Appendix 1.1 Protocol and Protocol Amendments

GWEP1521 Clinical Protocol Annex 2 V2 26Apr18

GWEP1521 Clinical Protocol Annex 2 Am 1 V1 26Apr18

GWEP1521 Clinical Protocol Annex 1 V3 15Apr19

GWEP1521 Clinical Protocol Annex 1 Am 2 V1 15Apr19

GWEP1521 Clinical Protocol Annex 1 Am 1 V1 26Apr18

GWEP1521 Clinical Protocol V8 23Apr19

GWEP1521 Clinical Protocol Amendment 7 V1 23Apr19

GWEP1521 Clinical Protocol Amendment 6 V1 06Sep18

GWEP1521 Clinical Protocol Amendment 5 V1 07Aug18

GWEP1521 Clinical Protocol Amendment 4 V1 27Jun17

GWEP1521 Clinical Protocol Amendment 3 V1 05Dec16

GWEP1521 Clinical Protocol Amendment 2 V1 25Aug16

GWEP1521 Clinical Protocol Amendment 1 V1 21Oct15

GWEP1521 Blinded Phase: NCT02544763
GWEP1521 Open-Label Extension: NCT02544750
Note: These NCT numbers have been applied to the document for purposes of posting on clinicaltrials.gov.

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

EudraCT Number: 2015-002154-12

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

Print Name: PPD Date: PPD

Clinical Manager (DD Month YYYY)

Signature: PPD

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

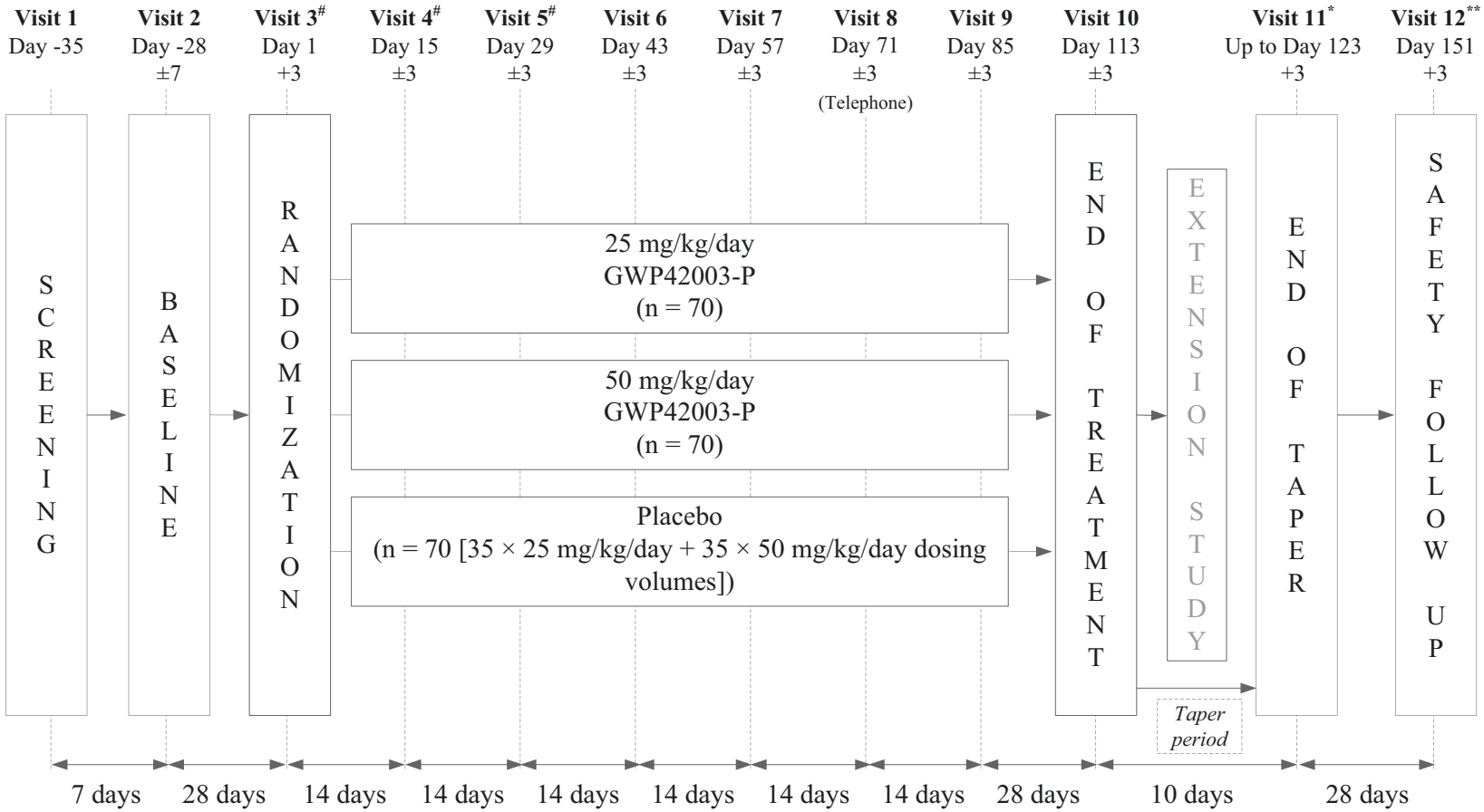
	for: – Hematology – Biochemistry – Urinalysis – Urine/serum pregnancy tests (Visits 5, 7, 9 and 10, if appropriate) – Serum IGF-1 (Visit 10) – PK (Visit 10; patients > 20 kg only) – AED concentrations (Visits 5, 7, 9 and 10) • Review of patient diary • IMP dispensing, collection and compliance review **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

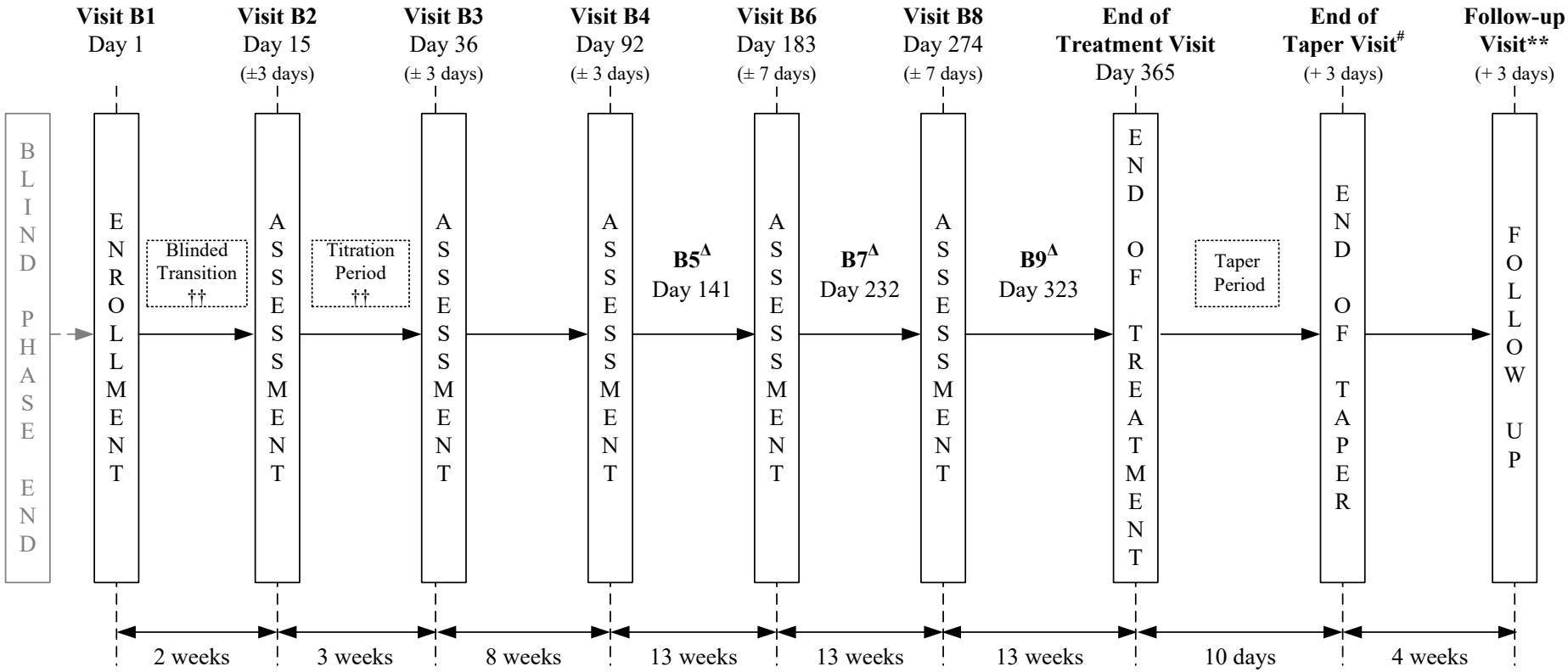


* For patients not entering the open-label extension at Visit 10.

