Blinded Phase:** A total of 210 patients will be targeted to be enrolled. The 210 patients will be randomly allocated to one of four treatment groups (GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy. If it is assumed that patients in the placebo group will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per group will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level. **Open-label Extension:** All patients who wish to continue on IMP following completion

	of the blinded phase.
Summary of Patient Eligibility Criteria	Inclusion: Patients meeting the following criteria will be considered eligible for this study: • Patient is male or female aged between one and 65 years inclusive. • Patient and/or parent(s)/legal representative is willing and able to give informed consent/assent for participation in the study. • Patient and their caregiver are willing and able (in the investigator's opinion) to comply with all study requirements (including accurate diary and IVRS completion). • Well-documented clinical history of epilepsy, which is not completely controlled by their current AEDs. • Clinical diagnosis of TSC according to criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference. • Taking one or more AEDs at a dose which has been stable for at least four weeks prior to screening. • All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for one month prior to screening and the patient is willing to maintain a stable regimen throughout the study. • Patient is willing to keep any factors expected to affect seizures stable (such as the level of alcohol consumption and smoking). • Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law. • Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant (if they have one) to be notified of participation in the study, if mandated by local law. **At the end of the baseline period patients must also meet the following criteria:** • Experienced **at least** eight seizures during the first 28 days of the baseline period with at least one seizure occurring in at least three of the four weeks (seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures [tonic–clonic, tonic, clonic or atonic]) that are countable.

	• Completed at least 90% of calls to IVRS during the first 28 days of the baseline period (a minimum of 25 completed calls). Exclusion: The patient may not enter the study if ANY of the following apply: • Patient has a history of pseudo-seizures. • Patient has clinically significant unstable medical conditions other than epilepsy. • Patient has an illness in the four weeks prior to screening or randomization, other than epilepsy, which in the opinion of the investigator could affect seizure frequency. • Patient has undergone general anesthetic in the four weeks prior to screening or randomization. • Patient has undergone surgery for epilepsy in the six months prior to screening. • Patient is being considered for epilepsy surgery or any procedure involving general anesthesia during the blinded phase of the study. • Patient has been taking felbamate for less than one year prior to screening. • Patient is taking an oral mammalian target of rapamycin (mTOR) inhibitor. • Patient has, in the investigator's opinion, clinically significantly abnormal laboratory values. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil. • Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS in the last month or at screening. • Patient is currently using or has in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the three months prior to screening and is unwilling to abstain for the duration for the study. • Patient has tumor growth which, in the opinion of the investigator, could affect the primary endpoint. • In the opinion of the investigator the patient has clinically significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which will interfere with the ability to read their ECGs. • Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit 3),

	defined as **any** of the following: – Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN). – TBL* [serum total bilirubin] ≥ 2 × ULN **or** international normalized ratio [INR] > 1.5 (*TBL ≥ 2 × ULN exclusion will not apply for patients diagnosed with Gilbert's disease). – Serum ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). *This criterion can only be confirmed once the laboratory results are available.* • Patient is female and of childbearing potential, or is male whose partner is of child bearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the study and for three months thereafter. • Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter. • Patient has received an IMP less than 12 weeks prior to the screening visit. • Patient has 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 may affect the patient's ability to take part in the study. • Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they take part in the study. • Patient has donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the study. • Patient has been previously randomized into this study. • Patient has any known or suspected history of alcohol or substance abuse. • Patient has travel outside the country and/or state of residence planned during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.

Criteria for Withdrawal	The patient must be withdrawn from the study if any of the following apply: • Administrative decision by the investigator, GW or regulatory authority. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient. • Withdrawal of patient consent/assent. • Withdrawal of parent(s)/legal representative consent. • ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • ALT or AST > 8 × ULN. • ALT or AST > 5 × ULN for more than two weeks. • ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5). • Lost to follow-up. *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.* The patient may also be withdrawn from the study for any of the following: • Did not meet eligibility criteria. • Patient non-compliance. • AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study. • Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS. • Any evidence of drug abuse or diversion. • General anesthesia (blinded phase only). • Addition of a new AED (blinded phase only).
Investigational Medicinal Product: Formulation,	GWP42003-P solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol, sweetener [sucralose] and strawberry flavoring). Placebo solution (sesame oil) containing the excipients anhydrous

Mode of Administration, Dose and Regimen	ethanol, sweetener (sucralose) and strawberry flavoring. **Blinded Phase:** Patients will titrate the IMP up to the required dose over four weeks as per randomization. Patients will then remain at this maintenance dose for 12 weeks. Dose escalation for each patient is subject to the investigator's assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study. Patients will be on treatment for a total of 16 weeks. Patients not entering the OLE or who withdraw early will down-titrate over a period of 10 days. Patients who decide to enter the open-label extension will enter the Open-label Extension Transition. Titration from 0–25 mg/kg/day will begin at 5 mg/kg/day and will be increased in increments of 5 mg/kg/day every two days (patients will remain on each dose level for two days before they progress on to the next dose). Titration from 25–50 mg/kg/day will continue at smaller increments of 2.5 mg/kg/day every two days. IMP will be taken twice daily (morning and evening). **Open-label Extension Transition:** This double-blind transition phase will take two weeks to complete. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P: • Patients from the placebo group will titrate up to 25 mg/kg/day. • Patients from the 25 mg/kg/day group will continue to take 25 mg/kg/day. • Patients from the 50 mg/kg/day will taper down (10% per day for 5 days) to 25 mg/kg/day. **Open-label Extension:** Patients may titrate the IMP up to the target dose of 50 mg/kg/day. Patients will then remain at this dose until the 'End of Treatment' visit, with the option for doses to be increased or decreased if deemed necessary by the investigator, to a maximum of 50 mg/kg/day. Following the 'End of Treatment' visit or decision to withdraw, doses of the IMP will be tapered down (10% per day for 10 days) at home until the 'End of Taper' visit. IMP will be taken twice daily (morning and evening). In the UK, enrollment of patients between the ages of 12 and

	23 months will only commence once 15 patients over the age of 23 months have been dosed for a minimum of 4 weeks and no new safety issues have been observed.
Control Group	The control group will receive equal volumes of matching placebo.
Procedures	**Screening Assessments (Blinded Phase) Will Include:** • Informed consent/assent • Demographic assessment • Full medical history (including seizure information since diagnosis and all prior AEDs taken) • Concomitant medication review (including AEDs) • Physical examination • Vital signs assessment • Postural blood pressure • Clinical laboratory samples (blood and urine) will be taken for: – Hematology – Biochemistry – Urinalysis – Urine/serum THC screen – Urine/serum pregnancy tests (if appropriate) – *TSC1* and *TSC2* mutation status (if not known previously) if the patient/parent(s)/legal representative provide consent • ECG • Suicidality Patients who satisfy all inclusion and none of the exclusion criteria will be assigned a unique patient number. After the screening visit, investigators will submit the patient's documented history of seizures directly to the Epilepsy Study Consortium (ESC) for verification of seizure types. The ESC may ask the investigator for additional information to assist in their decision. The ESC will provide written confirmation directly to the investigator. **Baseline Visit:** Following written confirmation of seizure classification from the ESC patients will attend a Baseline Visit before beginning the 28-day baseline observation period. The patient's attendance is preferred, but if this is not possible the primary caregiver can attend alone provided that this caregiver (not the patient) will be responsible for seizure identification, IVRS use, and paper diary

	completion. The following assessments will be completed: • Concomitant medication review (including AEDs) • AE review • Epilepsy-related hospitalizations review • IVRS training • Patient diary issue and training The investigator will review and train the patient or their caregiver to identify the patient's expected seizure types. Patients or their caregivers will make a daily IVRS call to record daily seizure information including all seizures and episodes of *status epilepticus*. Patients or their caregivers will be given a paper diary to record usage of IMP, rescue medication, concomitant AEDs, and AEs and will be instructed on how to do so. **Randomization Visit Assessments:** Following the 28-day baseline observation period the investigator will assess the patient's daily number of seizures from IVRS data. Patients who continue to satisfy all inclusion and none of the exclusion criteria will be randomized. Patients will then receive sufficient IMP, as assigned by IVRS, every 14 to 28 days for the 16-week treatment period. Before taking their first dose of IMP in clinic the following assessments will be completed: • Concomitant medication review (including AEDs) • AE review • Epilepsy-related hospitalizations review • Physical examination • Tanner Staging (where appropriate) • Details of menstruation (for females) • ECG (including pre-dose baseline and +4 hours [±30 minutes] after first dose) • Vital signs • Postural blood pressure • Suicidality • SGIC-SD or CGIC-SD • Vineland-II • Wechsler Tests • CBCL or ABCL • SCQ • QOLCE or QOLIE-31-P • CGIC or SGIC • PGIC

	• Clinical laboratory samples (blood and urine) will be taken for: – Hematology – Biochemistry – Urinalysis – Urine/serum pregnancy tests (if appropriate) – Serum IGF-1 – PK (patients > 20 kg only) – AED concentrations • Review of IVRS and patient diary • IMP dispensing **Post Randomization Assessments:** Clinic visits will occur on Day 15, Day 29, Day 43, Day 57, Day 85 and Day 113 with a telephone visit occurring on Day 71. Additional safety telephone calls will be completed every two days during titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or the Monday after the weekend instead. The following assessments will be completed at every clinic visit except where indicated: • Concomitant medication review (including AEDs) • AE review • Epilepsy-related hospitalizations review • Physical examination • Tanner Staging, where appropriate (Visit 10) • Details of menstruation (for females) (Visit 10) • ECG • Vital signs • Postural BP (Visit 5) • Suicidality • SGIC-SD or CGIC-SD (Visit 10) • Vineland-II (Visit 10) • Wechsler Tests (Visit 10) • CBCL or ABCL (Visit 10) • SCQ (Visit 10) • QOLCE or QOLIE-31-P (Visit 10) • CGIC or SGIC (Visit 10) • PGIC (Visit 10) • Clinical laboratory samples (blood and urine) will be taken

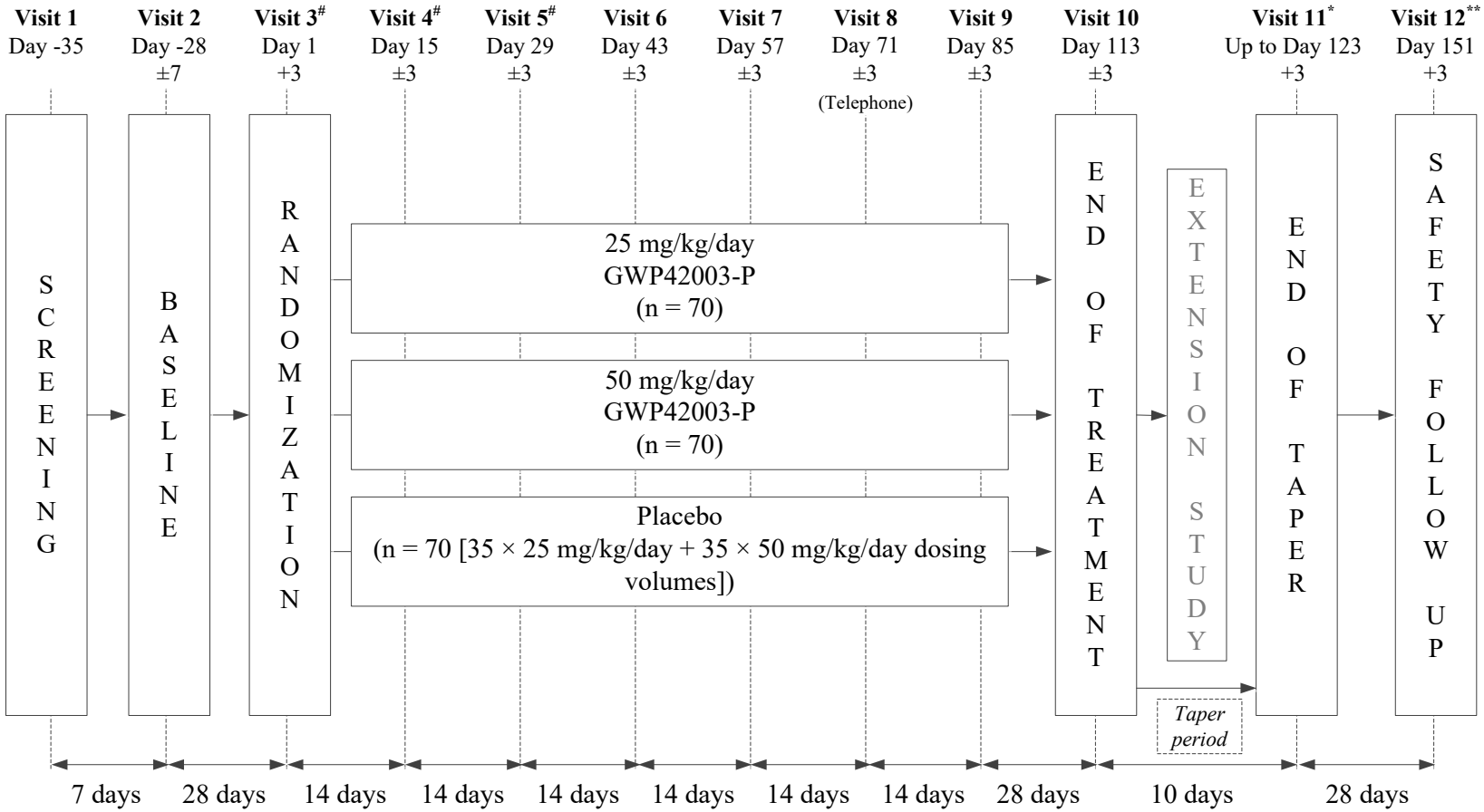
	for: – Hematology – Biochemistry – Urinalysis – Urine/serum pregnancy tests (Visits 5, 7, 9 and 10, if appropriate) – Serum IGF-1 (Visit 10) – PK (Visit 10; patients > 20 kg only) – AED concentrations (Visits 5, 7, 9 and 10) • Review of patient diary • IMP dispensing, collection and compliance review **PK:** Blood sample collection for PK analysis of CBD and its major metabolites will be taken at Visits 3 and 10 for patients weighing more than 20 kg. Where appropriate, blood samples will be taken as follows: • One sample pre-dose (i.e., prior to administration of IMP). • One sample between 2 and 3 hours post-dose. • One sample between 4 and 6 hours post-dose. • One sample between 8 and 10 hours post-dose (patients 18 years and above only). Blood samples will be collected for analysis of plasma concentrations of concomitant AEDs (if possible) ideally at the following time points: • Visit 3 - Pre-IMP-dose. • Visit 5 - Pre-IMP-dose. • Visit 7 - Pre-IMP-dose. • Visit 9 - Pre-IMP-dose. • Visit 10 - Pre-IMP-dose. Additional blood samples may be taken for AED monitoring if there is a suspicion of changes in AED levels, with the aim to keep the AED plasma levels within the patient's therapeutic level. **Open-label Extension Transition and Open-label Extension:** Following completion of the blinded phase of the study, patients will enter a 2-week blinded transition followed by a 3-week titration. Safety telephone calls will be conducted every two days during this 5-week period and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. OLE visits will occur on Day 15, Day 36, Day 92 and then every 13 weeks up to 1 year. Additional IMP Re-supply Visits will be

	scheduled between Assessment Visits. The following assessments will be completed at all visits during the OLE, except where indicated (full listing by visit included in Section 9.1.2): • Concomitant medication review (including AEDs) • AE review • Review of patient diary • IMP dispensing, collection and compliance review • Physical examination • Tanner Staging, where appropriate (Visit B10) • ECG • Vital signs • Suicidality • SGIC-SD or CGIC-SD (Visits B4, B6, B8 and B10) • Vineland-II (Visits B6 and B10) • Wechsler Tests (Visits B6 and B10) • CBCL or ABCL (Visits B6 and B10) • SCQ (Visits B6 and B10) • QOLCE or QOLIE-31-P (Visits B6 and B10) • CGIC or SGIC (Visits B6 and B10) • PGIC (Visits B6 and B10) • Clinical laboratory samples (blood and urine) will be taken for: – Hematology – Biochemistry – Urinalysis – Urine/serum pregnancy tests (Visits B4, B6, B8 and B10, if appropriate) – Serum IGF-1 (Visits B6 and B10) – AED concentrations Additional re-supply visits are scheduled during the OLE and will include a review of concomitant medications (including AEDs), AEs, patient diary and IMP dispensing, collection and compliance review. **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 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 of the blinded phase (Visit 10 or 11) and again at their final dosing visit of the OLE (Visit B10 or B11). 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	**Blinded Phase:** Each of the primary and secondary endpoints will be described and compared between treatment groups, using appropriate statistical methods, over the 16-week, double-blind maintenance and titration period. Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Each endpoint, including the primary will have 2 comparisons against placebo (25 mg/kg/day GWP42003-P and 50 mg/kg/day GWP42003-P vs. placebo). Also, 3 key secondary endpoints have been defined. The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure. One must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis is not rejected then testing will stop and all subsequent analyses will be declared not statistically significant. The secondary endpoints will be tested hierarchically, starting with the key secondary endpoints followed by all other and exploratory secondary endpoints. No multiplicity adjustments will be made for all other secondary endpoints. All other statistical tests will be two-tailed and carried out at the 5% level of significance. All safety data will be summarized using appropriate statistical methods. **Open-label Extension:** All data collected during this study will be summarized across

	time, using appropriate statistical methods. Where baseline data are available from the blinded phase, changes from baseline will also be presented. 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: Blinded Phase