** 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. PPD . 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.

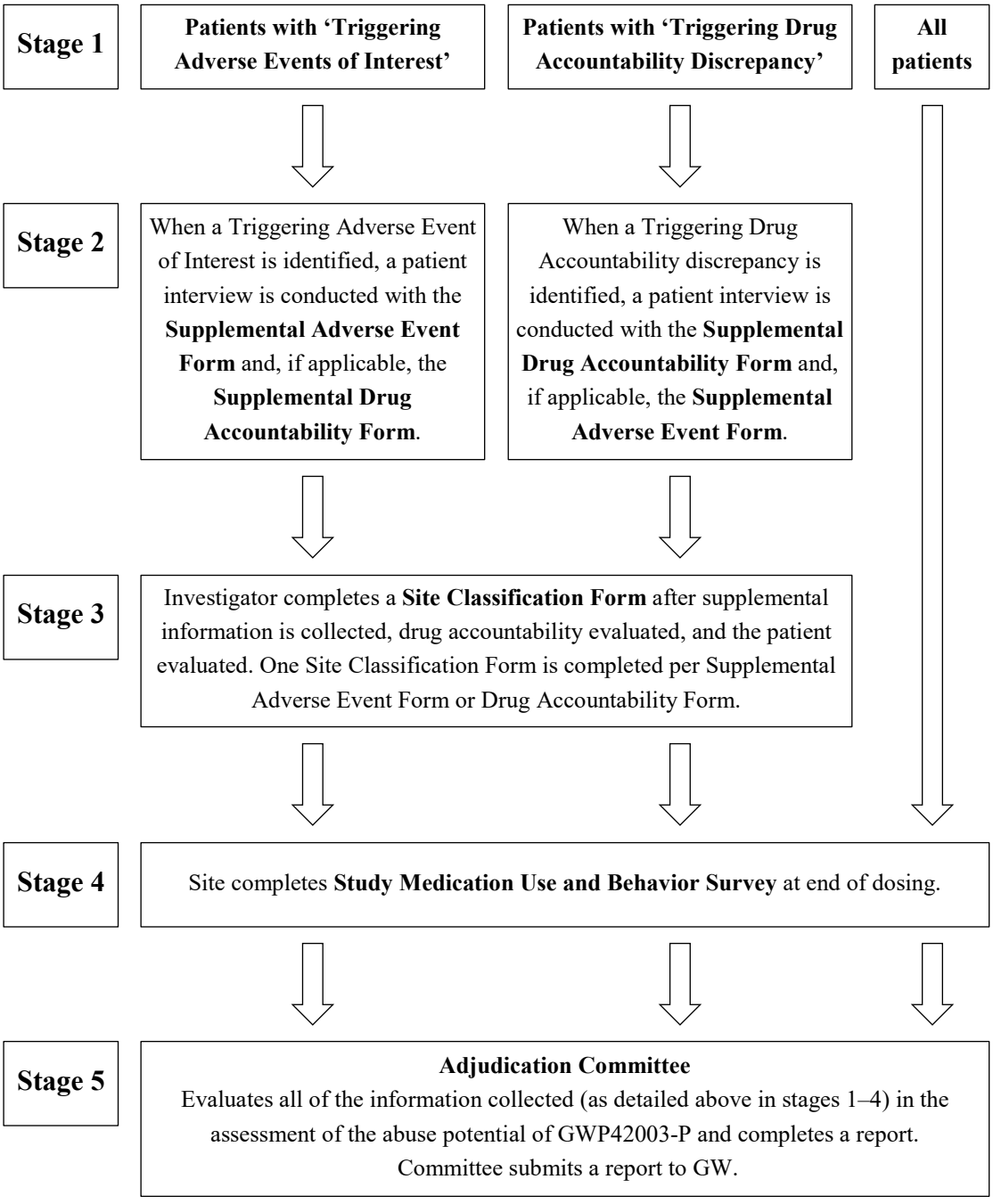
A detailed charter will be agreed, which will describe the roles, responsibilities and duties of the members of Adjudication Committee. The Committee will review all of the information collected in the process and in the assessment of the abuse potential of GWP42003-P, such as:

- 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.

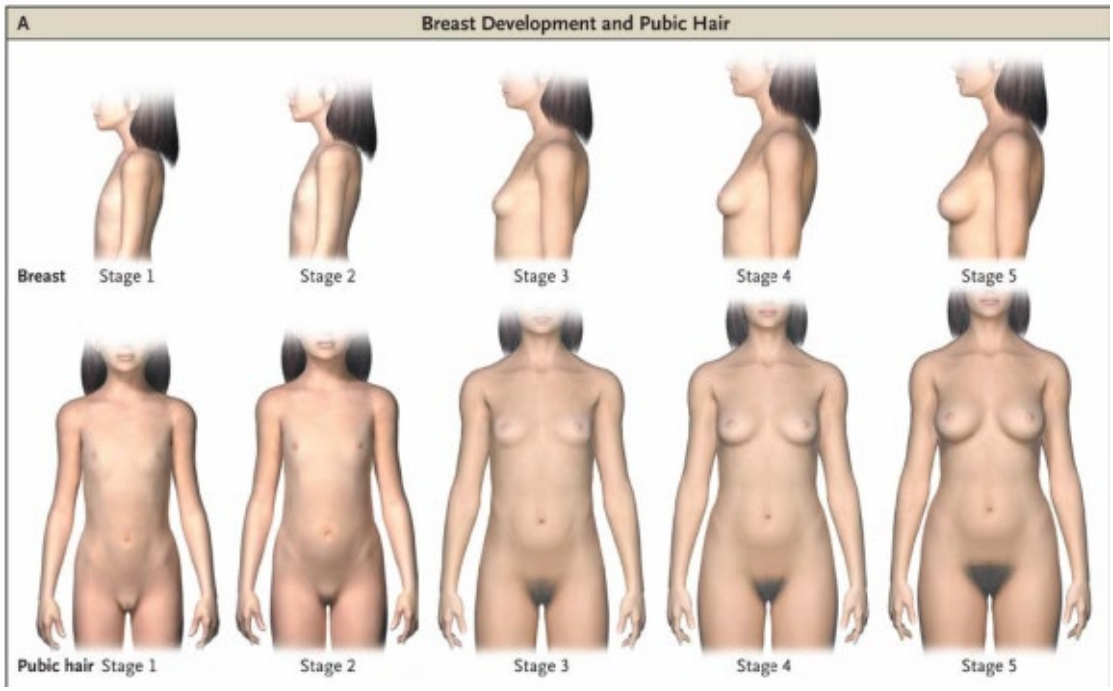
†Performed at final dosing visit (End of Treatment/Withdrawal visit or End of Taper visit, as applicable) for patients 12 years of age and older only.

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)

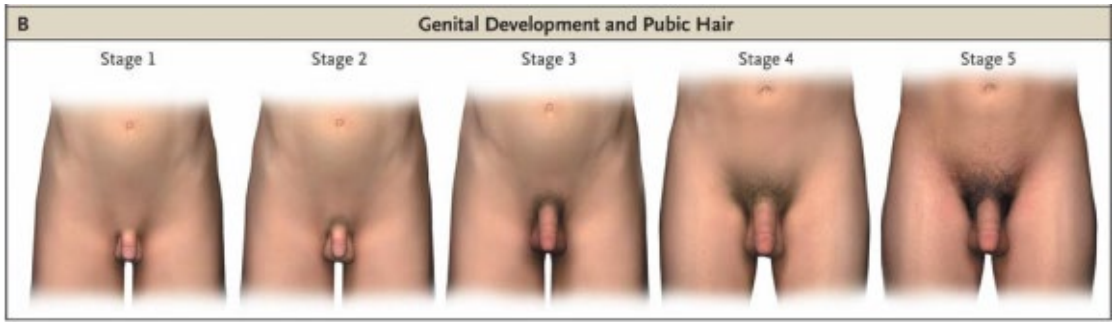
- Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast.
- Adult-like hair quality, extending across pubis but sparing medial thighs.