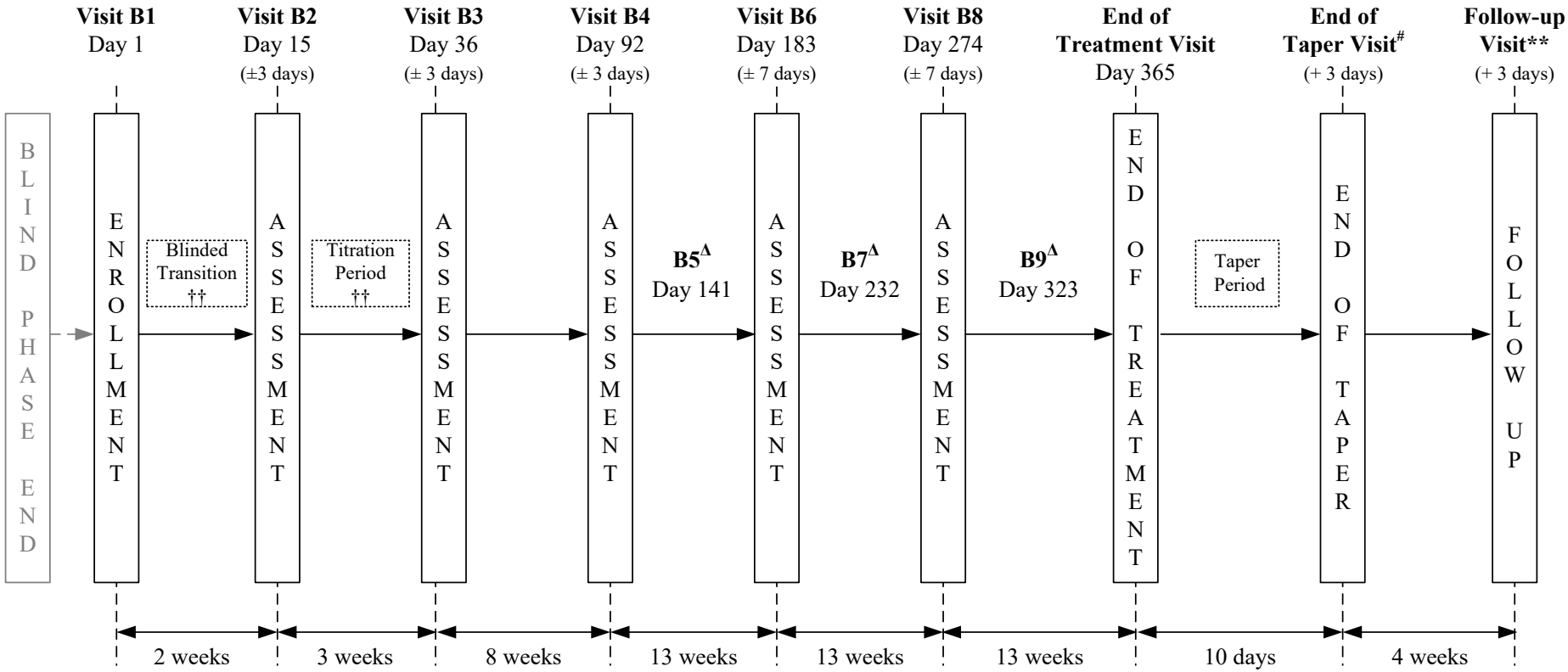


* For patients not entering the open-label extension at Visit 10.

** For patients not entering the open-label extension; can be conducted by telephone.

Safety telephone calls must be completed every two days during titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

Figure 1-2 Study Design and Treatment Schema: Open-label Extension



* To avoid double-dosing of IMP at Visit 1, patients will be instructed to begin titration of IMP the following day, which will be regarded as Day 1. As such, Visit 1 will occur on Day −1 with no clinic visit on Day 1.

Following the 'End of Taper Period' visit, a safety telephone call must be made two weeks later to collect seizure information, and to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

** Can be conducted by telephone.

[Δ]B5, B7 and B9 – Re-supply visits.
[††] Safety telephone calls must be completed every two days during blinded transition, titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

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List of Abbreviations

ABCL	Adult Behavior Checklist
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
AED	Antiepileptic Drug(s)s
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
CBCL	Child Behavior Checklist
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CGIC-SD	Caregiver Global Impression of Change in Seizure Duration
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DRF	Diagnostic Review Form for Epilepsy Study Consortium
EAP	Expanded Access IND Program
EC	Ethics Committee
ECG	12-Lead Electrocardiogram
EEG	Electroencephalogram
ESC	Epilepsy Study Consortium
EU	European Union
FDA	U.S. Food and Drug Administration
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GW	GW Research Ltd
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IGF-1	Insulin-like growth factor-1

IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to treat
IVRS	Interactive Voice Response System
MAR	Missing at Random
MNAR	Missing Not at Random
mTOR	Mammalian target of rapamycin
MI	Multiple Imputation
OLE	Open-label Extension
PGIC	Physician Global Impression of Change
PI	Principal investigator
PK	Pharmacokinetics
PP	Per protocol
PRN	Packaging Reference Number
PVD	Pharmacovigilance Department
QOLCE	Quality of Life in Childhood Epilepsy
QOLIE-31-P	Quality of Life in Epilepsy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCQ	Subject Communication Questionnaire
SGIC	Subject Global Impression of Change
SGIC-SD	Subject Global Impression of Change in Seizure Duration
SEGAs	Subependymal giant-cell astrocytomas
SENs	Subependymal nodules
SMC	Safety Monitoring Committee
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAND	TSC-associated neuropsychiatric disorders
TBL	Total Bilirubin
THC	Δ^9-Tetrahydrocannabinol

TSC	Tuberous sclerosis complex
ULN	Upper Limit of Normal
VFDs	Visual field defects
VGB	Vigabatrin

Definition of Terms

Term	Definition
Baseline	The 28-day (+3 days) period from screening to randomization.
Day 1	The day a patient first receives investigational medicinal product in this study.
End of study	Last patient last visit or last contact, whichever occurs last.
Enrolled patient	Patient is considered enrolled in the study from the time of providing written informed consent.
IMP	Investigational Medicinal Product (Study Medication).
International Normalized Ratio	A calculation made to standardize prothrombin time.
Investigator	Study principal investigator or a formally delegated study physician.
Status epilepticus	Any seizure lasting 30 minutes or longer.

2 OBJECTIVES

2.1 Primary

Blinded Phase:

To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with tuberous sclerosis complex (TSC).

Open-label Extension:

To evaluate via the adverse events (AE) profile the long term safety and tolerability of GWP42003-P as add-on therapy in children and adults with TSC who experience inadequately-controlled seizures.

2.2 Secondary

Blinded Phase:

- To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.
- To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.
- To evaluate the effects of GWP42003-P on quality of life compared with placebo.
- To evaluate the safety and tolerability of GWP42003-P compared with placebo.

Open-label Extension:

- To evaluate the long term effects of GWP42003-P, as add-on therapy, on antiepileptic measures.
- To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old).
- To evaluate the long term effects of GWP42003-P on quality of life.
- To evaluate the long term safety and tolerability of GWP42003-P.

2.3 Exploratory

Blinded Phase:

- To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.
- To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.
- To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), if applicable.

Open-label Extension:

- To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features.

3 BACKGROUND AND RATIONALE

3.1 Disease

TSC is a genetic disorder characterized by the formation of nonmalignant tumors (tubers) in multiple organ systems. The clinical signs of TSC arise as a result of inactivating mutations in either of two tumor suppressor genes: *TSC1* (located on chromosome 9q34.13[1]) or *TSC2* (located on chromosome 16p13.3[2]). *TSC1* encodes the 130-kDa protein TSC1 (hamartin)[1] whilst *TSC2* encodes the 200-kDa protein TSC2 (tuberin)[2]. TSC1 and TSC2 share no homology yet bind to each other with high affinity to form a functional heterodimer[3] which suppresses the mammalian target of rapamycin (mTOR), a key regulator of cell growth and proliferation[4]. Thus, inactivating mutations in *TSC1* and *TSC2* lead to inadequate suppression of mTOR signaling, resulting in abnormal cellular growth and tumorigenesis[5,6]. TSC is transmitted in an autosomal dominant pattern of inheritance, although two-thirds of all cases are caused by *de novo* mutations[2,7,8]. Mutations in *TSC1* account for approximately 15% of all cases of TSC whilst approximately 70% of all cases are due to mutations in *TSC2*; ~15% of TSC patients have no identifiable mutation in the coding regions of either gene[8,9]. Generally, *TSC2* mutations result in a more severe disease phenotype compared with *TSC1* mutations[8,9]. The birth incidence of TSC is estimated to be 1 in 6,000 with approximately 50,000 individuals in the United States and 1 million individuals worldwide affected[10,11].

Tumors in TSC patients can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin and lungs[12]. The random location, number, size and distribution of tumors result in a great variety of clinical manifestations, yet most patients exhibit dermatological, renal and/or neurological abnormalities, which appear at distinct developmental points[13]. Dermatological abnormalities generally first appear in infancy or early childhood and include hypomelanotic macules, which are present in more than 90% of TSC patients, and facial angiofibromas, found in approximately 75% of TSC patients[7,14,15]. In contrast, renal abnormalities tend not to develop until late childhood/adolescence and include angiomyolipomas (found in 50–70% of TSC patients), renal cysts (found in 25–35% of TSC patients) and, very rarely, renal-cell carcinomas (found in 2–3% of TSC patients)[16,17,18]. Neurological abnormalities first appear during embryogenesis and include cerebral cortical tubers and subependymal nodules (SENs), each of which are found in 80–90% of TSC

patients, as well as subependymal giant-cell astrocytomas (SEGAs), which are presumed to derive from SENs and are found in 5–15% of TSC patients[19]. Whereas SENs and SEGAs are usually asymptomatic, the presence of cortical tubers is widely believed to underlie the neurologic manifestations of TSC, which include epilepsy, cognitive disability and autism[12,13,19].

Epileptic seizures are the most common clinical manifestation of TSC, affecting more than 70% of patients[9,20,21,22]. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80% of TSC patients[13,20]. The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms[20]. Interictal electroencephalogram (EEG) recordings at onset typically show hypsarrhythmia, characterized by focal or multifocal spike discharges and irregular slow-wave activity[23]. Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex focal seizures (with or without secondary generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences[20]. Although infantile spasms resolve with time, the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy, including Lennox–Gastaut syndrome[20]. Cognitive impairment (intelligence/developmental quotient < 70) is observed in around 60% of all TSC patients with a history of seizures and in approximately three-quarters of all TSC patients with a history of refractory epilepsy[20]. Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences[22,24].

In both the European Union and the United States, the drug of first choice for the treatment of infantile spasms secondary to TSC is vigabatrin (VGB), which was approved by the U.S. Food and Drug Administration (FDA) in 2009 (as Sabril®) to treat infantile spasms in children aged 1 month to 2 years[25]. VGB is a structural analog of γ-aminobutyric acid (GABA; the major inhibitory neurotransmitter in the central nervous system) that irreversibly inhibits GABA-transaminase and thereby increases brain levels of GABA[26]. The initial prospective clinical study compared VGB (100–150 mg/kg/day) with adrenocorticotropic hormone (ACTH; 10 IU/day) in 42 patients with infantile spasms, only 4 of whom were diagnosed with TSC (3

received VGB; 1 received ACTH)[27]. Although all 4 TSC patients became spasm-free after 20 days' treatment (irrespective of which therapy was received), VGB was considered more effective than ACTH for the treatment of infantile spasms due to TSC[27]. In a separate randomized trial which compared VGB (150 mg/kg/day, $n = 11$) with the oral steroid hydrocortisone (15 mg/kg/day, $n = 11$) for the treatment of infantile spasms due to TSC, 100% of patients taking VGB were spasm-free after 1 month's treatment compared with 45% taking hydrocortisone[28]. Furthermore, of the non-responders who received hydrocortisone, all became spasm-free on switching to VGB therapy[28]. A larger study compared 2 doses of VGB in treatment-naïve patients with infantile spasms[29,30]. Of the patients with TSC, 52% were spasm-free after 2 weeks' treatment compared with 16% of patients with other etiologies[29]. Furthermore, 92% of TSC patients who began VGB therapy were spasm-free after 71 days' treatment, although whether these patients received additional treatments during this time is unclear[29]. Following recruitment of more patients into the trial and use of intent-to-treat analysis, however, only 21% of TSC patients could be classed as primary responders after 2 weeks' treatment compared with 9% of patients with other etiologies[30]. Although VGB is generally well tolerated, long term treatment with VGB is associated with irreversible peripheral visual field defects (VFDs), the risk of which increases with increasing dose and cumulative exposure[26]. The prevalence of VGB-associated VFDs in children with refractory complex focal seizures is approximately 15%[26]; however, a very recent study found that 60% of TSC patients who received VGB treatment for infantile spasms subsequently developed VFDs[31]. Furthermore, there is evidence that spasms may relapse and become refractory to VGB following discontinuation of treatment in children with focal cortical dysplasia/TSC[32].

ACTH (corticotropin) is a long-established therapy for infantile spasms and was approved by the FDA in 2010 (as Acthar® Gel) as monotherapy in infants and children younger than 2 years. Although a number randomized controlled trials have demonstrated efficacy for ACTH in the treatment of infantile spasms and resolution of hypsarrhythmia, many of these studies do not provide TSC-specific data[33]. Side effects are common with ACTH treatment and long term exposure is associated with serious adverse events (SAEs), including fulminant infections secondary to immunosuppression, hypertension, glucosuria and metabolic abnormalities[25,34]. Furthermore, there is evidence that ACTH may contribute to the enlargement of

cardiac rhabdomyoma in TSC patients[35,36]. ACTH treatment is therefore generally short-term (~2 weeks followed by taper) and close monitoring is required in TSC patients with cardiac rhabdomyoma. Relapse rates following effective ACTH treatment range from 15–60%[33]. Oral corticosteroids (prednisone/prednisolone) have also been used to treat infantile spasms, although randomized controlled trials demonstrate that even at very high doses only ~30–60% of patients achieve freedom from spasms[37,38,39,40].

The mTOR inhibitor everolimus (the 40-*O*-[2-hydroxyethyl] derivative of sirolimus/rapamycin) has demonstrated efficacy in reducing seizure frequency in TSC patients with SEGA[41]. In an open-label study of add-on everolimus (3 mg/m^2/day; $n = 16$), 56% of patients had a clinically-relevant reduction in total seizure frequency at 6 months[42]. In a randomized controlled trial comparing everolimus (4.5 mg/m^2/day; $n = 78$) with placebo ($n = 39$), analysis of change in seizure frequency was inconclusive because most patients had no seizures at baseline or at 24 weeks' follow-up[43]. As both studies demonstrated significant reductions in SEGA volume, the FDA approved everolimus in 2010 (as Afinitor®) and in 2012 (as Afinitor Disperz™) for the treatment of TSC patients with SEGA who are not eligible for curative surgical resection. In addition to resective surgery, other non-pharmacological treatments of TSC-associated epilepsy include vagus nerve stimulation and the introduction of a ketogenic diet[22].

3.2 GWP42003-P Background

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 purified (≥ 98%) CBD that typically contains less than 0.15% (w/w) THC (for oral formulations). The purified 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. To date, 2 G-protein-coupled receptors for cannabinoids have been identified, designated CB_1 receptor and CB_2 receptor. CBD does not bind to either of these receptors with any great affinity but does

modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects conduction of ion channels and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1[44] and the orphan receptor GPR55[45]. Importantly, CBD lacks the psychoactivity associated with THC. Further to this, CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity[46]. Very little data concerning AEs of CBD in humans currently exist; however, in the small number of placebo-controlled trials published to date investigating the anticonvulsant effects of CBD, few side effects have been reported after 4–12 months of 200–300 mg/day CBD[46].

3.3 Rationale

The pharmacological therapies currently available for TSC-associated epilepsy often produce serious adverse effects, and a significant proportion of patients (37–63%) become resistant to treatment[20,21]. Consequently, there is a clear need for new, efficacious pharmaceutical treatments for refractory epilepsy. Given the limitations of current synthetic AEDs, it has been suggested that CBD should be tested for anticonvulsive efficacy in randomized controlled clinical trials, especially in infantile epileptic syndromes[46]. Although there are no published reports to date investigating the efficacy of CBD for seizures in TSC patients, a recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures whilst taking CBD-enriched cannabis, with over half of those reporting > 80% reduction in seizure frequency[47]. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

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 the GW Research Ltd (GW) clinical study GWMD09112[48], 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[49], 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 Individual and Intermediate Expanded Access Investigational New Drug (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/day CBD; doses up to 22 mg/kg/day had been well tolerated in an individual pediatric patient. The sponsor reviews all safety information on an ongoing basis from the patients in the Individual Expanded Access IND studies and is not aware of any safety issues arising from the dosing used to date.

In the Expanded Access IND program (EAP), clinical dosing is determined on a case-by-case basis, balancing seizure control with tolerability, and shows that patients had tolerated doses up to 50 mg/kg/day. In a data review of the EAP, the median dose was 25 mg/kg/day among 230 patients treated for at least 12 weeks (EAP; data cut Sep 2015).

The first patient was dosed on 22 Jan 2014 and at the Sep 2015 data cut 350 patients with severe treatment-resistant epilepsies in the EAP (predominantly children) had received CBD oral solution; the median duration of exposure was 202 days. The available safety data collected from these patients showed that the reported AEs were usually mild or moderate in severity and resolved without treatment. There had been few withdrawals due to AEs. The median dose of CBD oral solution was 25 mg/kg/day after 12 weeks of treatment. 24 patients achieved a dose > 30 mg/kg up to and including 40 mg/kg and 37 patients were dosed in the higher category > 40 mg/kg up to and including 50 mg/kg. The highest dose had been 51 mg/kg (1 patient).

Doses of 25 and 50 mg/kg/day have been chosen for the GWEP1521 study to cover the doses of CBD oral solution most likely to have an effect in controlling multiple seizure types in TSC. The two doses will also allow demonstration of a possible dose response in TSC. Dose escalation for each patient in this study is subject to the investigator's assessment of safety and tolerability. If AEs become dose limiting, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study. Dose limiting AEs have so far recovered/were resolving with dose adjustment or cessation.

The maximum dose patients can receive during the maintenance period of the blinded phase will be 50 mg/kg/day. During the open-label phase, the maximum dose patients can receive will be 50 mg/kg/day although all patients will initially titrate to 25 mg/kg/day. The maximum dose was based on data from the Intermediate EAP at the time of initiation of GWEP1521.

Please refer to the Investigator's Brochure (IB)[51] and Development Core Safety Information for the most current safety data.

3.4 Clinical Hypothesis

The primary clinical hypothesis is that there will be a difference between the GWP42003-P dose groups and placebo in their effect on focal seizure frequency.

This study will also evaluate the effect of GWP42003-P compared with placebo on further measures of antiepileptic efficacy (responder analysis, focal seizure score, number of focal seizure-free days, number of seizures by subtype, number of infantile/epileptic spasms, usage of rescue medication, number of episodes of *status epilepticus*, duration of seizure subtypes), cognitive and behavioral function, autistic features, and quality of life. These endpoints are among those recommended by the European Medicines Agency guideline on clinical investigation of medicinal products in the treatment of epileptic disorders[50].

The dose response relationship between two GWP42003-P Dose Levels (25 mg/kg/day and 50 mg/kg/day) and placebo will also be explored.

4 EXPERIMENTAL PLAN

4.1 Study Design

This multicenter study consists of a randomized, placebo-controlled, double-blind phase followed by an open-label extension (OLE) phase.

Blinded Phase:

The blinded phase of the study is a randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P versus placebo. Patients will complete a 1-week screening period and a 4-week baseline period before they are randomized to receive 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or equivalent volumes of placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients will begin a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded IMP for 12 weeks.

Dose escalation for each patient is subject to the investigator's assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study.

Clinic visits will occur for screening (Day −35), baseline (Day −28), randomization (Day 1) and, on Days 15 and 29 during titration and on Days 43, 57, 71 (telephone) and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 10 to Visit 12 (refer to Section 9.1.2.14 for further details on safety telephone calls). If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

Patients will be required to perform daily interactive voice response system (IVRS) telephone calls to record seizure information. They will also complete a daily paper diary with information about their IMP and concomitant AED administration.

Following completion of the blinded phase, patients will be invited to continue to receive GWP42003-P in an OLE.

Those patients opting not to enter the OLE will complete a 10-day taper period (down-titrating 10% per day for 10 days).

Open-label Extension Transition:

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, patients will enter a 2-week blinded transition to the OLE. OLE IMP will be

titrated up to 25 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P:

- Patients from the placebo group will titrate up to 25 mg/kg/day GWP42003-P.
- Patients from the 25 mg/kg/day GWP42003-P group will continue to take 25 mg/kg/day GWP42003-P.
- Patients from the 50 mg/kg/day GWP42003-P group will taper down (10% per day) to 25 mg/kg/day GWP42003-P.

Safety telephone calls will be completed every two days throughout the OLE transition. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

Open-label Extension:

The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The initial OLE period will last for a maximum of 1 year.

Following titration according to the titration schedule, patients will continue with their optimal GWP42003-P dose. However, investigators may decrease the dose if a patient experiences intolerance, or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found. Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg/kg/day every two days. Patients whose dose has been decreased can have their dose increased again provided there is adequate tolerance. Safety telephone calls will be completed every two days throughout the OLE titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. If seizure freedom is achieved with use of GWP42003-P during the study, the investigator should consider reducing the dose of concomitant AEDs after six months of seizure freedom.

4.1.1 Primary Endpoint

Blinded Phase:

The primary endpoint is the change in number of TSC-associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.

*Primary endpoint TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Open-label Extension:

The safety of GWP42003-P will be evaluated by assessing the incidence, type and severity of AEs.

4.1.2 Secondary Endpoint(s)

Blinded Phase:

The following endpoints will be compared between treatment groups over the 16-week, double-blind treatment period (all changes relative to baseline):

Key:

- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure* frequency.
- Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
- Change in total seizures.

Other:

Antiepileptic Efficacy Measures:

- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in TSC-associated seizure* frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure* frequency.
- Change in number of TSC-associated seizure*-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (in patients less than 18 years old):

- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:

- Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score.
- Change in Physician Global Impression of Change (PGIC) score.

Safety and Tolerability:

- AEs.
- Clinical laboratory parameters.
- 12-lead electrocardiogram (ECG).
- Physical examination parameters (including height and weight).
- Vital signs.
- Columbia-Suicide Severity Rating Scale (C-SSRS; 19+ years) or C-SSRS Children's (6–18 years) score, where applicable.
- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

Open-label Extension:

The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase:

*TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (generalized tonic–clonic, tonic, clonic or atonic) that are countable.

Key:

- Percentage change in number of TSC-associated seizures* (average per 28 days).

- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency*.
- Change in CGIC or SGIC score.
- Change in total seizures.

Other:

Antiepileptic Efficacy Measures:

- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50% %, ≥ 75% or 100% reduction in TSC-associated seizure* frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in TSC-associated seizure* frequency.
- Change in number of TSC-associated seizure*-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (patients less than 18 years):

- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:

- Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in PGIC score.

Safety and Tolerability:

- Clinical laboratory parameters.
- ECG.
- Physical examination parameters (including height and weight).
- Vital signs.
- C-SSRS (19+ years) or C-SSRS Children's (6–18 years) score, where applicable.

- Number of inpatient hospitalizations due to epilepsy.
- Abuse liability.
- Effects on menstruation cycles (in females).

Exploratory Endpoints (Double-blind and OLE)

Antiepileptic Efficacy Measures:

- Change in composite focal seizure score (frequency × severity).
- Change in number of seizures by subtype.
- Change in use of rescue medication.
- Change in the number of episodes of *status epilepticus* (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

TAND:

Cognitive and Behavioral Function:

- Changes in Vineland Adaptive Behavior Scales, Second Edition (Vineland-II).
- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL).

Autistic Features:

- Change in Social Communication Questionnaire (SCQ) score.

PK (Double-blind only):

- The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable time-point will be calculated.
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

4.2 Number of Centers

Approximately 40 centers are expected to participate in this study.

4.3 Number of Patients

Blinded Phase:

A total of 210 patients will be targeted to be enrolled. The 210 patients will be randomly allocated to one of four treatment groups (GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy. If it is assumed that patients in the placebo group will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per group will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.

Open-label Extension:

All patients who wish to continue on IMP following the blinded phase.

The sample size calculation is explained fully in Section 13.1.

5 INVESTIGATIONAL MEDICINAL PRODUCT

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

5.1 GWP42003-P Solution

GWP42003-P solution is presented as a clear, colorless to yellow solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol (10% v/v) with added sweetener (sucralose) and strawberry flavoring (Table 5.1-1).

Table 5.1-1 Formulation of GWP42003-P Solution

Material	Quantity
CBD	100 mg/mL
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.2 Placebo Solution

Placebo solution is presented as a clear, colorless to yellow oily solution containing the excipients sesame oil and anhydrous ethanol (10% v/v) with added sweetener (sucralose) and strawberry flavoring (Table 5.2-1).

Table 5.2-1 Formulation of Placebo Solution

Material	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

5.3 Packaging, Storage and Drug Accountability

5.3.1 Packaging and Labeling

The IMP will be manufactured, packaged, labeled and/or distributed by G-Pharm or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each relevant visit considering the dose group and weight of each patient. A unique identification number will be used to identify each box and the IMP it contains. The unique identification number together with the packaging reference number (PRN) will permit full traceability of manufacture, pack and label activities conducted at or on behalf of G-Pharm and the IMP information held on the IVRS. G-Pharm will

ensure that all IMP provided is fully labeled and packaged. Label text will include the following information, as a minimum:

- Sponsor's name.
- Product identification (e.g., "GWP42003-P/placebo").
- Dose and/or Potency.
- Expiry date.
- Storage conditions.
- Instruction: "For clinical trial use only".
- Instruction: "Keep out of the sight and reach of children".

In addition, any local country requirements in accordance with local Drug Law or Regulatory Requirement will be included in the final label text.

The IMP labels for the blinded phase and the open-label phase of the trial will have different colors, so these can be easily distinguished by the patients. Directions of use, name, address and the telephone number of the investigator (or main contact for information about the product or the clinical trial) will be provided separately to the patient. Patients will be instructed to retain and carry this information with them at all times.

5.3.2 Storage

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

The IMP must be stored in compliance with the local regulations for a controlled drug (if applicable to country). The sponsor must approve storage location and facilities. Temperature records of the clinical site storage location must be maintained (recording a minimum of Monday–Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each center. 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. Temperature records taken during transit of IMP to center must be checked on receipt.

Should storage conditions deviate from these specified requirements, the GW study monitor must be contacted immediately to confirm if the IMP remains suitable for

use. IMP should be placed under quarantine until written confirmation is received that IMP is suitable for use.

IMP will be transported to country depots and clinical sites in compliance with Good Distribution Practice guidelines.

5.3.3 Supply and Return of Investigational Medicinal Product

All IMP will be shipped to approved depot facilities and clinical sites with a Product Release Certificate that includes a physical description of the product for confirmation of identity on receipt.

Once a center has been activated via the IVRS at study initiation, IMP will be shipped to the identified responsible person, such as the pharmacist, at the investigator's center, who will check the amount received (against the IVRS Shipment Request) and condition of the drug (i.e., integrity, physical appearance, temperature during transit). Details of IMP received will be recorded in the IMP accountability record (see Section 5.3.4). The center 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 IVRS. As directed, all supplies, including unused, partially used, or empty containers, will be returned to G-Pharm/depot or destroyed at a G-Pharm-approved site if agreed in writing by the study monitor.

5.3.4 Investigational Medicinal Product Accountability

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

- Study Code.
- PRN, Treatment number, date of receipt and quantity of IMP received.
- Patient's trial identification and/or Treatment number.
- Date and quantity of IMP dispensed.
- The initials of the dispensing/dosing party.
- Date and quantity of IMP returned to the investigator.
- IMP expiry dates.

IMP will be dispensed at Visits 3, 4, 5, 6, 7, 9 and 10 (patients not entering the OLE) during the blinded phase and Visits B1, B2, B3, B4, B5, B6, B7, B8 and B9. All patients will be asked to return all IMP (used and unused) to each subsequent visit. Any discrepancies will be discussed with the patient or their caregiver at the time of the visit and documented accordingly within the patient's source documents.

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

A record of returned IMP must be completed and included in the shipment of used and unused IMP to GW or the relevant Drug Distribution Depot. At the end of the study, a record/statement of reconciliation must be completed and provided to GW.

These inventories must be made available for inspection by an authorized GW 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 are responsible for confirming patient eligibility and will be required to maintain a log that includes limited information about all screened patients (initials, age, sex; as allowed per local regulations) and outcome of screening. After the screening visit, investigators will submit the patient's documented history of seizures directly to the Epilepsy Study Consortium (ESC) for verification of seizure types. The ESC may ask the investigator for additional information to assist in their decision. The decision will be made within 14 days of receipt of all required information and the ESC will provide written confirmation directly to the investigator.

6.1 Inclusion Criteria

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

6.1.1 Patient is male or female aged between one and 65 years inclusive.

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

6.1.3 Patient and their caregiver are willing and able (in the investigator's opinion) to comply with all study requirements (including accurate diary and IVRS completion).

6.1.4 Well-documented clinical history of epilepsy, which is not completely controlled by their current AEDs.

6.1.5 Clinical diagnosis of TSC according to the criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference[19].

6.1.6 Taking one or more AEDs at a dose which has been stable for at least four weeks prior to screening.

6.1.7 All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for one month prior to screening and the patient is willing to maintain a stable regimen throughout the study.

6.1.8 Patient is willing to keep any factors expected to affect seizures stable (such as the level of alcohol consumption and smoking).

6.1.9 Patient and/or parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.

6.1.10 Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant (if they have one) to be notified of participation in the study, if mandated by local law.

At the end of the baseline period, patients must also meet the following criteria:

6.1.11 Experienced at least eight seizures during the first 28 days of the baseline period, with at least one seizure occurring in at least three of the four weeks (seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures ([tonic–clonic, tonic, clonic or atonic] that are countable).

6.1.12 Completed at least 90% of calls to IVRS during the first 28 days of the baseline period (a minimum of 25 completed calls).

6.2 Exclusion Criteria

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

6.2.1 Patient has a history of pseudo-seizures.

6.2.2 Patient has clinically significant unstable medical conditions other than epilepsy.

6.2.3 Patient has an illness in the four weeks prior to screening or randomization, other than epilepsy, which in the opinion of the investigator could affect seizure frequency.

6.2.4 Patient has undergone general anesthetic in the four weeks prior to screening or randomization.

6.2.5 Patient has undergone surgery for epilepsy in the six months prior to screening.

6.2.6 Patient is being considered for epilepsy surgery or any procedure involving general anesthesia during the blinded phase of the study.

6.2.7 Patient has been taking felbamate for less than one year prior to screening.

6.2.8 Patient is taking an oral mTOR inhibitor.

6.2.9 Patient has, in the investigator’s opinion, clinically significantly abnormal laboratory values.

6.2.10 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.