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:** PPD **USA Toll Free Fax:** PPD Tel: PPD
Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: PPD Fax: PPD
Medical Monitor:	Refer to Study Contact List in the site file.
Clinical Project Manager/Clinical Operations Director:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: PPD Fax: PPD
Clinical Trial Supplies:	G-Pharm Ltd Tel: PPD Fax: PPD

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				
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+16				
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+21				
+22				
+23				
+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.

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 7

to be incorporated into the Protocol, creating

CLINICAL PROTOCOL VERSION 8
DATE 23 APR 2019

GW Research Ltd

Sovereign House

Vision Park

Chivers Way

Histon

Cambridge CB24 9BZ

United Kingdom

Tel: PPD

Fax: PPD

Confidentiality Statement

1 PROTOCOL SYNOPSIS

Trial 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.
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.
Trial 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.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way

	Histon Cambridge CB24 9BZ United Kingdom

Table of Contents

List of Appendices

2 RATIONALE

This clinical protocol amendment 7 (will be incorporated into the Protocol creating Clinical Protocol Version 8 Date 23 April 2019) addresses the following issue(s):

2.1 Change in Hierarchy for Analysis

Following review of the original hierarchy for analysis, the Global Impression of Change (GIC) and total seizure endpoints were deemed of lower critical importance compared with the TSC-associated seizure endpoints. Therefore, the GIC and total seizure endpoints were moved down in the hierarchy so that all TSC-associated seizure endpoints are tested first.

2.2 Minor Corrections and Clarifications

- ICH definition changed on 23 October 2015 from 'International Conference on Harmonisation' to 'International Council for Harmonisation'. References to ICH updated accordingly throughout.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 8, Date 23 April 2019. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Version 7, Date 06 September 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Amendment 7 [Clinical Protocol Version 8, Date 23 April 2019]** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Investigator Agreement p. 2	(…) 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 **~~Conference on~~** Harmonisation Tripartite Guideline**~~s~~** for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required.	(…) 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.	See Section 2.2
List of Abbreviations	ICH International **~~Conference of~~** Harmonisation	ICH International **Council for** Harmonisation	See Section 2.2

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Version 7, Date 06 September 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Amendment 7 [Clinical Protocol Version 8, Date 23 April 2019]** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
p.32			
Section 9.2.1 Informed Consent/Assent p. 83	(...) 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 **~~Conference on~~** Harmonisation [ICH] Tripartite Guideline for GCP Topic E6(R2)[52], section 4.8.9)	(...) 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)**.**	See Section 2.2
Section 13.6 Endpoints and Statistical Methods Table 13.6-1 p. 115	<See APPENDIX 1 for changes to the Table>	<See APPENDIX 1 for changes to the Table>	See Section 2.1

5 REFERENCES

N/A.

APPENDIX 1 AMENDED TABLE

Original Table from Clinical Protocol Version 7, Date 06 September 2018

(Deleted wording is struck through and in bold; deleted lines are in bold and dotted)

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 in CGIC/SGIC	25 mg/kg/day GWP42003-P vs. Placebo
4	Change from baseline in total seizures	25 mg/kg/day GWP42003-P vs. Placebo
5	~~**Change from baseline in number of TSC-associated seizures**~~	~~**50 mg/kg/day GWP42003-P vs. Placebo**~~
6	~~**50% responder analysis**~~	~~**50 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

Revised Figures from Clinical Protocol Version 8, Date 14 April 2019

(Revised wording is underscored and in bold; revised lines are in bold)

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

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 6

to be incorporated into the Protocol, creating CLINICAL PROTOCOL VERSION 7 DATE 06 SEPTEMBER 2018

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Confidentiality Statement

1 PROTOCOL SYNOPSIS

Trial 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.
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.
Trial 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.

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2 RATIONALE

This clinical protocol amendment 6 (will be incorporated into the Protocol creating Clinical Protocol Version 7, Date 06 September 2018) addresses the following issue(s):**Change in Primary Endpoint Analysis Method and Wording**

A suitable modelling approach to seizure count data would be superior to the non-parametric Wilcoxon rank-sum test as it allows estimates of effect size that are meaningful and can easily be interpreted, can incorporate the stratification variable, can be used to explore potential effect modifying variables, and might be expected to provide more power. Exploration of data from previous epilepsy trials in Dravet syndrome and Lennox–Gastaut syndrome indicate that modelling of seizure counts implemented within the framework of general linear models, using the negative binomial response distribution, provides an optimal fit to the data. Additionally, this modelling approach also has advantages such as being able to model the exact seizure count during the treatment period, incorporating the number of days with data as an offset within the model, without requiring the seizure count to be transformed into a frequency prior to analysis. For example, if there are patients who withdraw early in the trial prior to experiencing a seizure, calculating a seizure frequency and percentage change could lead one to assume a patient had a 100% reduction in seizure frequency when in fact they might not have been evaluated for a sufficient amount of time. The negative binomial model accounts for the number of days each patient is evaluated for and so is not impacted. Accordingly, the proposed primary analysis method has been updated from the Wilcoxon rank-sum test to a negative binomial regression analysis.

As percentage change does not apply to negative binomial regression, the primary endpoint wording has been changed throughout the protocol to remove the words 'percentage change' as follows:

> *'Percentage change from baseline in number of TSC-associated seizures* (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.'*

has been amended to:

> *'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.'*

Similar changes have been made for percentage change in other seizure types under key secondary, other secondary, and exploratory endpoints.

2.2 Changes to the Proposed Sensitivity Analyses

The proposed sensitivity analyses have been changed as follows:

- Addition of the replaced primary analysis of Wilcoxon rank-sum test as a sensitivity analysis;
- Where appropriate, other sensitivity analyses using the Wilcoxon rank-sum test will now use the same method as the primary analysis (i.e., negative binomial regression).

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 7, Date 06 September 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Version 6, Date 07 August 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Amendment 6 (Clinical Protocol Version 7, Date 06 September 2018)** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 1 Protocol Synopsis Primary Endpoint p. 6 and Section 4.1.1 Primary Endpoint p. 46	The primary endpoint is the **~~percentage~~** change **~~from baseline~~** in number of TSC-associated seizures* **~~(average per 28 days)~~** during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo. (…)	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. (…)	See Section 2.1
Section 13.6.2 Primary Endpoint(s) p. 116	(…) The primary endpoint is the **~~percentage~~** change **~~from baseline~~** in number of seizures* **~~(average per 28 days)~~** during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo. (…) Data will be analyzed using **~~a Wilcoxon rank-sum test~~**.	(…) 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. (…) Data will be analyzed using **negative binomial regression on the sum of the seizure counts during**	See Section 2.1 See Section 2.1

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 6, Date 07 August 2018 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 6 (Clinical Protocol Version 7, Date 06 September 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 13.6.2 Primary Endpoint(s) p. 116 (continued)		**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.**	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.1
	~~An estimate of the median difference between~~	**The estimated ratio of least squares means for**	See Section 2.1

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 6, Date 07 August 2018 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 6 (Clinical Protocol Version 7, Date 06 September 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 13.6.2 Primary Endpoint(s) p. 116 (continued)	~~**each GWP42003-P group and placebo, together with approximate**~~ 95% confidence intervals (CI~~**,**~~ will be ~~**calculated using the Hodges-Lehmann approach**~~. (…)	**treatment period to baseline period and** 95% confidence intervals (CI**s**) 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.** (…)	See Section 2.1
Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 117–118	(…) • ~~**Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during the treatment period**~~	(…) • **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.	See Section 2.2 See Section 2.2

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 6, Date 07 August 2018 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 6 (Clinical Protocol Version 7, Date 06 September 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 117–118 (continued)	using the PP analysis set. • ~~**Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during**~~ the maintenance period (Day 29 to the end of the evaluable period). • ~~**Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during the treatment period,**~~ 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. (…) • ~~**Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during**~~ 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).	• **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. (…) • **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**.	See Section 2.2 See Section 2.2 See Section 2.2

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 6, Date 07 August 2018 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 6 (Clinical Protocol Version 7, Date 06 September 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	(…)	(…)	
Section 13.6.3 Secondary Endpoint(s) p. 120	(…) For **~~changes in composite focal seizure score,~~** 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. (…) The **~~percentage~~** change in total seizures, the number of seizures **~~(average per 28 days)~~** by subtype and the number of 'other' seizures **~~(average per 28 days)~~** will be analyzed using **~~a Wilcoxon rank-sum test as per~~** the primary endpoint. (…)	(…) 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. (…) The **<u>changes in composite focal seizure score,</u>** change in total seizures, the number of seizures by subtype and the number of 'other' seizures will be analyzed using **<u>the same analysis as</u>** the primary endpoint. (…)	See Section 2.1 See Section 2.1

5 REFERENCES

N/A

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 5

to be incorporated into the Protocol, creating CLINICAL PROTOCOL VERSION 6, DATE 07 AUGUST 2018

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Confidentiality Statement

1 PROTOCOL SYNOPSIS

Trial 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.
Indication	Seizures[a] in patients with tuberous sclerosis complex (TSC).
Trial 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 either 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 telephone calls to record seizure information. They will also complete a paper diary daily with information about their IMP and concomitant antiepileptic drug (AED) administration.

[a] 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.

Trial Design (continued)	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.

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List of Appendices

2 RATIONALE

This clinical protocol amendment 5 (will be incorporated into the Protocol creating Clinical Protocol Version 6, Date 07 August 2018) addresses the following issue(s):**Clarification of Eligibility Criteria**

The primary objective of the trial is 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). To comply with this, an inclusion criterion has been added to ensure that eligible patients must be taking one or more antiepileptic drugs (AEDs) at a dose which had been stable for at least four weeks prior to screening. In addition, as eligible patients must experience at least eight seizures during baseline, the inclusion criteria have been amended to clarify that eligible patients must have a well-documented clinical history of epilepsy which is not completely controlled by their current AEDs.

2.2 Correction of the Treatment Allocation Ratio

The treatment allocation ratio has been amended to clarify that patients will be 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, and that the two placebo groups will be pooled for the analyses of efficacy. The planned sample size has not changed.

2.3 Use of mTOR Inhibitors and General Anesthesia in the OLE

As everolimus (a mammalian target of rapamycin [mTOR] inhibitor) is approved in the European Union (and now also in the United States) for the treatment of refractory partial-onset seizures associated with TSC, oral mTOR inhibitors are excluded from use in the blinded phase of the trial. Similarly, due to its effects on seizure control, general anesthesia is excluded from use in the blinded phase.

As it would not be medically ethical to exclude on-label use of mTOR inhibitors (for the treatment of seizures or tumors) or general anesthesia following completion of the blinded phase, the protocol has been amended to clarify that their use is permitted in the open-label extension (OLE) in accordance with local licensing and after discussion and approval by the GW medical advisor(s).

2.4 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol:

- Removal of wording for investigational medicinal product (IMP) dispensing in countries where controlled drugs can only be prescribed for a maximum of 28 days' treatment as this is not applicable to any of the countries in which the trial is being conducted.
- As there is now a 1 mL accuracy for measuring IMP instead of the quarter bottle estimate/range within interactive voice response system (IVRS), the dosing calculator is now the only accurate measure of expected IMP usage. Further details for determining expected usage will therefore be provided in the Pharmacy Manual rather than the protocol, where the text has been simplified.
- Clarification that the exploratory objective for the OLE phase does not involve comparison of GWP42003-P with placebo.
- Clarification that for all pregnancy tests, both serum and urine tests will be performed.
- Clarification that the blood draw for testing *TSC1* and *TSC2* mutation status can be performed only if the patient/parent(s)/legal representative provide consent.
- Clarification that the 4-hour post-dose 12-lead electrocardiogram (ECG) performed at Visit 3 (Randomization) has a ±30-minute time window.
- Clarification that pharmacokinetic (PK) blood samples must be taken at Visits 3 and 10 for patients weighing > 20 kg 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; and for patients 18 years and above only: one sample between 8 and 10 hours post-dose. There must be a minimum period of at least 2 hours between each of the blood sampling time points.
- Clarification that dose selection was based on the data available at the time of trial initiation.
- Clarification that if the maintenance dose of IMP becomes poorly tolerated or an adverse event (AE) occurs (e.g., somnolence, transaminase elevation **not meeting** withdrawal criteria specified in Sections 10 and 12.8 of the protocol), the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period following discussion with the GW medical

advisor(s). In addition, in cases where the transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant AED with known hepatoxicity should be reduced following discussion with the GW medical advisor(s).

- A footnote to Table 8.1.2-3 explains how the OLE Day 15 dose is derived.
- Clarification that the investigator must contact the GW medical monitor to discuss best management of potential drug-drug interactions arising during the blinded and OLE phases of the study, with decisions based on clinical symptoms and not plasma levels of AEDs. In addition, clarification that concomitant AED dose reductions are permitted on clinical grounds (e.g., due to AEs or transaminase elevations **not meeting** withdrawal criteria specified in Sections 10 and 12.8 of the protocol) following discussion with the GW medical advisor(s).
- For consistency with the Schedule of Assessments, the protocol has been amended to clarify that eligibility must be assessed at Visit 1 (Screening) and Visit 3 (Randomization) according to the criteria specified in Section 6 of the protocol.
- Clarification that although the attendance of the patient is preferred, it is not required for Visit 2 (Baseline) 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.
- Clarification that the investigator must retain oversight of all safety telephone calls.
- Clarification of timings of IVRS calls to be made by the patient/caregiver following the date of End of Treatment/Withdrawal in the blinded and OLE phases.
- Clarification that only patients who successfully complete the blinded phase of the study will be invited to participate in the OLE.
- Clarification that patients in the US and Poland may have the opportunity to continue in the OLE beyond 1 year.
- Text in Section 9.1.2.2 has been corrected to state that patients will receive sufficient open-label IMP for three weeks' home dosing.

- Clarification that continued use of GWP42003-P following the 'End of Treatment' visit of the OLE refers to use of GWP42003-P outside of the GWEP1521 study.
- Simplification of language regarding provision of instructions for tapering the dose at Visit B10.
- Clarification that postural blood pressure assessments should be performed if it is possible for the patient to stand, and that the ECG will be performed after 5 minutes in a supine position, if this is possible.
- Clarification in Table 9.2.9-1 that international normalized ratio (INR) is derived from prothrombin time (PT).
- Clarification that meal times are to be recorded only for patients who undergo PK blood sampling.
- Clarification that in patients with profound cognitive impairment aged 6 years or older, where completion of the Columbia-Suicide Severity Rating Scale (C-SSRS) is not appropriate, suicidality is assessed by the investigator's clinical judgment following interview of the patient. In addition, the text has been amended to clarify that for C-SSRS assessments, "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 the trial since obtaining the training certificate[1].
- The references section has been updated to cite the most recent versions of the regulatory guidelines and the CBD Investigator's Brochure.
- Clarification that the Study Medication Use and Behavior Survey should be administered at the final dosing visit of the blinded phase and again at the final dosing visit of the OLE.
- Additional assessments for patients who withdraw early and taper IMP were listed in the Visit B11 section of the protocol but these apply to all patients who taper IMP.
- Clarification that the blinded phase of this study will be locked and unblinded prior to completion of the OLE and that the statistical analysis plan (SAP) covering the blinded phase will be finalized prior to unblinding the blinded phase. Cuts of the OLE data will be conducted as required.

- Clarification in the schedules of assessment that patient diary review includes review of both the patient's IVRS data and paper diary.
- Clarification in the open-label phase schedule of assessments that vital signs assessments include measurement of blood pressure.
- For consistency within the protocol it has been clarified that informed assent is sought alongside informed consent.
- Correction, per Section 9.2.10, that IMP dispensing information for Visit B1 (Section 9.1.2.1) will not be provided by IVRS.
- Minor formatting/spelling/punctuation/grammatical corrections have been made to improve consistency and readability; however, in the interest of brevity, not all of these changes are captured in Section 4 of this amendment document.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 6, Date 07 August 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Version 5, Date 27 June 2017** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Amendment 5 (Clinical Protocol Version 6, Date 07 August 2018)** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 1 Protocol Synopsis Exploratory Objectives p. 4 and Section 2.3 Exploratory p. 37	(…) • To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features **~~compared with placebo~~**.	(…) • To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features.	See Section 2.4
Section 1 Protocol Synopsis Study Design p. 4 and Section 4.1 Study Design p. 45	(…) The blinded phase of the study is a **~~1:1:1~~** 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 **~~either~~** 25 mg/kg/day GWP42003-P,	(…) 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,	See Section 2.2 See Section 2.2

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Section 1 Protocol Synopsis Study Design p. 4 and Section 4.1 Study Design p. 45 (continued)	50 mg/kg/day GWP42003-P or placebo. (…) **~~Patients in the placebo group will be split into two equivalent cohorts; half receiving 25 mg/kg/day dosing volumes and half receiving 50 mg/kg/day dosing volumes.~~** (…)	50 mg/kg/day GWP42003-P or **equivalent volumes of** placebo. (…) (…)	See Section 2.2
Section 1 Protocol Synopsis Sample Size p. 9, Section 4.3 Number of Patients p. 51, and Section 13.1 Sample Size, Power and Significance	(…) The 210 patients will be randomly allocated **~~on a 1:1:1 basis (~~**25 mg/kg/day GWP42003-P**~~,~~** 50 mg/kg/day **~~and~~** placebo**~~, 70 patients per group)~~**. **~~Patients in the placebo group will be split into two cohorts (35 patients receiving 25 mg/kg/day dosing volumes and 35 patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can~~** be pooled for the	(…) 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.	See Section 2.2 See Section 2.2