6.2.11 Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS in the last month or at screening.

6.2.12 Patient is currently using or has in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the three months prior to screening and is unwilling to abstain for the duration for the study.

6.2.13 Patient has tumor growth which, in the opinion of the investigator, could affect the primary endpoint.

6.2.14 In the opinion of the investigator the patient has clinically significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which will interfere with the ability to read their ECGs.

6.2.15 Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit 3), defined as **any** of the following:

i) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN).

ii) TBL* [serum total bilirubin] ≥ 2 × ULN **or** international normalized ratio [INR] > 1.5 (*TBL ≥ 2 × ULN exclusion will not apply for patients diagnosed with Gilbert's disease).

iii) Serum ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

This criterion can only be confirmed once the laboratory results are available.

6.2.16 Patient is female and of child bearing potential, or is male whose partner is of child bearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the study and for three months thereafter.

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

6.2.18 Patient has received an IMP less than 12 weeks prior to the screening visit.

6.2.19 Patient has 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 may affect the patient's ability to take part in the study.

6.2.20 Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they take part in the study.

6.2.21 Patient has donated blood during the past 12 weeks and is unwilling to abstain from donation of blood during the study.

6.2.22 Patient has been previously randomized into this study.

6.2.23 Patient has any known or suspected history of alcohol or substance abuse.

6.2.24 Patient has travel outside the country and/or state of residence planned during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.

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 forms (ICF) 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 and, if allowed per local regulations, assent forms prior to any procedures being performed (refer to Section 9.2.1 and Section 15.2).

In the UK, enrollment of patients between the ages of 12 and 23 months will only commence once 15 patients over the age of 23 months have been dosed for a minimum of 4 weeks and no new safety issues have been observed.

7.1 Treatment Assignment

At the start of Visit 1, enrolled patients will be allocated a unique patient number using an IVRS. The patient number is preceded by the letter T and consists of a four-digit GW center number and a three-digit patient identification number. For example, T1234001, denoting patient 001 at site 1234. After confirmation of eligibility at Visit 3, patients will be randomly allocated to 25 mg/kg/day, 50 mg/kg/day or placebo using the IVRS. G-Pharm will provide all IMP in a packed and labeled state and the IVRS will identify the pack number to be dispensed to the patient at each relevant visit, according to the treatment assigned in the randomization schedule.

7.2 Randomization

The allocation of IMP to treatment number will be done according to a randomization schedule produced by an independent statistician. The randomization schedule will be held centrally and not divulged to any other person involved in the study until the database has been locked and unblinding authorized by the relevant GW personnel. For access to blinded treatment assignment, see Section 8.5.

The randomization will be stratified by age group (1–6 years, 7–11 years, 12–17 years and 18–65 years).

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration and Schedule

The use of placebo in the current study was deemed necessary to determine the efficacy and safety of the current intervention, since the best proven intervention had already been tried or may be given as an adjuvant treatment, failing to fully alleviate the patient's symptoms. For details regarding IMP formulations, see Section 5.

Patients will be assigned to receive GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy.

8.1.1 Dose Administration

The IMP will be administered by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided and may be taken with other concomitant medications, as directed by the investigator.

Patients may not be randomized into the study if using a gastrostomy/nasogastric tube, unless the patient is able to still take medication orally. 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 and Dose Adjustments

All patients will be weighed during Visit 3 and the daily volumes of IMP solution to be taken during the maximum four-week titration period and for the remainder of the blinded phase maintenance period will be calculated via the IVRS and the dosing regimen provided to the patient and/or caregiver. Doses may be altered during the OLE according to changes in patient weight. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

Titration from 0–25 mg/kg/day will begin at 5 mg/kg/day and will be increased in increments of 5 mg/kg/day every two days (patients will remain on each dose level for two days before they progress on to the next dose). Titration from 25–50 mg/kg/day will continue at smaller increments of 2.5 mg/kg/day every two days.

Table 8.1.2-1 Dose Titration Regimen*

Day	Dose Level 1 (25 mg/kg/day)	Dose Level 2 (50 mg/kg/day)
1	5.0 mg/kg	5.0 mg/kg
2	5.0 mg/kg	5.0 mg/kg
3	10.0 mg/kg	10.0 mg/kg
4	10.0 mg/kg	10.0 mg/kg
5	15.0 mg/kg	15.0 mg/kg
6	15.0 mg/kg	15.0 mg/kg
7	20.0 mg/kg	20.0 mg/kg
8	20.0 mg/kg	20.0 mg/kg
9	25.0 mg/kg	25.0 mg/kg
10	25.0 mg/kg	25.0 mg/kg
11	25.0 mg/kg	27.5 mg/kg
12	25.0 mg/kg	27.5 mg/kg
13	25.0 mg/kg	30.0 mg/kg
14	25.0 mg/kg	30.0 mg/kg
15	25.0 mg/kg	32.5 mg/kg
16	25.0 mg/kg	32.5 mg/kg
17	25.0 mg/kg	35.0 mg/kg
18	25.0 mg/kg	35.0 mg/kg
19	25.0 mg/kg	37.5 mg/kg
20	25.0 mg/kg	37.5 mg/kg
21	25.0 mg/kg	40.0 mg/kg
22	25.0 mg/kg	40.0 mg/kg
23	25.0 mg/kg	42.5 mg/kg
24	25.0 mg/kg	42.5 mg/kg
25	25.0 mg/kg	45.0 mg/kg
26	25.0 mg/kg	45.0 mg/kg
27	25.0 mg/kg	47.5 mg/kg
28	25.0 mg/kg	47.5 mg/kg
29	25.0 mg/kg	50.0 mg/kg

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

Each patient will take their first dose of IMP at Visit 3 (Day 1) and their final maintenance dose of IMP at Visit 10 (Day 113). If an unacceptable AE develops at any time during the titration period, dosing should initially be suspended or amended, at the investigator's discretion, until the event has resolved. During the maintenance period, patients should continue on a stable dosing regimen at the target Dose Level. If that dose becomes poorly tolerated or an AE occurs (e.g., somnolence, transaminase elevation **not meeting** withdrawal criteria specified in Section 10 and Section 12.8), the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period following discussion with the GW medical monitor. It is recommended that patients with poor tolerability have their daily dose reduced by 10 mg/kg every seven days unless, in the investigator's opinion, smaller or

larger or more rapid dose reductions are clinically indicated. Where possible, the patient should be encouraged to return to the target Dose Level.

Patients entering the OLE will first complete a two-week blinded transition phase. OLE IMP will be titrated up to 25 mg/kg/day whilst blinded IMP is **simultaneously** tapered down to zero. All patients will complete the transition and enter the OLE taking 25 mg/kg/day GWP42003-P.

Following completion of the blinded transition patients may complete a three-week titration up to a target dose of 50 mg/kg/day. Beginning at 25 mg/kg/day the dose will increase in increments of 2.5 mg/kg/day every two days.

Table 8.1.2-2 is an example of the OLE transition (Visit B1 to Visit B2) for patients transitioning from each group of the randomized phase.

Table 8.1.2-2 Blinded Transition

Day Blinded Transition/OLE	Patients randomized to 25 mg/kg/day group		Patients randomized to 50 mg/kg/day group		Patients randomized to placebo group	
	Blinded	Open-label	Blinded	Open-label	Placebo	Open-label
1	25	0	50	0	0	0
2	22.5	0	45	0	0	0
3	20	5	40	5	0	5
4	17.5	5	35	5	0	5
5	15	10	30	10	0	10
6	12.5	10	25	10	0	10
7	10	15	20	15	0	15
8	7.5	15	15	15	0	15
9	5	20	10	20	0	20
10	2.5	20	5	20	0	20
11	0	25	0	25	0	25
12	0	25	0	25	0	25
13	0	25	0	25	0	25
14	0	25	0	25	0	25

Following completion of the blinded transition patients may complete a three-week titration up to a target dose of 50 mg/kg/day. Beginning at 25 mg/kg/day the dose will increase in increments of 2.5 mg/kg/day every two days (Table 8.1.2-3).

Table 8.1.2-3 OLE Titration Schedule

OLE Day	Daily Dose (mg/kg/day)
15 (Visit B2)	26.25[a]
16	27.5
17	30
18	30

Table 8.1.2-3 OLE Titration Schedule	
OLE Day	**Daily Dose (mg/kg/day)**
19	32.5
20	32.5
21	35
22	35
23	37.5
24	37.5
25	40
26	40
27	42.5
28	42.5
29	45
30	45
31	47.5
32	47.5
33	50
34	50
35	50
36 (Visit B3)	50

[a] Derived from an AM dose based on 25 mg/kg/day and a PM dose based on 27.5 mg/kg/day.

Patients who do not enter the OLE study at Visit 10 or withdraw early will have their dose of IMP tapered gradually (10% each day) over a period of 10 days unless continued dosing is not possible due to an AE. Patients not entering the OLE will return used and unused IMP to the clinic at Visit 11.

8.2 Concomitant Therapy

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant AEDs must have been stable for at least four weeks prior to screening and must remain stable throughout the blinded study period. If during the blinded or OLE phase plasma concentrations of concomitant AEDs are found to be altered following administration of IMP, or if there are side-effects suspected of being related to an elevation in the concomitant AED concentration, the investigator must contact the GW medical monitor to discuss best management. Decisions should be based on clinical symptoms and not plasma levels of AEDs. Further information on drug interactions can be found in the IB[51].

Concomitant AED dose reductions are permitted on clinical grounds (e.g., due to AEs or transaminase elevations **not meeting** withdrawal criteria specified in Section 10 and Section 12.8) following discussion with the GW medical monitor.

Additional new AEDs (including oral mTOR inhibitors) are not allowed to be added during the randomized phase of the trial but may be considered on a case-by-case basis for the OLE phase in accordance with local licensing and after consultation with the GW medical monitor.

The use of rescue medication is allowed when necessary. Any medication, other than the IMP, taken during the study must be recorded on the Case Report Form (CRF).

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

8.3 Prohibited Therapy During Study Period

The following medications are prohibited for the duration of the study beginning from acquisition of patient consent/assent. However, any patients taking these medications after randomization should not be withdrawn from the study unless there are safety concerns. If applicable, the possible effects of these medications on the primary endpoint will be considered during the assessment of the evaluable period (see Section 13.6.1).

- Any new medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) or changes in dosage.
- Recreational or medicinal cannabis or synthetic cannabinoid-based medications (including Sativex®).
- Any other IMP taken as part of a clinical trial.

Care should be taken with drugs, or their metabolites, that are cytochrome P450 2C19 substrates, such as N-desmethylclobazam. Care should also be taken with drugs, or their metabolites, that are solely or primarily metabolized by UDP-glucuronosyltransferase 1A9 and 2B7.

8.4 Compliance in Investigational Medicinal Product Administration

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

- Visit 3 (Day 1)
- Visit 4 (Day 15)
- Visit 5 (Day 29)
- Visit 6 (Day 43)

- Visit 7 (Day 57)
- Visit 9 (Day 85)
- Visit 10 (Day113) (patients not entering the OLE)
- All OLE visits until the end of treatment

The patient or their caregiver will record the volume of solution taken on each treatment day in the diary.

Patients should return all IMP (used and unused) at each of visits 4, 5, 6, 7, 9, 10 and 11 during the blinded phase and at all OLE visits. The usage recorded in the diary and the usage projected in the dose calculator will be checked and any discrepancies discussed with the patient or their caregiver at the time of the visit and documented accordingly within the patient's source documents.

Records of IMP accountability will be maintained according to Section 5.3.4.

8.5 Access to Blinded Treatment Assignment (Blinded Phase and OLE Transition Only)

The identity of IMP assigned to patients will be held by the IVRS. The principal investigator (PI) at each center, or his/her designee, is responsible for ensuring that information on how to access the IVRS for an individual patient is available to the relevant staff in case of an emergency and unblinding is required. A patient's treatment assignment should only be unblinded when knowledge of the treatment is essential to make a decision on the medical management of the patient. Unblinding for any other reason will be considered a protocol deviation.

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

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

9 STUDY PROCEDURES

A list of the required study procedures is provided in the subsections that follow; refer also to the Schedule of Assessments (APPENDIX 1). Assessments or tests that are not done and examinations that are not conducted must be reported as such in 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 Procedures by Visit

Patients and their parent(s)/legal representative will be invited to take part in the study and will be issued with the patient information and informed consent/assent or the patient/parent(s)/legal representative information and informed consent. Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, as wished, patients/parent(s)/legal representatives who provide written informed consent/assent will be screened for entry into the study.

9.1.1 Blinded Phase

9.1.1.1 Visit 1 (Day −35, Screening)

Eligibility must be assessed according to the criteria specified in Section 6.

The following observations will be made at Visit 1: demographics, medical history (including seizure information since diagnosis, history of epilepsy-specific genetic testing and all prior AEDs taken), concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, postural blood pressure and visit procedure-related AEs. With the patient/parent(s)/legal representative's consent, a further blood test will be carried out to determine the mutation status of *TSC1* and *TSC2,* if it is unknown.

The patient's documented history of TSC will be sent to the ESC to confirm seizure classification.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and a urine/serum THC screen. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.

9.1.1.2 Visit 2 (Day −28, Baseline)

This visit will occur 7 days after Visit 1. A visit window of ±7 days from the scheduled visit is permitted to ensure ESC confirmation of seizure classification, but it is preferred that the visit is performed on the scheduled visit day where possible.

Attendance of the patient is not required for this visit provided the primary caregiver is able to attend and that this caregiver (not the patient) will be responsible for seizure identification, IVRS use, and paper diary completion. However, it is preferred that the patient attend where possible.

The following observations will be made at Visit 2: review of concomitant medications (including AEDs), AEs and epilepsy-related hospitalizations.

Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will begin the 28 (+3)-day baseline period. The investigator will review and train the patient or their caregiver to identify the patient's expected seizure types. Patients or their caregivers will be issued with IVRS details and will be instructed on how to use it to record daily seizure information. Patients or their caregivers will also be given a paper diary to record usage of IMP, rescue medication, concomitant AEDs and AEs and will be instructed on how to do so.

9.1.1.3 Visit 3 (Day 1, Randomization)

This visit will occur 28 days after Visit 2. A visit window of +3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

The following observations will be made at Visit 3: concomitant medications, (including AEDs), physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (for patients aged 10–17 years [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), ECG, vital signs, postural blood pressure, epilepsy-related hospitalizations, AEs and paper diary review. The ECG will be repeated four hours (±30 minutes) after the first dose of IMP.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum IGF-1 levels (for

patients less than 18 years of age). Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. PK samples (patients > 20 kg in weight only) will be taken in accordance with Section 9.2.9.1.

The investigator must assess the patient's daily number of seizures from the patient's IVRS data, record the patient's attendance at the visit, and confirm the outcome of the visit prior to randomization. Patients who have experienced at least eight seizures during the first 28 days of the baseline period, and who meet all of the other inclusion and none of the exclusion criteria specified in Section 6, will be eligible to continue in the study.

Eligible patients will then be randomized to receive GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent at a 2:2:1:1 ratio.

Following randomization at Visit 3, patients will remain at the clinic where the following baseline assessments will be performed prior to the administration of study medication: QOLCE/QOLIE-31-P, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

Patients/caregivers and investigators will be asked to write a brief description of their/the patient's overall condition and assess the average duration of seizure subtypes as a memory aid for the PGIC, SGIC/CGIC and SGIC-SD/CGIC-SD; these will be referred to at relevant, subsequent visits or withdrawal.

IMP will be dispensed for the following 2 weeks and patients or their caregivers will be provided with individual dosing schedules as described in Section 8.1 Each patient will then receive a titration regimen. The first dose of IMP will be administered in clinic.

Following Visit 3, during titration, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. A further call must be completed one week after the end of titration. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.

9.1.1.4 Visit 4 (Day 15)

This visit will occur 14 days after Visit 3 (randomization). 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 observations will be made at Visit 4: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis.

Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the titration regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive a new treatment pack of the IMP.

Following Visit 4, during titration, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.

9.1.1.5 Visit 5 (Day 29)

This visit will occur 28 days after Visit 3. 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 observations will be made at Visit 5: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, postural BP, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the titration regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients will then receive a new treatment pack of the IMP.

A safety telephone call must be made one week after the end of titration (Visit 5). During this call, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of the safety telephone call.