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Levels p. 112	analyses of efficacy.		
Section 1 Protocol Synopsis Summary of Patient Eligibility Criteria p. 10	(…) • Well-documented clinical history of epilepsy. (…) (…)	(…) • Well-documented clinical history of epilepsy**, which is not completely controlled by their current AEDs**. (…) • **Taking one or more AEDs at a dose which has been stable for at least four weeks prior to screening.** (…)	See Section 2.1 See Section 2.1
Section 1 Protocol Synopsis Procedures p. 14–19	(…) • Informed consent (…)	(…) • Informed consent**/assent** (…)	See Section 2.4

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Section 1 Protocol Synopsis Procedures p. 14–19 (continued)	(…) – ~~**Serum**~~ pregnancy ~~**test**~~ (if ~~**applicable**~~) – *TSC1* and *TSC2* mutation status (if not known previously) (…) ~~**• C-SSRS or Children's C-SSRS, where applicable**~~ (…) (…) Patients will make a daily IVRS call to record daily seizure information including all seizures and episodes of *status epilepticus*. (…) • ECG (including baseline and +4 hours after first dose)	(…) – **Urine/serum** pregnancy **tests** (if **appropriate**) – *TSC1* and *TSC2* mutation status (if not known previously) **if the patient/parent(s)/legal representative provide consent** (…) • **Suicidality** (…) 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. (…) Patients **or their caregivers** will make a daily IVRS call to record daily seizure information including all seizures and episodes of *status epilepticus*. (…) • ECG (including pre-dose baseline and +4 hours **[±30 minutes]** after first dose)	See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4 Clarification for consistency See Section 2.4

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Section 1 Protocol Synopsis Procedures p. 14–19 (continued)	(…) • **~~C-SSRS or Children's C-SSRS, where applicable~~** (…) – **~~Serum~~** pregnancy **~~test~~** (if **~~applicable~~**) (…) • **~~C-SSRS or Children's C-SSRS, where applicable~~** (…) – **~~Serum~~** pregnancy **~~test~~** (Visits 5, 7, 9 and 10, if **~~applicable~~**) (…) – PK (Visit 10) (…) Blood sample collection for PK analysis of CBD and its major metabolites will be taken at **~~the following time points:~~** • **~~Visit 3 (Randomization) - Pre-IMP dose, 2–3 hours post-dose, 4–6 hours post-dose and 8–10 hours post-dose (patients 18 years and above only).~~**	(…) • **Suicidality** (…) – **Urine/serum** pregnancy **tests** (if **appropriate**) (…) • **Suicidality** (…) – **Urine/serum** pregnancy **tests** (Visits 5, 7, 9 and 10, if **appropriate**) (…) – PK (Visit 10**; patients > 20 kg only**) (…) 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.**	See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4

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Section 1 Protocol Synopsis Procedures p. 14–19 (continued)	• ~~**Visit 10 (End of Treatment) - Pre-IMP dose, 2–3 hours post dose, 4–6 hours post-dose and 8–10 hours post-dose (patients 18 years and above only).**~~	**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).**	See Section 2.4
	(…)	(…)	
	• ~~**C-SSRS or Children's C-SSRS, where applicable**~~	• **Suicidality**	See Section 2.4
	(…)	(…)	
	– ~~**Serum**~~ pregnancy ~~**test**~~ (Visits B4, B6, B8 and B10, if ~~**applicable**~~)	– **Urine/serum** pregnancy **tests** (Visits B4, B6, B8 and B10, if **appropriate**)	See Section 2.4
	(…)	(…)	
	Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit ~~**(Visit 9 or**~~	Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit of the	Clarification for consistency

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	~~**the Withdrawal visit)**~~ of the blinded phase and again at their final dosing visit of the OLE).	blinded phase **(Visit 10 or 11)** and again at their final dosing visit of the OLE **(Visit B10 or B11)**.	
Section 1 Protocol Synopsis Figure 1-2 Study Design and Treatment Schema: Open-label Extension p. 22	(…) ~~**In addition to the re-supply visits, scheduling of extra dispensing visits/review of visit windows is required in order to comply with countries where controlled drugs can only be dispensed for a maximum of 28 days. Arrangements must be made with patients (or their caregivers) to come in every 4 weeks to be dispensed further GWP42003-P and return of used/unused GWP42003-P.**~~ (…)	(…) (…)	See Section 2.4
Section 3.3.1 Selection of Study Dose p. 42–43	(…) GWP42003-P ~~**is currently**~~ 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.	(…) **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.	See Section 2.4

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Section 3.3.1 Selection of Study Dose p. 42–43 (continued)	In the ongoing Individual Expanded Access IND studies, the initial dosing **~~has~~** been cautious (100 mg [morning] + 150 mg [afternoon/evening]), progressively increasing to 400 mg/day CBD; doses up to 22 mg/kg/day **~~have~~** been well tolerated in an individual pediatric patient. (…)	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. (…)	See Section 2.4
	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 **~~have~~** tolerated doses up to 50 mg/kg/day.	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.	See Section 2.4
	In **~~the last~~** data review of the EAP, the median dose was 25 mg/kg among 230 patients treated for at least 12 weeks (EAP; data cut Sep **~~15~~**).	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**).	See Section 2.4
	The first patient was dosed on 22 Jan 2014 and at the **~~latest~~** data cut **~~(Sep 2015)~~** 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 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.	See Section 2.4

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Section 3.3.1 Selection of Study Dose p. 42–43 (continued)	(…) There ~~**have**~~ been few withdrawals due to AEs. (…) ~~**There has been 1 patient who received a dose higher than 50 mg/kg.**~~ (…) The maximum dose ~~**is**~~ based on emerging data from the Intermediate EAP. ~~**Based on the available safety data, no dose-related changes in benefit-risk have been established.**~~	(…) There **had** been few withdrawals due to AEs. (…) **The highest dose had been 51 mg/kg (1 patient).** (…) 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.**	See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4
Section 5.3.4 Investigational Medicinal Product Accountability p. 54	(…) ~~**In countries where controlled drugs can only be dispensed for a maximum of 28 days, arrangements must be made with patients (or their caregivers) to come in every 4 weeks to be dispensed further GWP42003-P and return of used/unused GWP42003-P.**~~ (…)	(…) (…)	See Section 2.4

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	~~**The center will check the returned IMP against the usage recorded in the IVRS.**~~ (…)	(…)	See Section 2.4
Section 6.1 Inclusion Criteria p. 56–57	*<Criteria 6.1.6 through 6.1.11 in Protocol Version 5 have become criteria 6.1.7 through 6.1.12 in Protocol Version 6>* (…) 6.1.4 Well-documented clinical history of epilepsy. (…) (…)	*<Criteria 6.1.6 through 6.1.11 in Protocol Version 5 have become criteria 6.1.7 through 6.1.12 in Protocol Version 6>* (…) 6.1.4 Well-documented clinical history of epilepsy**, which is not completely controlled by their current AEDs**. (…) **6.1.6 Taking one or more AEDs at a dose which has been stable for at least four weeks prior to screening.** (…)	See Section 2.1 See Section 2.1 See Section 2.1

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Section 8.1 Investigational Medicinal Product Dosage, Administration and Schedule p. 61	(…) Patients will be assigned ~~**one of two Dose Levels of active IMP or placebo on a 1:1:1 basis (64 patients per treatment group)**~~. ~~**Patients in the placebo group will be split into two cohorts (32 receiving Low Dose Level dosing volumes and 32 receiving High Dose Level dosing volumes), but it is assumed that these two cohorts can**~~ be pooled for the analyses of efficacy.	(…) 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.	See Section 2.2 See Section 2.2
Section 8.1.2 Dose Escalation and Dose Adjustments p. 62	(…) If that dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period.	(…) 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**.	See Section 2.4

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	(…)	(…)	
Section 8.1.2 Dose Escalation and Dose Adjustments Table 8.1.2-3 OLE Titration Schedule p. 63–64	*<See Appendix 1 for changes to table>*	*<See Appendix 1 for changes to table>* **[a] Derived from an AM dose based on 25 mg/kg/day and a PM dose based on 27.5 mg/kg/day.**	See Section 2.4 See Section 2.4
Section 8.2 Concomitant Therapy p. 64	(…) If 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, **then the dosage of concomitant AEDs may be modified, depending on the clinical need, following discussion with** the GW medical monitor. **However, it is encouraged that management of possible interactions be on emerging clinical**	(…) 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.**	See Section 2.4 See Section 2.4

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Section 8.2 Concomitant Therapy p. 64 (continued)	~~**symptoms with discussion with the GW medical monitor.**~~ (…)	(…) **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.**	See Section 2.4
	Additional new AEDs are not allowed to be added during the randomized phase of the trial, but may be considered on a case-by-case basis after consultation with the GW medical monitor ~~**for the OLE phase of the trial**~~. (…)	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. (…)	See Section 2.3

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Section 8.4 Compliance in Investigational Medicinal Product Administration p. 66	(…) The usage recorded in the diary and the usage projected in the dose calculator **~~and IVRS system~~** 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. (…)	(…) 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. (…)	See Section 2.4
Section 9.1.1.1 Visit 1 (Day −35, Screening) p. 67	 (…) Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine/serum THC screen **~~and a pregnancy test (using a serum sample, if appropriate)~~**. Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Baseline) or, in patients with profound cognitive impairment, by interview and~~**	**Eligibility must be assessed according to the criteria specified in Section 6.** (…) 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**.	See Section 2.4 See Section 2.4 See Section 2.4

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	~~**clinical judgment**~~. (…)	(…)	
Section 9.1.1.2 Visit 2 (Day −28, Baseline) p. 68	(…) (…)	(…) **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.** (…)	See Section 2.4 See Section 2.4
Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 68–69	(…) The ECG will be repeated four hours after the first dose of IMP. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, determination of serum IGF-1 levels (for patients less than 18 years of age) ~~**and a pregnancy test if appropriate (using both a serum sample and a urine dipstick)**~~.	(…) 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).	See Section 2.4 See Section 2.4

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Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 68–69 (continued)	(…) 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, will be eligible to continue in the study. (…) **~~At Visit 3 e~~**ligible patients will be randomized to receive **~~either~~** 25 mg/kg/day GWP42003-P, 50 mg/kg/day **~~GWP42003-P~~** or placebo **~~on a 1:1:1 basis~~**. (…) Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment~~**. (…) **~~Patients or their caregivers will be instructed on how to record the diary information, including both the paper and IVRS diaries.~~**	(…) 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. (…) **E**ligible 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**. (…) Suicidality will be assessed **in accordance with Section 9.2.12.8**. (…)	See Section 2.4 See Section 2.2 See Section 2.4 Already covered at Visit 2

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	(…)	(…) **The investigator must retain oversight of safety telephone calls.**	See Section 2.4
Section 9.1.1.4 Visit 4 (Day 15) p. 70	(…) Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment~~**. (…)	(…) Suicidality will be assessed **in accordance with Section 9.2.12.8**. (…) **The investigator must retain oversight of safety telephone calls.**	See Section 2.4 See Section 2.4
Section 9.1.1.5 Visit 5 (Day 29) p. 70	(…) Clinical laboratory samples (blood and urine [where possible]), including **~~a~~** pregnancy **~~test~~** if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. (…) Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in~~**	(…) 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. (…) Suicidality will be assessed **in accordance with Section 9.2.12.8**.	See Section 2.4 See Section 2.4

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Section 9.1.1.5 Visit 5 (Day 29) p. 70 (continued)	~~**patients with profound cognitive impairment, by interview and clinical judgment**~~. (…)	(…) **The investigator must retain oversight of the safety telephone call.**	See Section 2.4
Section 9.1.1.6 Visit 6 (Day 43) p. 71	(…) Suicidality will be assessed ~~**using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment**~~. (…)	(…) Suicidality will be assessed **in accordance with Section 9.2.12.8**. (…)	See Section 2.4
Section 9.1.1.7 Visit 7 (Day 57) p. 71, and Section 9.1.1.9 Visit 9 (Day 85) p. 72	(…) Clinical laboratory samples (blood and urine [where possible]), including ~~**a**~~ pregnancy ~~**test**~~ if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry and urinalysis. (…) Suicidality will be assessed ~~**using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in**~~	(…) 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. (…) Suicidality will be assessed **in accordance with Section 9.2.12.8**.	See Section 2.4 See Section 2.4

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	~~patients with profound cognitive impairment, by interview and clinical judgment~~. (…)	(…)	
Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/ Withdrawal Visit) p. 72–73	(…) **~~In countries where controlled drugs can only be dispensed for a maximum of 28 days, there will not be a +3 day visit window, only a −3 day visit window.~~** (…) Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, determination of serum IGF-1 levels (for patients less than 18 years of age) **~~and a pregnancy test (using a serum sample, if appropriate),~~** to be performed by the central laboratory. (…) PK samples (patients >20 kg in weight only) will be taken **~~at baseline and at 2 hours and 4 hours after the last dose of IMP (taken in clinic)~~**.	(…) (…) 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. (…) PK samples (patients > 20 kg in weight only) will be taken **in accordance with Section 9.2.9.1**.	See Section 2.4 See Section 2.4 See Section 2.4

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Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/ Withdrawal Visit) p. 72–73 (continued)	~~**An additional PK sample will be taken six hours after the first dose for patients aged 18 years or above.**~~		See Section 2.4
	(…)	(…)	
	Suicidality will be assessed ~~**using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment**~~.	Suicidality will be assessed **in accordance with Section 9.2.12.8**.	See Section 2.4
	(…)	(…)	
	For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.	For patients 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.	See Section 2.4
	(…)	(…)	
	Patients should continue to complete the IVRS and paper diary and should return for Visit 11 (the 'End of Taper Period' visit), if possible.	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.	See Section 2.4
	(…)	(…)	
	Patients not entering the OLE at this visit will be	Patients not entering the OLE at this visit will be	See Section 2.4

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	given a 10-day supply of IMP (if required) and instructions for tapering the dose, during which time IVRS and paper diary information will continue to be recorded.	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.	
Section 9.1.1.11 Visit 11 (Day 123, End of Taper) p. 74	(…) The following observations will be made at Visit 11: **~~seizure information,~~** 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 **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment~~**. (…)	(…) 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**. (…) **The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and IVRS data and record the patient's**	Clarification for consistency See Section 2.4 Clarification for consistency

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Section 9.1.1.11 Visit 11 (Day 123, End of Taper) p. 74 (continued)	(…)	**attendance at the visit.** (…) **Following Visit 11 (or date of final dosing) the IVRS seizure reporting diary should only be completed once more (see APPENDIX 4).**	See Section 2.4
Section 9.1.2 Open-Label Extension p. 74–75	Patients **~~and their parent(s)/legal representative~~** will be invited to participate in the OLE when they reach the End of Treatment visit (Visit 10) of the **~~B~~**linded **~~P~~**hase. (…) The OLE period will last for a maximum of 1 year.	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 **b**linded **p**hase. (…) 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.**	See Section 2.4; clarification of text See Section 2.4 See Section 2.3

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Section 9.1.2.1 Visit B1 (Day 1) p. 75–76	(…) 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, serum IGF-1 levels **~~(~~**patients less than 18 years of age**~~)~~** and pregnancy **~~test~~ ~~(~~**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, 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 **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in~~**	(…) 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**.	Clarification for consistency See Section 2.4

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Section 9.1.2.1 Visit B1 (Day 1) p. 75–76 (continued)	~~**patients with profound cognitive impairment, by interview and clinical judgment**~~. (…) ~~**Eligibility will be assessed according to the entry criteria, as specified in Section 6.**~~ ~~**Eligible**~~ patients or their caregivers will receive sufficient IMP for two weeks' home dosing together with a blinded transition phase ~~**provided via the IVRS**~~. (…)	(…) Patients or their caregivers will receive sufficient IMP for two weeks' home dosing together with a blinded transition phase. (…) **The investigator must retain oversight of safety telephone calls.**	See Section 2.4 See Section 2.4 See Section 2.4
Section 9.1.2.2 Visit B2 (Day 15) p. 76–77	(…) The following assessments will be made at Visit B2: ~~**vital signs,**~~ physical examination (including height and body weight) ~~**and ECG**~~. (…) Suicidality will be assessed ~~**using the C-SSRS/**~~	(…) 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**. (…) Suicidality will be assessed **in accordance with**	Clarification for consistency See Section 2.4