9.1.1.6 Visit 6 (Day 43)

This visit will occur 42 days after Visit 3 (randomization). 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 observations will be made at Visit 6: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

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

9.1.1.7 Visit 7 (Day 57)

This visit will occur 56 days after Visit 3 (randomization). 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 observations will be made at Visit 7: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

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

9.1.1.8 Visit 8 (Day 71)

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

Visit 8 will be completed by telephone and will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

9.1.1.9 Visit 9 (Day 85)

This visit will occur 84 days after Visit 3 (randomization). 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 observations will be made at Visit 9: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

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

9.1.1.10 Visit 10 (Day 113, End of Treatment/Withdrawal Visit)

This visit will occur 112 days after Visit 3 (randomization) or earlier if the subject withdraws from the study. A visit window of ±3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

The following observations will be made at Visit 10/the Withdrawal visit: concomitant medications (including AEDs), physical examination (including height and body weight), Tanner Staging (for patients aged 10–17 years [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), details of menstruation (for females), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum IGF-1 levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. PK samples (patients > 20 kg in weight only) will be taken in accordance with Section 9.2.9.1.

The following assessments will also be performed: QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data, record the patient's attendance at the visit and confirm the outcome of the visit.

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 who do not enter the taper period, 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 withdraw early, the IVRS will be contacted to confirm withdrawal from the study. Patients who withdraw should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator's clinical judgment. If tapering is undertaken, a 10-day supply of IMP (if required) and instructions for tapering the dose will be provided. Patients/caregivers should continue to complete the IVRS (see APPENDIX 4) and paper diary and should return for Visit 11 (the 'End of Taper Period' visit), if possible.

Patients who have completed all of the scheduled study visits will be offered the option of entering an OLE. Entry is to be on the same day as Visit 10 (Day 113).

Patients not entering the OLE at this visit will be given a 10-day supply of IMP (if required) and instructions for tapering the dose, during which time IVRS (see APPENDIX 4) and paper diary information will continue to be recorded.

9.1.1.11 Visit 11 (Day 123, End of Taper)

This visit is required only for those patients who do not enter the OLE on the day of Visit 10 or for those who withdraw early and taper IMP. For patients who complete the study but opt not to enter the OLE, Visit 11 should occur 10 (+3) days after Visit 10 (i.e., on Day 123 [+3]). For patients who withdraw early and taper IMP, this visit should occur 10 (+3) days after the Withdrawal visit. For patients who begin to taper IMP but subsequently withdraw/do not complete the full taper period, this visit should occur on the final day of dosing or as soon as possible after this date.

The following observations will be made at Visit 11: concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs, physical examination (including height and body weight), vital signs, ECG and clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). Suicidality will be assessed in accordance with Section 9.2.12.8.

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.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

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

Following Visit 11 (or date of final dosing) the IVRS seizure reporting diary should only be completed once more (see APPENDIX 4).

9.1.1.12 Visit 12 (Day 151, Safety Follow-up)

This visit is required for patients who do not enter the OLE or who withdraw from the study early. This visit should occur four weeks after Visit 11 (+3 days), or date of final dosing, and can be conducted over the telephone. The following observations will be made at Visit 12: concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

9.1.2 Open-label Extension

Patients who successfully complete the blinded phase will be invited to participate in the OLE when they reach the End of Treatment visit (Visit 10) of the blinded phase. They will be issued with the OLE 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 B1 will be enrolled into the OLE. The OLE period will last for a maximum of 1 year; however, patients in the US and Poland may have the opportunity to continue in the OLE beyond this.

On-label use of mTOR inhibitors (for the treatment of seizures or tumors) and general anesthesia are permitted in the OLE phase of the trial.

9.1.2.1 Visit B1 (Day 1)

Day 1 is regarded as the first day of IMP dosing. The following data collected at the 'End of Treatment' visit of the blinded phase will also be considered as Visit B1 data: vital signs, physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (patients aged 10–17 [inclusive]), ECG, clinical laboratory samples (blood and urine for hematology, biochemistry, urinalysis, determination of serum IGF-1 levels [patients less than 18 years of age], and pregnancy tests [if appropriate]), IVRS and paper diary information from the blinded phase (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, AEs, concomitant medications and/or changes to medication, QOLCE/QOLIE-31-P, PGIC,

SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

Patients will take their final dose of the blinded phase IMP in the morning of Visit B1, followed by collection of the blinded phase 'End of Treatment' assessments. Patients will be instructed to begin the Blinded Open-label transition, taking their first dose of Blinded Transition OLE IMP in the evening of Visit B1 (Day 1).

Patients or their caregivers will receive sufficient IMP for two weeks' home dosing together with a blinded transition phase. If an unacceptable AE develops at any time during transition, dosing should initially be suspended or amended, at the investigator's discretion, until the event has resolved or is well tolerated.

Patients or their caregivers will be given a paper diary to record information regarding AEs, IMP, usage of rescue medication, concomitant AEDs and IMP dosing. In addition, patients/caregivers will be instructed to complete a weekly seizure reporting diary until the Follow-up 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 SGIC/CGIC, the patient/caregiver is to compare to the memory aid from the Baseline of the blinded phase. If the memory aid is not available from the Baseline of the blinded phase then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit B1.

In order to complete the SGIC-SD/CGIC-SD, the patient/caregiver would have been asked to assess and note the average duration of the patient's seizures at the Baseline of the blinded phase as a memory aid for subsequent visits. If the memory aid is not available from the Baseline of the blinded phase then the patient/caregiver should do this from memory, if possible, and complete a memory aid at Visit B1.

Following Visit B1, during the blinded transition, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.

9.1.2.2 Visit B2 (Day 15)

Visit B2 will take place 14 days after Visit B1. 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 B2: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations, and AEs. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the titration regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

Upon completion of the two-week blinded transition at Visit B2 all patients will be taking 25 mg/kg/day. All blinded IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. Patients/caregivers will then receive sufficient open-label IMP for three weeks' home dosing together with a titration schedule. Patients may titrate up to the target dose of 50 mg/kg/day according to the defined titration schedule. 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.

Following Visit B2, during titration, safety telephone calls must be made every two days. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead. An additional call should be completed one week after the end of titration. During these calls, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. The investigator must retain oversight of safety telephone calls.

9.1.2.3 Visit B3 (Day 36)

Visit B3 will take place 35 days after Visit B1. 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 B3: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, postural blood pressure, epilepsy-related hospitalizations, and AEs. Suicidality will be assessed in accordance with Section 9.2.12.8. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The investigator must assess adherence to the titration regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

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 sufficient open-label IMP for eight weeks' home dosing.

9.1.2.4 Visit B4 (Day 92)

This visit will occur 91 days after Visit B1. 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 observations will be made at Visit B4: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The following assessments will also be performed: SGIC-SD/CGIC-SD. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data, record the patient's attendance at the visit and confirm the outcome of the visit.

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 sufficient open-label IMP until the next scheduled visit.

9.1.2.5 Visit B5 (Day 141, Re-supply Visit)

This visit will occur 140 days after Visit B1. 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.

Attendance of the patient is not required for this re-supply visit provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

The visit will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data, record the patient's/caregiver's attendance at the visit and confirm the outcome of the visit.

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 sufficient IMP until the next scheduled visit.

9.1.2.6 Visit B6 (Day 183)

This visit will occur 182 days after Visit B1. 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 observations will be made at Visit B6: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis and determination of serum IGF-1 levels (for patients less than 18 years of age) to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The following assessments will also be performed: QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data, record the patient's attendance at the visit and confirm the outcome of the visit.

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 sufficient open-label IMP until the next scheduled visit.

9.1.2.7 Visit B7 (Day 232, Re-supply Visit)

This visit will occur 231 days after Visit B1. 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.

Attendance of the patient is not required for this re-supply visit provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

The visits will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data, record the patient's/caregiver's attendance at the visit and confirm the outcome of the visit.

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 sufficient IMP until the next scheduled visit.

9.1.2.8 Visit B8 (Day 274)

This visit will occur 273 days after Visit B1. 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 observations will be made at Visit B8: concomitant medications, (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations and AEs.

Clinical laboratory samples (blood and urine [where possible]), including pregnancy tests if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis to be performed by the central laboratory. Provided that the risk/benefit outcome is favorable in the investigator's opinion, prior to the first daily dose of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.

The following assessments will also be performed: SGIC-SD/CGIC-SD. Suicidality will be assessed in accordance with Section 9.2.12.8.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data, record the patient's attendance at the visit and confirm the outcome of the visit.

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 sufficient open-label IMP until the next scheduled visit.

9.1.2.9 Visit B9 (Day 323, Re-supply Visit)

This visit will occur 322 days after Visit B1. 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.

Attendance of the patient is not required for this re-supply visit provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

The visits will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.

The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data, record the patient's/caregiver's attendance at the visit and confirm the outcome of the visit.

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 sufficient IMP until the next scheduled visit.

Patients in the US and Poland may have the opportunity to continue in the OLE beyond Visit B10. Please refer to Protocol Annex 1 (US based patients) or Protocol Annex 2 (Poland based patients) for the remaining visit schedule.

9.1.2.10 Visit B10 (Day 365, End of Treatment/Withdrawal Visit)

This visit will occur 364 days after Visit B1or following early withdrawal from the study. 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 at the 'End of Treatment'/Withdrawal visit: vital signs, physical examination (including height and body weight), details of menstruation (for females), Tanner Staging (patients aged 10–17 [inclusive]), ECG, clinical laboratory samples (blood and urine for hematology, biochemistry, urinalysis, determination of serum IGF-1 levels [patients less than 18 years of age] and pregnancy tests if appropriate [using both a serum sample and a urine dipstick]), IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, concomitant medications and/or changes to medication, AEs, QOLCE/QOLIE-31-P, SGIC/CGIC, PGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed in accordance with Section 9.2.12.8. Provided that the risk/benefit outcome is favorable in the investigator's opinion, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs. 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 who withdraw early, 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 outside of the GWEP1521 study, the IVRS will be contacted to confirm the patient's completion of this study and the paper diaries will be collected.

For patients who do not immediately continue to use GWP42003-P following the 'End of Treatment' visit outside of the GWEP1521 study, IMP will be tapered at home (10% per day for 10 days). Additional IMP will be dispensed, if required, and instructions for tapering the dose will be provided. Patients who withdraw early should also begin the taper period following the Withdrawal visit (unless continued dosing is not possible due to an AE). Information will continue to be recorded in the paper diary during the taper period.

For patients 12 years of age and older who do not enter the taper period, 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 Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed according to APPENDIX 4.

For patients in the US and Poland who continue in the OLE beyond Visit B10, assessments are described in Protocol Annex 1 (US) and Protocol Annex 2 (Poland).

9.1.2.11 Visit B11 (Day 375, 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 and taper IMP. 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: concomitant medications (including AEDs), physical examination (including height and body weight), ECG, vital signs, epilepsy-related hospitalizations, and AEs. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, and urinalysis. Suicidality will be assessed in accordance with Section 9.2.12.8. The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data and record the patient's attendance at the visit.

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.

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

Following Visit B11 (or date of final dosing), the IVRS seizure reporting diary should only be completed once more (see APPENDIX 4).

9.1.2.12 B12 (Day 389, Post-taper Safety Telephone Call)

A safety telephone call must be made two 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.

Following this call, the IVRS seizure reporting diary should be completed up to the Follow-up visit.

9.1.2.13 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 four 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.

9.1.2.14 Safety Telephone Calls

Safety telephone calls must be made every two days during the two-week blinded transition and the two-week OLE titration period and one week after the end of titration to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

The investigator must retain oversight of safety telephone calls.

9.2 Study Procedure Listing

9.2.1 Informed Consent/Assent

Adult patients with an adequate level of understanding must personally sign and date the EC/IRB-approved / ICF 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. If an adult patient is unable to read (illiterate or visually impaired), or is physically unable to speak or write, an impartial witness should be present during the entire informed consent discussion. After the ICF is read and explained to the patient and after the patient has orally consented to participation in the trial and has signed and dated the ICF (if capable of doing so), the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF was accurately explained to and apparently understood by the patient and that informed consent was freely given by the patient (as outlined in the International Council for Harmonisation [ICH] Tripartite Guideline for GCP Topic E6(R2)[52], section 4.8.9).

The parent(s)/legal representative of minor patients must personally sign and date the EC/IRB-approved ICF before any study-specific procedures are performed or any patient-related data is recorded for the study. In addition, in cases where the patient

possesses adequate understanding, assent will be taken (if allowed per local regulations) 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.

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

If the patient cannot write, they can give consent/assent by "making their mark" on the consent/assent form (e.g., writing an "X").

GW requires a physician to be present for consent and assent and to sign the consent and assent forms also. Patients/parent(s)/legal representatives will be given the option of being informed about the summary outcome and results of the trial as part of the ICF. For further details, see Section 15.2.

9.2.2 Contraception Requirements

To be eligible for the study, the patient must have agreed that if they or their partner are of childbearing potential they are willing to use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of birth control 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[53]. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner (provided that partner is the sole sexual partner of the trial patient and that the vasectomized partner has received medical assessment of the surgical success), or sexual abstinence[54]. Abstinence, as referenced above, is only acceptable as true abstinence: when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception[54].

9.2.3 Demographics

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

9.2.4 Medical History

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

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

The mutation status of the *TSC1* and *TSC2* genes, if known, will be obtained through the patient's medical records.

9.2.5 Concomitant Medication

Details of all current and recent medication (i.e., taken within the previous 14 days) including AEDs will be recorded at the screening visit (Visit 1) and reviewed at each subsequent visit. AEDs used during the study should be maintained at a stable dose.

Any changes in concomitant medication during the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to enrollment, as defined in Section 8.2.

9.2.6 Physical Examination

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

9.2.7 Vital Signs and Blood Pressure

Vital sign measurements (body temperature, pulse rate, respiration rate), including blood pressure taken in a sitting position at rest for five minutes, will be completed alongside the physical examination. Where postural blood pressure is required it should be measured after five minutes in supine position followed by two minutes in

standing position, if it is possible for the patient to stand. Blood pressure must be recorded using the same arm throughout the study, where possible.

9.2.8 12-Lead Electrocardiogram

A 12-lead ECG will be performed after five minutes in a supine position, if possible. 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.

9.2.9 Clinical Laboratory Sampling

Laboratory tests will include hematology, biochemistry, urinalysis (provided urine can be obtained), urine/serum THC screening and a serum pregnancy test (if appropriate). In addition to serum pregnancy tests, urine dipstick pregnancy tests will also be performed (if appropriate) at the study center. Analysis of all clinical blood samples, pregnancy tests (using serum) and tests to detect the presence of THC will be conducted at a central clinical laboratory.

Urine samples for biochemistry will be analyzed at the study center by use of a dipstick with any relevant findings being sent for further urinalysis at the central laboratory (urinalysis, microscopy, culture and sensitivity, as applicable). In cases where urine samples cannot be analyzed at center due to local regulations, a full set of urine samples should be sent to the central laboratory for analysis. Sample volume requirements and processing procedures will be detailed in a separate laboratory manual.

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 9.2.9-1.

Table 9.2.9-1 Biochemistry, Hematology, Urinalysis and THC Screen

Biochemistry (Serum)[1]	Biochemistry (Serum)[1,3]	Hematology (Whole Blood)[1]	Urinalysis (Urine)[2]	Pregnancy Test (Serum[1] / Urine[2])	THC Screen (Serum[1] / Urine[1])
Alanine aminotransferase (ALT)	Insulin-like growth factor-1 (IGF-1)	Hematocrit	Bilirubin	Serum and urine	THC
Albumin		Hemoglobin	Blood		
Alkaline phosphatase		Mean cell volume	Glucose		
Aspartate aminotransferase (AST)		Mean corpuscular hemoglobin	Ketones		
Calcium		Platelets	Nitrites		
Creatinine		Red blood cell count	pH		
Estimates of glomerular filtration rate		White blood cell count with automated differential	Protein		
Gamma-glutamyl transferase			Specific gravity		
Glucose			Urobilinogen		
HDL-cholesterol					
Potassium					
Prolactin					
Prothrombin time (PT/INR) (plasma)					
Sodium					
Total bilirubin					
Total protein					
Triglycerides					
Urea (blood urea nitrogen [BUN])					
Creatine Kinase (CK)					

[1] Analyzed at a central laboratory.

[2] Analyzed at the study center by use of a dipstick (if allowed per local regulations).

[3] Only analyzed at Visits 3, 10/B1, B6 and B10).

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. The results of THC screening will be reported back to the study site to permit confirmation of eligibility. Any samples reported to be THC-positive at screening must be sent for analysis by gas chromatography–mass spectrometry at the central laboratory.

All laboratory results considered to represent an AE must be documented in the CRF. See Section 12.8 for guidance on evaluation of potential drug-induced liver injury.

Repeat samples will be taken, if required, for clinical follow-up or if the sample is lost or damaged. Any abnormal end of treatment clinical laboratory result of clinical significance must be repeated at regular intervals until it returns to normal, or until an investigator is satisfied that the abnormality is not related to the IMP and needs no further investigation.

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss. The volume of blood drawn at each visit should be tracked. Where the required blood draw volume for study samples exceeds guidance at a particular visit, safety parameters (biochemistry and hematology) should be prioritized.

9.2.9.1 Pharmacokinetic Blood Sampling

The plasma concentration/time curves of CBD and its major metabolites will be assessed at Visits 3 and 10 for patients weighing more than 20 kg. Where appropriate, blood samples will be taken as follows:

- One sample pre-dose (i.e., prior to administration of IMP).
- One sample between 2 and 3 hours post-dose.
- One sample between 4 and 6 hours post-dose.
- One sample between 8 and 10 hours post-dose (patients 18 years and above only).

There must be a minimum period of at least two hours between each of the blood sampling time points. In the event of an AE that, in the opinion of the investigator, is related to a concomitant AED, additional blood samples may be collected.

For patients who undergo PK blood sampling, the patient/caregiver will record all meal times and the types of meals consumed by the patient during all PK testing days (Visits 3 and 10).

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

The patient/caregiver must be advised that it may not be safe for them to undertake further blood tests within one month of any study-related blood draws and to inform the investigator if they suffered any blood loss during the one-month period leading up to a planned blood draw.

9.2.9.2 Determination of Plasma Concentrations of Concomitant Antiepileptic Drugs

Plasma concentrations of concomitant AEDs will be assessed at Visits 3, 5, 7, 9 and 10/ the Withdrawal visit (if possible) during the blinded phase and at Visits B2, B3, B4 and all subsequent Assessment Visits during the OLE. Samples will be collected for all patients provided that the risk/benefit outcome is favorable in the investigator's opinion. At each visit, blood samples will be taken prior to administration of IMP. Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.

Additional blood samples may be taken for AED monitoring if there is a suspicion of changes in AED levels, with the aim to keep the AED plasma levels within the patient's therapeutic level. AED doses should be adjusted, as appropriate, following discussion with the GW medical monitor in order to maintain stable AED plasma concentrations.

9.2.9.3 Determination of Mutation Status of the *TSC1* and *TSC2* Genes

If the mutation status of *TSC1* and *TSC2* is unknown at screening, genetic analysis will be carried out if the patient/parent(s)/legal representative provides consent (a blood sample will be taken during Visit 1).

9.2.10 Interactive Voice Response System

The IVRS will be used to collect patient reported diary data (refer to Section 9.2.11), to assign patients to treatment groups and to provide treatment allocation information in the event of patient unblinding. The IVRS will also be used to manage IMP supply.

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

- Allocate a patient number at screening (Visit 1).
- Randomize a patient (Visit 3).
- Obtain dispensing information (Visits 3, 4, 5, 6, 7, 9 and during OLE).

- Provide completion/taper/premature termination information (Visit 10).

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

9.2.11 Patient Diary

A diary will be completed daily throughout the study. Patients or their caregivers will be instructed on how to complete the diary and will be asked to record information daily. The number and type of seizures and the severity of focal seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from baseline (Visit 2). Information on IMP intake will also be recorded each day from randomization (Visit 3) until completion of dosing or withdrawal (Visit 10/Withdrawal visit).

Seizure information, including the number and seizure subtype, as well as the severity of focal seizures and the number of episodes of *status epilepticus* will be collected through an IVRS telephone diary completed daily throughout the blinded phase of the study by the patient or their caregiver. This IVRS telephone diary will be completed on a weekly basis during the OLE. The patient or their caregiver will also complete a paper diary daily to record AEs, concomitant AEDs, IMP intake and rescue medication throughout the study.

The following seizure subtypes will be collected daily in the IVRS telephone diary:

- Focal motor seizures without impairment of consciousness or awareness[#]
- Focal seizures with impairment of consciousness or awareness[#]
- Focal seizures evolving to bilateral generalized convulsive seizures[#]
- Generalized seizures:
  - Tonic–clonic[#]
  - Tonic[#]
  - Clonic[#]
  - Atonic[#]
- ‘Other’ seizures:
  - Absence seizures[**]
  - Myoclonic seizures[**]

  - Focal sensory seizures**
  - Infantile/epileptic spasms**
- Episodes of status epilepticus

To be included in primary seizure endpoint.
** To be included in composite 'other' seizure count.

For the purposes of calculating the composite seizure score, the severity of focal seizures will be assessed according to the following criteria:

- Type 1 - Focal motor seizures without impairment of consciousness or awareness.
- Type 2 - Focal seizures with impairment of consciousness or awareness.
- Type 3 - Focal seizures evolving to bilateral convulsive seizures.

9.2.12 Questionnaires and Assessments Completed at Scheduled Visits

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

9.2.12.1 Subject/Caregiver Global Impression of Change

The SGIC/CGIC, as appropriate, will be performed for all patients. At Visit 3 the patient or patient's caregiver will be asked to write a brief description of the patient's overall condition as a memory aid for the SGIC/CGIC at 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 seven-point scale:

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

The SGIC comprises the following question to be rated on a seven-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 three days.

9.2.12.2 Physician Global Impression of Change

The PGIC will be performed for all patients. At Visit 3 the investigator will be asked to write a brief description of the patient's overall condition as a memory aid for the PGIC at subsequent visits. It is preferred that the same investigator performs this assessment at each visit.

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

- Please assess the change in the patient's general functional abilities since Visit 3 (prior to the commencement of study medication).

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 three days.

9.2.12.3 Subject/Caregiver Global Impression of Change in Seizure Duration

The caregiver will be asked to assess the average duration of the patient's seizures at Visit 3 (i.e., prior to commencement of IMP) as a memory aid for subsequent visits.

The SGIC-SD/CGIC-SD comprises a question to be rated on a three-point scale for each seizure subtype:

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

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

CGIC-SD:

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

SGIC-SD:

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

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

The QOLCE and the QOLIE-31-P are composed of 16 and 31 subscales, respectively, assessing seven domains of Health Related Quality of Life (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life). The QOLCE (and QOLIE-31-P, 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. The questionnaires should take 20–30 minutes to complete.

9.2.12.5 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.

9.2.12.6 Child/Adult Behavior Checklist

Achenbach CBCL and ABCL, for ages 1½–5, 6–18 and 18–59 examine internalizing behaviors (such as depression and anxiety), externalizing behaviors (such as aggression), stress, obsessive-compulsive behaviors and 'sluggish cognitive tempo'. Statements about the patient's behavior are recorded on a Likert scale: 0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True.

The age appropriate checklist will be used for all patients.

9.2.12.7 Social Communication Questionnaire

The current version of the SCQ will be completed by the caregiver for all patients above the age of 4 years with a mental age of at least 2 years. The scale provides

sub-scores to assess the domains Reciprocal Social Interaction, Communication and Restricted, Repetitive and Stereotyped Patterns of Behavior. The scale assesses behavior over the most recent three month period using 40 questions, each to be answered 'yes' or 'no'.

9.2.12.8 Suicidality/ Children's/Columbia-Suicide Severity Rating Scale (Six Years of Age and Older)

Suicidality will be assessed either by using the C-SSRS/Children's C-SSRS or, in patients with profound cognitive impairment, by the investigator's clinical judgment following interview of the patient. Where the C-SSRS/Children's C-SSRS is not considered appropriate and clinical interview is used instead, the reason must be clearly documented by the investigator.

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. During the screening visit (Visit 1), questions will be in relation to lifetime experiences, and all subsequent 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 delegate at every visit as indicated in the Schedule of Assessments (see APPENDIX 1); "qualified delegate" is defined as anyone who has completed the C-SSRS training within the past two years or has continually administered the C-SSRS assessments throughout this trial since obtaining the training certificate. 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) whilst the C-SSRS will be used for patients aged 19 and older.

9.2.12.9 Wechsler Tests

The Wechsler Tests are age specific and 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 three days of the visit). Each assessment will need to be conducted by an experienced psychometrician. 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 tests as able. The following Wechsler Subtests will be used:

Age 2–6:

- WPPSI-4 - Vocabulary and Matrix Reasoning

Age 6–Adult:

- WASI-2 - Vocabulary and Matrix Reasoning
- WISC-4 and WAIS-4 Digit Span and Coding

9.2.13 Menstruation

Caregivers will be asked if the female patient is menstruating and details will be recorded as part of their baseline (Visit 3); any changes in normal cycles will be captured at Visit 10/Withdrawal visit and subsequent OLE visits.

9.2.14 Tanner Staging

The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all adolescent patients (i.e., 10 to 17 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) will be assessed using Tanner Staging[55] (see APPENDIX 2). The patients will undergo a discreet physical examination and be assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients only), and Breasts (female patients only).

Once a patient reaches a score of V (i.e., 5) the examination need not be performed again.

9.2.15 Investigational Medicinal Product Accountability

Records of IMP accountability will be maintained according to Section 5.3.4.

9.2.16 Adverse Events

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

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

pattern or severity. Any AE which meets SAE criteria should still be reported as a SAE.

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.

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

There are two triggers that will require the investigator or study coordinator to discuss abuse potential signals with the patient or their caregiver. These are either AEs of interest that may be reported by the patient/caregiver, or drug accountability issues regarding overuse of the IMP or missing bottles. Different questionnaires will be completed by the site depending upon which trigger occurs (see Figure 9.2.17.4-1, Section 9.2.17.4). 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) of the blinded phase and again at their final dosing visit of the OLE, 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.

9.2.17.1 Monitoring of Adverse Events

AE information will be collected according to Section 9.2.16.

9.2.17.1.1 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.

9.2.17.1.2 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.

9.2.17.1.3 Monitoring Drug Accountability Discrepancies

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

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

9.2.17.1.4 List of 'Triggering Drug Accountability Discrepancies'

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

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

9.2.17.1.5 Supplemental Drug Accountability Form

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

9.2.17.2 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.

9.2.17.3 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) of the blinded phase and again at the final dosing visit of the OLE. 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.

9.2.17.4 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.

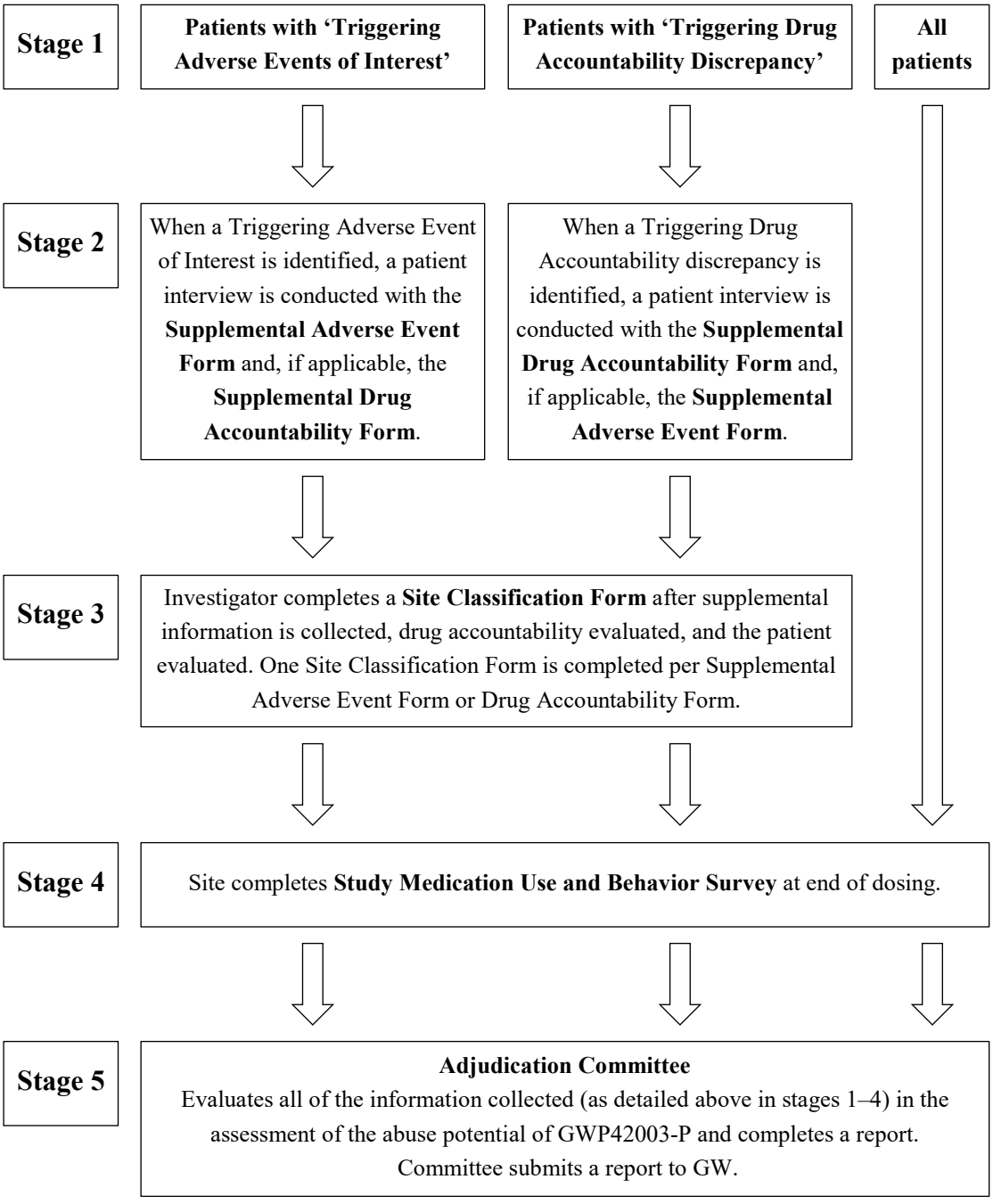
A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- 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 9.2.17.4-1.

Figure 9.2.17.4-1 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)



10 WITHDRAWAL

In accordance with the Declaration of Helsinki[56], the ICH Tripartite Guideline for GCP Topic E6(R2)[52], the U.S. FDA regulations relating to good clinical practice and clinical trials[57,58,59], the European Union (EU) Clinical Trials Directive[60], the EU Good Clinical Practice (GCP) Directive[61] 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 compromise potentially the safety of the patient.
- Withdrawal of patient consent/assent.
- Withdrawal of parent(s)/legal representative consent.
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than two weeks.
- ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).
- Lost to follow-up.

  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. In cases where the transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant AED with known hepatotoxicity should be reduced following discussion with the GW medical monitor.

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

- Did not meet eligibility criteria.
- Patient non-compliance.
- AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Suicidal ideation or behavior of type 4 or 5 during the treatment period, as evaluated with the C-SSRS.
- Any evidence of drug abuse or diversion.
- General anesthesia (blinded phase only).
- Addition of a new AED (blinded phase only).

Should a patient request or decide to withdraw from the study, all efforts must be made to complete all assessments of the End of Treatment/Withdrawal Visit (see Section 9.1.1.10 for withdrawals within the double-blind phase and Section 9.1.2.10 for withdrawals within the OLE phase). All observations should be reported as thoroughly as possible up to the date of withdrawal. Patients withdrawing due to an AE should be followed up according to Section 12.7. All information should be reported in the applicable CRF pages (refer to Section 9.2). Wherever possible, a post-study follow-up visit should take place 28-days after last dose of IMP (refer to Section 9.1.1.12 and Section 9.1.2.13). If withdrawing patients decline to give a reason for withdrawal of consent, the investigator must respect the patient's wishes.

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 Regulatory Authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the Regulatory Authorities and EC/IRB within three days.