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Section 9.1.2.2 Visit B2 (Day 15) p. 76–77 (continued)	**~~Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment~~**. **~~The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.~~** The investigator must assess adherence to the titration regimen. (…) Patients/caregivers will then receive sufficient open-label IMP for **~~two~~** weeks' home dosing together with a titration schedule **~~provided via the IVRS~~**. (…)	**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**. (…) Patients/caregivers will then receive sufficient open-label IMP for **three** weeks' home dosing together with a titration schedule. (…) **The investigator must retain oversight of safety telephone calls.**	Clarification for consistency Clarification for consistency See Section 2.4 See Section 2.4

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Section 9.1.2.3 Visit B3 (Day 36) p. 77	(…) The following assessments will be made at Visit B3: **~~vital signs, postural blood pressure,~~** physical examination (including height and body weight) **~~and ECG~~**. Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment~~**. (…) **~~The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP usage, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.~~** The investigator must assess adherence to the titration regimen. (…)	(…) 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**. (…) 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**. (…)	Clarification for consistency See Section 2.4 Clarification for consistency Clarification for consistency

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Section 9.1.2.4 Visit B4 (Day 92) p. 78	(…) Clinical laboratory samples (blood and urine [where possible]), including **~~a~~** pregnancy **~~test~~** 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. (…) Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment~~**. (…) Patients/caregivers will then receive sufficient open-label IMP **~~for eight weeks' home dosing~~**.	(…) 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. (…) Suicidality will be assessed **in accordance with Section 9.2.12.8**. (…) Patients/caregivers will then receive sufficient open-label IMP **until the next scheduled visit**.	See Section 2.4 See Section 2.4 Clarification for consistency
Section 9.1.2.6 Visit B6 (Day 183) p. 79	(…) Clinical laboratory samples (blood and urine [where possible]), including **~~a~~** pregnancy **~~test~~** 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	(…) 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	See Section 2.4

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Section 9.1.2.6 Visit B6 (Day 183) p. 79 (continued)	(for patients less than 18 years of age) to be performed by the central laboratory. (…) Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment~~**. (…) Patients/caregivers will then receive sufficient open-label IMP **~~for eight weeks' home dosing~~**.	(for patients less than 18 years of age) to be performed by the central laboratory. (…) Suicidality will be assessed **in accordance with Section 9.2.12.8**. (…) Patients/caregivers will then receive sufficient open-label IMP **until the next scheduled visit**.	See Section 2.4 Clarification for consistency
Section 9.1.2.8 Visit B8 (Day 274) p. 80	(…) Clinical laboratory samples (blood and urine [where possible]), including **~~a~~** pregnancy **~~test~~** 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. (…) Suicidality will be assessed **~~using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by~~**	(…) 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. (…) Suicidality will be assessed **in accordance with Section 9.2.12.8**.	See Section 2.4 See Section 2.4

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Section 9.1.2.8 Visit B8 (Day 274) p. 80 (continued)	~~**interview and clinical judgment**~~. (…) Patients/caregivers will then receive sufficient open-label IMP ~~**for eight weeks' home dosing**~~.	 (…) Patients/caregivers will then receive sufficient open-label IMP **until the next scheduled visit**.	Clarification for consistency
Section 9.1.2.9 Visit B9 (Day 323, Re-supply Visit) p. 81	(…) Patients in the US and Poland may have the opportunity to ~~**enter a second year of OLE**~~. (…)	(…) Patients in the US and Poland may have the opportunity to **continue in the OLE beyond Visit B10**. (…)	See Section 2.4
Section 9.1.2.10 Visit B10 (Day 365, End of Treatment/ Withdrawal Visit) p. 81–82	(…) 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~~**,**~~ serum IGF-1 levels ~~**(**~~patients less than 18 years of age~~**)**~~ and pregnancy ~~**test (**~~using both a serum sample and a urine dipstick~~**, if appropriate)**~~, IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue	(…) 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	Clarification for consistency and see Section 2.4

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Section 9.1.2.10 Visit B10 (Day 365, End of Treatment/ Withdrawal Visit) p. 81–82 (continued)	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.	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 ~~**using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment**~~.	Suicidality will be assessed **in accordance with Section 9.2.12.8**.	See Section 2.4
	(…)	(…)	
	For patients who immediately continue to use GWP42003-P following the 'End of Treatment' visit, the IVRS will be contacted to confirm the patient's completion of this study and the paper diaries will be collected.	For patients 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.	See Section 2.4
	For patients who do not immediately continue to use GWP42003-P following the 'End of Treatment' visit, IMP will be tapered at home (10% per day for 10	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	See Section 2.4

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Section 9.1.2.10 Visit B10 (Day 365, End of Treatment/ Withdrawal Visit) p. 81–82 (continued)	days). Additional IMP will be dispensed, if required. (…) **~~The IVRS will generate the patient's daily IMP dosing volumes for the 10-day taper period, during which time diary i~~**information will continue to be recorded in the paper diary. For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver. (…) Following the 'End of Treatment'/Withdrawal visit, the IVRS seizure reporting diary should **~~only~~** be completed **~~up to the Follow-up visit~~**.	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**. (…) **I**nformation 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**.	See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4

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Section 9.1.2.11 Visit B11 (Day 375, End of Taper Period Visit) p. 82	(…) The following assessments will be made: **~~vital signs and~~** physical examination (including height and body weight). **~~Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.~~** **~~In addition, the following assessments will be made for patients who withdraw early and taper IMP (including withdrawal during the taper period): ECG and clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis).~~** **~~The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP usage, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.~~**	(…) The following assessments will be made: **<u>concomitant medications (including AEDs),</u>** physical examination (including height and body weight), ECG, **<u>vital signs, epilepsy-related hospitalizations, and AEs</u>**. **<u>Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, and urinalysis.</u>** **<u>Suicidality will be assessed in accordance with Section 9.2.12.8</u>**.	Clarification for consistency See Section 2.4 See Section 2.4 See Section 2.4

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Section 9.1.2.11 Visit B11 (Day 375, End of Taper Period Visit) p. 82 (continued)	The investigator must assess adherence to the dosing regimen. (…) Following **~~the 'End of Taper Period' visit~~** (or date of final dosing), the IVRS seizure reporting diary should be completed **~~up to the Follow-up visit~~**.	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**. (…) Following **Visit B11** (or date of final dosing), the IVRS seizure reporting diary should **only** be completed **once more (see APPENDIX 4)**.	Clarification for consistency See Section 2.4
Section 9.1.2.14 Safety Telephone Calls p. 83	(…)	(…) **The investigator must retain oversight of safety telephone calls.**	See Section 2.4
Section 9.2.7 Vital Signs and Blood Pressure p. 85	(…) Where postural blood pressure is required it should be measured after five minutes in supine position followed by two minutes in standing position, if possible. (…)	(…) 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**. (…)	See Section 2.4

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Section 9.2.8 12-Lead Electrocardiogram p. 85	A 12-lead ECG will be performed after five minutes in a supine position. (…)	A 12-lead ECG will be performed after five minutes in a supine position, **if possible**. (…)	See Section 2.4
Section 9.2.9 Clinical Laboratory Sampling p. 86	(…) ~~**At screening, a**~~ urine dipstick pregnancy ~~**test**~~ will also be performed (if appropriate) at the study center ~~**to assess eligibility**~~. (…)	(…) **In addition to serum pregnancy tests,** urine dipstick pregnancy **tests** will also be performed (if appropriate) at the study center. (…)	See Section 2.4
Section 9.2.9 Clinical Laboratory Sampling Table 9.2.9-1 Biochemistry, Hematology, Urinalysis and THC Screen p. 87	*<See Appendix 1 for changes to table>*	*<See Appendix 1 for changes to table>*	See Section 2.4

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Section 9.2.9.1 Pharmacokinetic Blood Sampling p. 88	(…) There must be a minimum period of at least two hours between each of the ~~**three**~~ blood sampling time points. (…) ~~**T**~~he 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). (…)	(…) There must be a minimum period of at least two hours between each of the blood sampling time points. (…) **For patients who undergo PK blood sampling, t**he 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). (…)	See Section 2.4 See Section 2.4
Section 9.2.9.3 Determination of Mutation Status of the *TSC1* and *TSC2* Genes p. 89	If the mutation status of *TSC1* and *TSC2* is unknown at screening, genetic analysis will be carried out~~**, with** the patient/parent(s)/legal r**epresentative's**~~ consent~~**, during the study analysis**~~ (a blood sample will be taken during Visit 1).	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).	See Section 2.4