12 ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

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

Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings when relevant), or diagnosis or worsening of a pre-existing condition, which occurs following screening (Visit 1) and at any point up to the post-treatment, safety follow-up visit (Visit 12 and Visit OLE Follow-up), which may or may not be considered to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

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

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

12.1.2 Investigator

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

12.2 Serious Adverse Events

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

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

- Results in death.
- Is life-threatening*.

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

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

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

The sponsor considers all convulsive and non-convulsive *status epilepticus* events to be medically significant and should be reported to the Sponsor as medically significant SAEs.

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

The investigator is not obliged to actively monitor for any new SAEs which occurred after the last formal follow-up observational period (Visit 12 or OLE Follow-up).

However, if the investigator becomes aware of any deaths or a new IMP-related SAE occurring within 28 days of the final dose of IMP, these should be reported to the GW PVD.

Any other problem discovered outside these time limits (Visit 12 or OLE Follow-up) which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have taken part in the study must be treated as an SAE and reported to the GW PVD. Such post-study SAEs do not need to be recorded in the patient's CRF if editing rights to the CRF have been removed due to final study data lock. GW PVD may request safety follow-up information after the final study visit in order to investigate a potential safety issue.

Contact details for the GW PVD are provided at the front of the center 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, using the GW Pregnancy Monitoring forms provided. Where possible the investigator should provide the outcome of the pregnancy.

Pregnancy reports must be sent to the GW PVD using the fax number for SAE reporting (see Appendix 3.2) within 24 hours of becoming aware.

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. The 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 either "yes" or "no".

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

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual patients, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs, and especially SAEs, it is important that the investigator assess not only the possible role of the IMP but also other potential contributing factors. Factors for consideration of the underlying cause 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 screening (Visit 1) up to and including the post-study follow-up visit (Visit 12 or OLE Follow-up), whether or not attributed to IMP and observed by the investigator or patient.

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 in 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., *headache and fever due to pneumonia*).

B) Adverse Event Start Date and Stop Date

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

C) Outcome

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

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

D) Severity

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

If the severity of an AE fluctuates day-to-day, e.g., 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 or during the investigation of potential safety issues. Such requests for additional safety information may occur post Visit 11 or OLE Follow-up after the study.

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. If a safety concern is identified following withdrawal of a participant, GW may contact the investigator for additional follow-up information.

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

These reports must be sent to the GW PVD using the same fax number for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the patient's baseline laboratory results with all reports to the 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 participant cannot return to the investigational center, repeat assessments may be done at a local laboratory and the results sent to GW PVD.

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

In accordance with the EU Clinical Trials Directive[60], relevant parts of the FDA Code of Federal Regulations[62] and any national regulations, GW will inform investigators, Regulatory Authorities and relevant ECs/IRBs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Drug Reactions (SUSARs).

This information will be provided through three sources:

1) IB: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study. The IB is updated annually.
2) Development Core Safety Information: this document forms the safety section of the IB[51], or is updated as an addendum to the IB[51]. 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 ECs/IRBs which have approved the study and investigators. As required, the investigator should notify their regional ECs/IRBs of SAEs or SUSARs occurring at their center 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[57] 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 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.

In The Netherlands, all SAEs observed during the conduct of a study will be reported within the stipulated timelines to the De Medisch Ethische Toetsingscommissie/Centrale Commissie Mensgebonden Onderzoek ***only*** if it were considered an unanticipated problem involving risk to patients 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). All other SAEs will be reported in a cumulative summary as part of the Development Safety Update Report and updated on a yearly basis. This does not replace the ongoing obligation to report any SUSARs originating in The Netherlands, which do not meet the above criteria, to the accredited Medical Research Ethics Committee and competent authority.

The FDA guidance[62] 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 relevant ECs/IRBs of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the study does not necessarily constitute an unanticipated problem unless identified by GW in the submission cover letter.

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

13 STATISTICAL CONSIDERATIONS

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

13.1 Sample Size, Power and Significance Levels

Blinded Phase:

A total of 210 patients will be enrolled. The 210 patients will be randomly allocated to one of four treatment groups (GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose volume equivalent, or placebo 50 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The placebo groups will be pooled for the analyses of efficacy.

If it is assumed that patients in the placebo group will experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P will experience at least a 50% reduction in seizures and a common standard deviation of 60%, then this sample size of 70 patients per group will be sufficient to detect a difference in response distributions with 90% power. This test is based on a two-sided non-parametric Wilcoxon-Mann-Whitney test for continuous response data with a 5% significance level.

Open-label Extension:

All patients who wish to continue on IMP following the blinded phase.

13.2 Interim Analysis

Blinded Phase:

No interim analysis is planned for this study. The blinded phase of this study will be locked and unblinded prior to completion of the OLE. The SAP covering the blinded phase will be finalized prior to unblinding the blinded phase.

Open-label Extension:

A cut of the OLE data will be used to support New Drug Application and Marketing Authorization Application filings. Further data cuts may be conducted as required.

13.3 Analysis Sets

Blinded Phase:

There will be up to three analysis sets in the blinded phase:

Intention to Treat (ITT)

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

Per Protocol (PP)

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

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

Safety

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

Open-label Extension:

There will be one analysis set in the open-label extension phase:

Safety

All patients who received at least one dose of IMP in the open-label extension phase of the study will be included. Only patients for whom it has been confirmed that they did not take any IMP in the OLE phase will be excluded from this safety analysis set.

13.3.1 Protocol Deviations

Protocol deviations will be listed and reasons for exclusion from the analysis populations will be summarized.

13.4 General Considerations

Unless stated otherwise, continuous variables will be summarized showing the number of non-missing values (*n*), mean, standard deviation, median, minimum and maximum and categorical variables will be summarized showing the number and percentage of patients falling in each category.

Unless otherwise specified, tables for the blinded phases will be summarized by randomized treatment group, and for the OLE phase will be summarized overall.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

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

13.5.2 Baseline and Demographic Characteristics

Age, sex, ethnic origin (as allowed per local regulations) and any other demographic or baseline characteristics, including history of epilepsy and epilepsy-specific genetic testing, will be summarized, using appropriate summary statistics.

13.5.3 Medical History

Previous and current medical conditions will be summarized by System Organ Class (SOC), including details of epilepsy.

13.5.4 Concomitant Medication

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

13.6 Endpoints and Statistical Methods

Blinded Phase:

Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Each endpoint, including the primary will have 2 comparisons against placebo (25 mg/kg/day GWP42003-P and 50 mg/kg/day GWP42003-P vs. placebo). Also, 3 key secondary endpoints have been defined.

The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure, in the sequence given in Table 13.6-1. One must reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis is not rejected then testing will stop and all subsequent analyses will be declared not statistically significant.

Table 13.6-1 Hierarchy for Analysis

Test	Endpoint	Treatment Comparison
1	Change from baseline in number of TSC-associated seizures	25 mg/kg/day GWP42003-P vs. Placebo
2	50% responder analysis	25 mg/kg/day GWP42003-P vs. Placebo
3	Change from baseline in number of TSC-associated seizures	50 mg/kg/day GWP42003-P vs. Placebo
4	50% responder analysis	50 mg/kg/day GWP42003-P vs. Placebo
5	Change in CGIC/SGIC	25 mg/kg/day GWP42003-P vs. Placebo
6	Change from baseline in total seizures	25 mg/kg/day GWP42003-P vs. Placebo
7	Change in CGIC/SGIC	50 mg/kg/day GWP42003-P vs. Placebo
8	Change from baseline in total seizures	50 mg/kg/day GWP42003-P vs. Placebo

13.6.1 Evaluable Period

Blinded Phase:

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

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

- Day 113 of treatment for the IVRS reported efficacy data and the day of Visit 10 for the CRF-based efficacy data;
- The last day on which study IMP was taken (as stated on the study outcome CRF) for the IVRS reported efficacy data and the day after this for the CRF-based efficacy data;
- The day before a relevant change in prohibited or AED medications was made.

Open-label Extension:

All data collected during this phase will be summarized across time, using appropriate descriptive statistical methods. Changes from pre-randomization baseline will also be presented. Treatment compliance and exposure to treatment will also be summarized.

13.6.2 Primary Endpoint(s)

Blinded Phase:

The primary endpoint is the change in number of seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.

*Seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Data will be analyzed using negative binomial regression on the sum of the seizure counts during the treatment period. However, seizure frequency (average per 28 days) and percentage change in seizure frequency will be presented using summary statistics. A mixed effect model with repeated measures will be performed modelling the observed number of seizures in the baseline period and treatment period implemented within the framework of general linear models using the negative binomial response distribution. The model will include stratified age group (1–6 years, 7–11 years, 12–17 years and 18–65 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect. The log transformed number of days in which seizures were reported will be included as an offset. The time variable corresponds to an indicator for the baseline period and treatment period. The estimated ratio of least squares means for treatment period to baseline period and 95% confidence intervals (CIs) will be presented for each treatment arm. In addition, the estimated ratio of each GWP42003-P group to placebo and 95% CIs will be presented along with the p-value testing the null hypothesis that this ratio is 1.

The hypothesis testing approach for controlling the Type I error is described in Section 13.6 and Table 13.6-1.

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

Open-label Extension:

The primary endpoint is the safety of GWP42003-P, evaluated by assessing the incidence, type and severity of AEs. Data will be presented as per Section 13.6.5.2.

13.6.2.1 Sensitivity Analysis for the Primary Endpoint

Blinded Phase:

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

- Wilcoxon rank-sum test on percentage change from baseline in seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P group and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.
- Primary endpoint analysis repeated using the PP analysis set.
- Primary endpoint analysis repeated using the maintenance period (Day 29 to the end of the evaluable period) rather than the treatment period.
- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the mean from the non-missing data for each patient to impute missing data arising from unreported days in IVRS.
  - Any intermittent missing data for the number of seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period based on non-missing data:

    Number of seizures ÷ Number of reported days in IVRS.
- A rank ANCOVA on percentage change from baseline in number of seizures (average per 28 days) during the treatment period.
  - The ranks of the percentage change from baseline and the baseline number of seizures (average per 28 days) will be calculated. The rank of the percentage change from baseline will then be analyzed using an ANCOVA model with the rank of the baseline number of seizures (average per 28 days) and age group (1–6 years, 7–11 years, 12–17 years and 18–65 years) as covariates and treatment group as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-value will be presented.
- ANCOVA of log transformed number of seizures (average per 28 days) during the treatment period.

  - The number of seizures (average per 28 days) during the treatment period and the baseline number of seizures (average per 28 days) will be log transformed prior to analysis. The log transformed number of seizures (average per 28 days) during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline number of seizures (average per 28 days) and age group as covariates and treatment group as a fixed factor. The back transformed estimated treatment ratios, together with the 95% CIs and p-value will be presented.
  - If there are any patients with no seizures post-baseline, then 1 will be added to the number of seizures (average per 28 days) for all patients prior to log transformation.

- Primary endpoint analysis repeated using each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12-week maintenance period) rather than the treatment period.
  - This analysis will include only patients who have at least 7 days of seizure data within each corresponding 4-week period.
- Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption.
  - MNAR will be assumed for missing values resulting from two scenarios, discontinuation due to AEs, and discontinuation due to any reason in the GWP42003-P dose groups and missing at random (MAR) for others, including other patients discontinued in the GWP42003-P dose groups and patients in the placebo group.
  - MI will be performed on the seizure frequency, based on time points corresponding to each 14 calendar days of the treatment period. Intermittent missing values for intermediate 14-day time points before the last 14-day time-point will be imputed using the MCMC method in SAS PROC MI with an IMPUTE=MONOTONE statement for 100 times for each treatment group separately. Then, monotone missing data assumed under the MAR assumption at time-point *t* (i.e., patients in the placebo group and patients in the GWP42003-P groups who did not discontinue due to AEs or for any reason) will be imputed using the MI procedure with the 'MONOTONE REG' option, for each treatment group separately. The

imputation model will include baseline seizure frequency and each 14-day time-point up to time-point *t* (in chronological order). With the data imputed from above, monotone missing data of patients in the GWP42003-P groups under the MNAR assumption will be imputed. At each 14-day time-point *t*, the input dataset for the MI procedure will include all placebo patients and those patients from the GWP42003-P groups that have values missing under MNAR at that time-point. The imputation model will include seizure frequency at baseline and each 14-day time-point up to time-point *t* (in chronological order) and will be performed for each GWP42003-P group separately.

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

13.6.3 Secondary Endpoint(s)

The following endpoints will be compared between treatment groups over the treatment period, for the blinded phase, and during the open-label extension phase relative to the pre-randomization baseline of the blinded phase:

Antiepileptic Efficacy Measures:

Key:

- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in seizure frequency (blinded phase only).
- Change in CGIC or SGIC score.
- Change in total seizures.

The hypothesis testing approach for controlling the Type I error for these endpoints are described in Section 13.6 and Table 13.6-1.

Other:

- Percentage change from baseline in number of seizures (average per 28 days; OLE phase only).
- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50% (OLE phase only), ≥ 75% or 100% reduction in seizure frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25–50% improvement, 50–75% improvement or > 75% improvement in seizure frequency.

- Change in number of seizure-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

Growth and Development (patients less than 18 years):

- Change in serum IGF-1 levels.
- Change in Tanner Staging score (for patients aged 10–17 [inclusive]).

Quality of Life:

- Changes in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score.
- Change in PGIC score.

Blinded Phase:

The number of patient responders (including the key secondary endpoint) and the number of patients seizure-free will be summarized and analyzed using a Cochran–Mantel–Haenszel test stratified by age group. In addition, the difference in proportions and the odds ratio, together with 95% CIs, comparing the treatment groups will be presented.

For number of seizure-free days, use of rescue medication, number of episodes of *status epilepticus* (only if there is a sufficient number of patients with data), Vineland-II, Wechsler scales, CBCL, ABCL, SCQ, QOLCE and QOLIE-31-P scores, the data will be summarized at baseline and over the treatment period, and at each time-point (or 28-day period, as appropriate) during the maintenance period. Changes from baseline to the average over the treatment period (or at end of study) will be analyzed using ANCOVA (or appropriate non-parametric methods if data are found to be not normally distributed). The models will include baseline and age group as covariates and treatment group as fixed factor. The treatment difference, together with the 95% CIs will be presented.

The changes in composite focal seizure score, change in total seizures, the number of seizures by subtype and the number of 'other' seizures will be analyzed using the same analysis as the primary endpoint.

SGIC-SD/CGIC-SD, SGIC/CGIC and PGIC assessments recorded at the end of treatment will be analyzed with ordinal logistic regression using the proportional odds model.

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

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

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

Open-label Extension:

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

Exploratory Endpoints:

Antiepileptic Efficacy Measures:

- Change in composite focal seizure score (frequency × severity).
- Change in number of seizures by subtype.
- Change in use of rescue medication.
- Change in the number of episodes of *status epilepticus* (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).

TAND:

Cognitive and Behavioral Function:

- Changes in Vineland Adaptive Behavior Scales, Second Edition (Vineland-II).
- Changes in Wechsler Scales (pre-school, primary, children, adult).
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL).

Autistic Features:

- Change in Social Communication Questionnaire (SCQ) score.

PK (Blinded Phase Only):

- The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable time-point will be calculated.
- Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

13.6.4 Pharmacokinetics

Plasma concentrations for CBD and its major metabolites, following single and multiple doses of GWP42003-P will be summarized by treatment group. Estimates of PK parameters will also be summarized using the appropriate statistics.

Where available, plasma concentrations of concomitant AEDs will be summarized.

13.6.5 Safety

In the presentation of safety data for the blinded phase, data from the two cohorts of placebo patients (25 mg/kg/day and 50 mg/kg/day dosing volumes) will be presented separately and pooled together. This will allow the possibility to explore any effects of the volume of IMP on safety endpoints.

13.6.5.1 Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

13.6.5.2 Adverse Events

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

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

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

The following summaries will be produced:

- All-causality AEs.

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

13.6.5.3 Clinical Laboratory Data

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

13.6.5.4 Vital Signs, 12-Lead Electrocardiogram, Physical Examination and Other Safety Data

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

14 SAFETY MONITORING COMMITTEE

An independent Safety Monitoring Committee (SMC) will be used in this study. Details of the composition and standard operating procedures of the SMC will be detailed in a separate charter.

Furthermore, an independent ESC will be instated to verify the seizure types of screened patients on an ongoing basis. Investigators will submit a documented history of TSC directly to the ESC for verification of seizure types. The ESC will provide written documentation directly to the investigator and guidance on seizure types, if applicable, for inclusion in the patient file. Details of the composition and standard operating procedures of the ESC will be detailed in a separate charter.

15 REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the current version and subsequent amendments of the Declaration of Helsinki[56], the ICH Tripartite Guideline for GCP Topic E6(R2)[52], the EU Clinical Trials Directive[60], the EU GCP Directive[61] and the clinical trial regulations adopting European Commission Directives into national legislation[63,64,65,66,67].

15.2 Informed Consent/Assent

An initial generic ICF consent and assent form will be prepared by GW and provided to the investigator, who will tailor these for their center by adding the center's contact details and by using headed paper. 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 involvement in the trial, the investigator is responsible for obtaining written informed consent/assent (if allowed per local regulations) from the patient and/or along with written parent(s)/legal representative consent 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/or 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 ICF 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. The original signed ICF should be retained and a copy provided to the patient and/or parent(s)/legal representative.

15.3 Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICF, other patient information material, any proposed advertising material and any further documentation requested must be

submitted to the EC/IRB for written approval. GW must receive a copy of the written approval of the protocol and ICF before recruitment of patients into the study and shipment of IMP.

The investigator must submit and, where necessary, obtain approval from the EC/IRB for all subsequent protocol amendments and changes to the informed consent/assent documents. The investigator should notify the EC/IRB of deviations from the protocol, SAEs occurring at the center and other AE reports received from GW, in accordance with local procedures.

The investigator will be responsible for obtaining ongoing EC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the EC/IRB 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 EC/IRB-approved ICF and other patient information material.
- Copy of the EC/IRB approval of the protocol, ICF and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The EC/IRB composition and/or written statement of the EC/IRB in compliance with the FDA regulations relating to GCP and clinical trials[57,58,59,68], the EU Clinical Trials Directive[60], the EU GCP Directive[61], or the ICH Tripartite Guidelines for GCP Topic E6(R2)[52] where the EU Clinical Trials and GCP Directives do 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).
- Form FDA 1572, if required.
- Drug Enforcement Administration license (where applicable).

- 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. In the CRFs and within the IVRS databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials and ethnic origin (if allowed per local regulations) and their study screening number only. Documents that are not for submission to GW, e.g., signed ICFs, should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to good clinical practice and clinical trials[57,58,59,68], and the EU Clinical Trials Directive[60]/ICH Tripartite Guidelines for GCP Topic E6(R2)[52], it is required that the investigator and institution permit authorized representatives of the company, the Regulatory Authorities and the EC/IRB have 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 EC/IRB and Regulatory Authorities must be informed of all amendments and give approval for any substantial amendments. Amendments for administrational changes can be submitted to the EC/IRB for information only. The investigator must send a copy of the approval letter from the EC/IRB 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 EC/IRB 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 in 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 center, will be agreed with each center 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 the ICH Tripartite Guidelines for GCP Topic E6(R2)[52], section 8.2), suitable for inspection at any time by representatives from GW and/or applicable Regulatory Authorities. Elements should include:

- Patient files containing completed CRFs, ICFs and supporting copies of source documentation.
- Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see Section 15.4) and all correspondence to and from the EC/IRB 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 in 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 25 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements[61] or if needed by GW.

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, e.g., 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 in 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.

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[57,58,59,68], ICH Tripartite Guidelines for GCP Topic E6(R2)[52] 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.

16.4 Electronic Data collected by Interactive Voice Response System

Source data for the assessments collected via IVRS will be managed by the service provider in accordance with ICH Tripartite Guidelines for GCP Topic E6(R2)[52] and in adherence to a quality management system. All data will be stored in a secure (e.g., 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 the requirements outlined in the FDA Code of Federal Regulations Title 21, Part 11, Subpart B (Electronic Records)[68].

After database lock, all investigators will receive a certified copy of all 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, IVRS data via an agreed means of access.

16.5 Quality Assurance

In accordance with the FDA regulations[57,58,59,68], EU Clinical Trials Directive[60]/ICH Tripartite Guidelines for GCP Topic E6(R2)[52] and the sponsor's audit plans,

representatives from GW's Clinical Quality Assurance Department may select this study for audit. Inspection of center facilities, e.g., pharmacy, drug storage areas, laboratories, and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, the EU Clinical Trials Directive[60]/ICH Tripartite Guidelines for GCP Topic E6 (R2)[52] and applicable regulatory requirements.

16.6 Compensation

GW will indemnify the investigator and the study center in the event of any claim in respect of personal injury arising due to a patient's involvement 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/principal investigators. 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 analyzes 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 the GW Medical Writing Department and, as applicable, GW Publication Committee for corporate 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 reserves the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.8 Intellectual Property Rights

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

16.9 Confidential Information

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

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APPENDIX 1 SCHEDULE OF ASSESSMENTS

Blinded Phase

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 (Tel.)	Safety Calls*
Day	**-35**	**-28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**123**	**151**	
Visit Window		**±7**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	
Informed consent/assent	X												
Eligibility Criteria	X	X	X										
Randomization			X										
Demographics	X												
Medical history	X												
Vital signs and BP	X		X	X	X	X	X		X	X	X		
Postural BP	X		X		X								
Physical examination (including height and body weight)	X		X	X	X	X	X		X	X	X		
ECG	X		X[§]	X	X	X	X		X	X	X		
Clinical laboratory blood sampling	X		X	X	X	X	X		X	X	X		
Clinical laboratory IGF-1 testing			X							X			
Clinical laboratory urine sampling (dipstick urinalysis)	X		X	X	X	X	X		X	X	X		
Urine/serum THC screen	X												
Pregnancy tests (if appropriate)	X		X		X		X		X	X			

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12** (Tel.)	**Safety Calls***
Day	**-35**	**-28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**123**	**151**	
Visit Window		**±7**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	
Pharmacokinetic blood sampling♦			X							X			
AED concentration			X		X		X		X	X			
TSC1 and *TSC2* mutation status (if unknown and consent is given)	X												
AEs	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
Inpatient epilepsy-related hospitalizations		X	X	X	X	X	X	X	X	X	X	X	X
Suicidality/C-SSRS/Children's C-SSRS	X		X	X	X	X	X		X	X	X		
Vineland-II			X							X			
SGIC/CGIC			X							X			
PGIC			X							X			
SGIC-SD/CGIC-SD			X							X			
QOLCE/QOLIE-31-P			X							X			
Wechsler Tests			X							X			
CBCL/ABCL			X							X			
SCQ			X							X			
Tanner Staging (where appropriate)			X							X			
Menstruation question (where appropriate)			X							X			

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12** (Tel.)	**Safety Calls***
Day	**-35**	**-28**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**123**	**151**	
Visit Window		**±7**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	
Patient IVRS and paper diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)			X	X	X	X	X		X	X	X		
IVRS and diary training		X											
IMP dispensing			X	X	X	X	X		X	X			
Collection of IMP				X	X	X	X		X	X	X		
IMP compliance review				X	X	X	X		X	X	X		
Study Medication Use and Behavior Survey										X†			

*Telephone safety calls will be completed every two days during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit 10 to Visit 12. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

§ ECG must be re-assessed four hours (±30 minutes) post-dose.

♦Only for patients weighing > 20 kg.

†Performed at final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable) for patients 12 years of age and older only.

Open-label Extension

Visit Number	**B1**	**B2**	**B3**	**B4**	**Re-supply Visit B5**	**B6**	**Re-supply Visit B7**	**B8**	**Re-supply Visit B9**	**End of Treatment B10**	**End of Taper B11**	**Post-taper Safety Telephone Call B12**	**Follow up** (Tel)	**Safety Calls***
Day	**1**	**15**	**36**	**92**	**141**	**183**	**232**	**274**	**323**	**365**	**375**	**389**	**403**	
Visit Window		**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**+3**	**±3**	**+3**	
Informed consent/assent	X													
Vital signs and BP	X	X	X	X		X		X		X	X			
Postural blood pressure			X											
Physical examination (including height and body weight)	X	X	X	X		X		X		X	X			
ECG	X	X	X	X		X		X		X	X			
Clinical laboratory blood sampling	X	X	X	X		X		X		X	X			
Clinical laboratory IGF-1 testing	X					X				X				
Clinical laboratory urine sampling (dipstick urinalysis)	X	X	X	X		X		X		X	X			
Pregnancy tests (if appropriate)	X			X		X		X		X				
AED concentration		X	X	X		X		X		X				
AEs	X	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	X
Inpatient epilepsy-related	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	B1	B2	B3	B4	Re-supply Visit B5	B6	Re-supply Visit B7	B8	Re-supply Visit B9	End of Treatment B10	End of Taper B11	Post-taper Safety Telephone Call B12	Follow up (Tel)	Safety Calls*
Day	**1**	**15**	**36**	**92**	**141**	**183**	**232**	**274**	**323**	**365**	**375**	**389**	**403**	
Visit Window		**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**+3**	**±3**	**+3**	
hospitalizations														
Suicidality/C-SSRS/Children's C-SSRS	X	X	X	X		X		X		X	X			
Vineland-II	X					X				X				
SGIC/CGIC	X					X				X				
PGIC	X					X				X				
SGIC-SD/CGIC-SD	X			X		X		X		X				
QOLCE/QOLIE-31-P	X					X				X				
Wechsler Tests	X					X				X				
CBCL/ABCL	X					X				X				
SCQ	X					X				X				
Tanner Staging (where appropriate)	X									X				
Menstruation question (where appropriate)	X									X				
Patient IVRS and paper diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)	X	X	X	X	X	X	X	X	X	X	X			

Visit Number	**B1**	**B2**	**B3**	**B4**	**Re-supply Visit B5**	**B6**	**Re-supply Visit B7**	**B8**	**Re-supply Visit B9**	**End of Treatment B10**	**End of Taper B11**	**Post-taper Safety Telephone Call B12**	**Follow up** (Tel)	**Safety Calls***
Day	**1**	**15**	**36**	**92**	**141**	**183**	**232**	**274**	**323**	**365**	**375**	**389**	**403**	
Visit Window		**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**+3**	**±3**	**+3**	
IVRS and diary training	X													
IMP dispensing	X	X	X	X	X	X	X	X	X	X				
Collection of IMP		X	X	X	X	X	X	X	X	X	X			
IMP compliance review		X	X	X	X	X	X	X	X	X	X			
Study Medication Use and Behavior Survey										X†				

*Telephone safety calls will be completed every two days during the blinded transition, titration and one week after the end of titration. If the call falls on a weekend, it is permitted to schedule the call for the Friday before or Monday after the weekend instead.

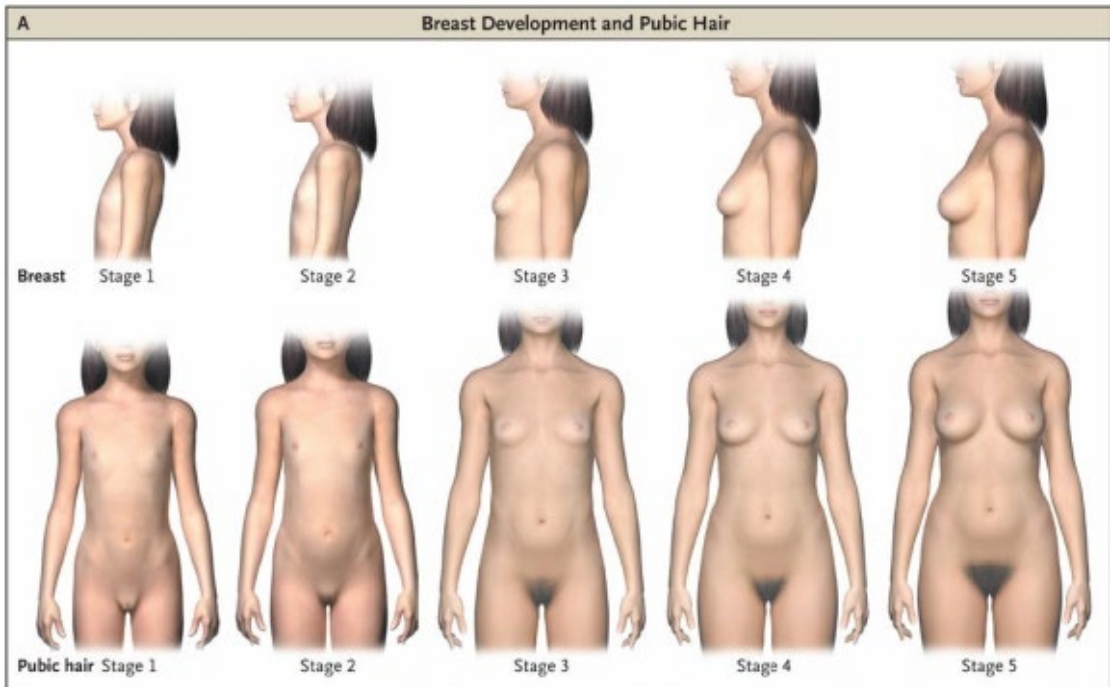
†Performed at final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable) for patients 12 years of age and older only.

APPENDIX 2 TANNER STAGING

(Reproduced with permission from the New England Journal of Medicine)[55].

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)

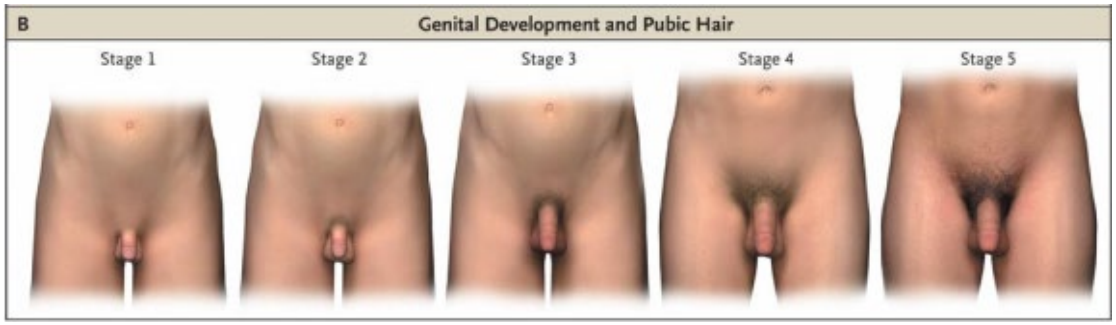
- Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast.
- Adult-like hair quality, extending across pubis but sparing medial thighs.

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., 12 to less than 18 years of age at the time of signing the informed consent/assent form).

Male Genital Development & Pubic Hair



Please check the box next to the most appropriate stage.

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

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

Tanner Stage 2 (9–11 years)

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

Tanner Stage 3 (11–12.5 years)

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

Tanner Stage 4 (12.5–14 years)

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

Tanner Stage 5 (14+ years)

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

APPENDIX 3 STUDY PERSONNEL

Appendix 3.1 Investigator Details

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

Appendix 3.2 Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting:	**Fax: +44 (0)1223 233 319** **USA Toll Free Fax:** **1 866 2341 751** Tel: +44 (0)1223 233 410
Sponsor:	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
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Clinical Trial Supplies:	G-Pharm Ltd Tel: +44 (0)1795 431 650 Fax: +44 (0)1795 475 439

APPENDIX 4 IVRS CALLS FOLLOWING END OF TREATMENT/WITHDRAWAL

Timings of IVRS calls to be made by the patient/caregiver following the date of End of Treatment/Withdrawal in the blinded or OLE phase are summarized overleaf.

Relative Day	Blinded Phase[a]		OLE Phase	
	IMP Not Tapered	IMP Tapered	IMP Not Tapered	IMP Tapered
Date of End of Treatment/Withdrawal[b]	X	X		X
+1		X		
+2		X		
+3		X		
+4		X		
+5		X		
+6		X		
+7		X		X
+8		X		
+9		X		
+10				
+11				
+12				
+13				
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+24				
+25				
+26				
+27	X		X	
+28				
+29				
+30				
+31				
+32				
+33				
+34				
+35				
+36				
+37		X		X
+38				
+39				
+40				

Note: Gray shading denotes visit windows.

[a] Only for patients who do not enter the OLE on the day of Visit 10 or for those who withdraw early from the blinded phase.

[b] Date of End of Treatment/Withdrawal should match the date reported in interactive web/voice response system.