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Section 9.2.12.8 Suicidality/ Children's/ Columbia-Suicide Severity Rating Scale (Six Years of Age and Older) p. 93–94	9.2.12.8 Children's/Columbia-Suicide Severity Rating Scale Suicidality will be assessed using the C-SSRS/Children's C-SSRS or, in patients with profound cognitive impairment, by ~~**interview and**~~ clinical judgment. (…) The C-SSRS is to be completed by the investigator or his/her qualified ~~**designee**~~ at every visit as indicated in the Schedule of Assessments (see APPENDIX 1); "qualified ~~**designee**~~" is defined as ~~**a physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant, who is licensed and**~~ has completed the C-SSRS training within the past two years. (…)	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**. (…) 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**. (…)	See Section 2.4 See Section 2.4 See Section 2.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 5, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 5 (Clinical Protocol Version 6, Date 07 August 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 9.2.17 Monitoring of Abuse Liability (for Patients 12 Years of Age and Older) p. 96	(…) Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit ('End of Treatment'/Withdrawal visit or 'End of Taper Period' visit, as applicable) and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator. (…)	(…) 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. (…)	See Section 2.4
Section 9.2.17.1.3 Monitoring Drug Accountability Discrepancies p. 97	(…) • 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 ~~**IVRS report and**~~ paper diary. (…)	(…) • 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. (…)	See Section 2.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 5, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 5 (Clinical Protocol Version 6, Date 07 August 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 9.2.17.1.4 List of 'Triggering Drug Accountability Discrepancies' p. 98	(…) • Compliance issues where one or more bottles are used compared to what was the expected use, according to the **~~IVRS report and~~** paper diary. (…) • Greater than the target daily dose as recorded in the **~~IVRS report and~~** paper diary.	(…) • Compliance issues where one or more bottles are used compared to what was the expected use, according to the paper diary. (…) • Greater than the target daily dose as recorded in the paper diary.	See Section 2.4 See Section 2.4
Section 9.2.17.3 Study Medication Use and Behavior Survey p. 98	(…) The trained investigator or study coordinator will complete this survey as an interview with the patient/caregiver at the final dosing visit ('End of Treatment'/Withdrawal visit or 'End of Taper Period' visit, as applicable). (…)	(…) The 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**. (…)	See Section 2.4
Section 10 WITHDRAWAL p. 101	(…)	(…) **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**	See Section 2.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 5, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 5 (Clinical Protocol Version 6, Date 07 August 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	(…)	**discussion with the GW medical monitor.** (…)	
Section 13.2 Interim Analysis p. 112	(…) (…) **~~At least one interim analysis may be conducted~~** to support New Drug Application and Marketing Authorization Application filings. Further **~~interim analyses maybe~~** conducted as required.	(…) **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.** (…) **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.	See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4
Section 17 REFERENCES p. 136–137	(…) [51] Investigator Brochure — CBD medicine. GW Pharma Ltd. Edition **~~9~~**. September **~~2016~~**. [52] **~~International Conference on Harmonisation Topic E6(R1): Guideline for good clinical practice — Note for guidance on good clinical practice (CPMP/ICH/135/95). July 2002.~~**	(…) [51] Investigator**'s** Brochure — CBD medicine. GW Pharma Ltd. Edition **10**. September **2017**. [52] **ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). November 2016.**	See Section 2.4 See Section 2.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 5, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 5 (Clinical Protocol Version 6, Date 07 August 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 17 REFERENCES p. 136–137 (continued)	[53] **~~International Conference on Harmonisation guideline M3(R2)~~** on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals **~~(EMA/CPMP/ICH/286/1995)~~**. **~~December~~** 2009. (…) [57] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs) Part 50 — Protection of human subjects. **~~February 2013~~**. [58] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs) Part 312 — Investigational New Drug application. April **~~2012~~**. [59] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs) Part 56 — Institutional Review Boards. **~~March 2013~~**. (…) [68] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs)	[53] **ICH Harmonised Tripartite Guideline: Guidance on** nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals **M3(R2)**. **June** 2009. (…) [57] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs) Part 50 — Protection of human subjects. **April 2018**. [58] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs) Part 312 — Investigational New Drug application. April **2018**. [59] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs) Part 56 — Institutional Review Boards. **April 2018**. (…) [68] U.S. Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs)	Change to cite global ICH version over EMA adopted version See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 5, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 5 (Clinical Protocol Version 6, Date 07 August 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	Part 11 — Electronic records; electronic signatures (Subpart B — Electronic records). ~~**March 1997**~~.	Part 11 — Electronic records; electronic signatures (Subpart B — Electronic records). **April 2018**.	
APPENDIX 1 SCHEDULE OF ASSESSMENTS Blinded Phase p. 138–140	*<See Appendix 1 for changes to table>* (…) ~~∞ **In countries where controlled drugs can only be dispensed for a maximum of 28 days, there will not be a +3 day visit window, only a −3 day visit window.**~~ (…)	*<See Appendix 1 for changes to table>* (…) § **ECG must be re-assessed four hours (±30 minutes) post-dose.** (…) † **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.**	See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 5, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 5 (Clinical Protocol Version 6, Date 07 August 2018) *(Revised wording is underscored and in bold)*	Rationale for the amendment
APPENDIX 1 SCHEDULE OF ASSESSMENTS Open-label Extension p. 141–143	*<See Appendix 1 for changes to table>* (…)	*<See Appendix 1 for changes to table>* (…) **‡ 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.**	See Section 2.4 See Section 2.4
APPENDIX 4 IVRS CALLS FOLLOWING END OF TREATMENT/ WITHDRAWAL p. 148–149	*<This appendix is absent from Clinical Protocol Version 5>*	**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.** *<See Appendix 1 for presentation of the new table>* **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.**	See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4 See Section 2.4

5 REFERENCES

1 Training for Researchers The Columbia Lighthouse Project [Internet]. The Columbia Lighthouse Project. [cited 2018 Mar 14]; Available from: http://cssrs.columbia.edu/training/training-research-setting/

APPENDIX 1 AMENDED FIGURES AND TABLES

Original Tables from Clinical Protocol Version 5, Date 27 June 2017

(Deleted wording is struck through and in bold)

Table 8.1.2-3 OLE Titration Schedule	
OLE Day	Daily Dose (mg/kg/day)
15 (Visit B2)	26.25
16	27.5
17	30
18	30
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

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 (plasma)					
Sodium					
Total bilirubin					
Total protein					
Triglycerides					
Urea (blood urea nitrogen [BUN])					
Creatine Kinase (CK)					

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 ~~6~~	+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 ~~test~~ (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 ~~±6~~	+3	+3	
Pharmacokinetic blood sampling♦			X							X			
AED concentration			X		X		X		X	X			
TSC1 and *TSC2* mutation status	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 ~~±6~~	+3	+3	
Patient 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			

Open-label Extension

Visit Number	B1	B2	B3	B4	Re-~~S~~upply Visit B5	B6	Re-~~S~~upply Visit B7	B8	Re-~~S~~upply Visit B9	End of Treatment B10	End of Taper	Post-~~T~~aper 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	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				
Pregnancy ~~**test, where**~~ 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

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	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	
Inpatient epilepsy-related hospitalizations	X	X	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			
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 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	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				

Revised Tables from Clinical Protocol Amendment 5
(Clinical Protocol Version 6, Date 07 August 2018)
(Revised wording is underscored and in bold)

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
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

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)					

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‡			

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

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	
Inpatient epilepsy-related hospitalizations	X	X	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			
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				

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	
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			
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‡				

APPENDIX 4 IVRS CALLS FOLLOWING END OF TREATMENT/WITHDRAWAL

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				
+14				
+15				
+16				
+17				
+18				
+19				
+20				
+21				
+22				
+23				
+24				
+25				
+26				
+27	X		X	
+28				
+29				
+30				
+31				
+32				
+33				
+34				
+35				
+36				
+37		X		X
+38				
+39				
+40				

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 4

to be incorporated into the Protocol, creating CLINICAL PROTOCOL VERSION 5, DATE 27 June 2017

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Confidentiality Statement

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.
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.
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 1:1:1 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 either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients in the placebo group will be split into two equivalent cohorts; half receiving 25 mg/kg/day dosing volumes and half receiving 50 mg/kg/day dosing volumes. 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 open-label extension (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 antiepileptic drug

	(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 open-label extension 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.

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2 RATIONALE

This clinical protocol amendment 4 (will be incorporated into the Protocol creating Clinical Protocol Version 5, Date 27 June 2017) addresses the following issue(s):

2.1 Amendments to Trial Design

- Secondary endpoints have been sub divided into three categories: key, other and exploratory, in order to better reflect the importance of each in the overall trial design and to enable prioritization during data analysis.
- The statistical analysis has been amended to reflect the re categorization of secondary endpoints. The hierarchy of analysis of key secondary endpoints has been clearly defined.
- Clarification of exclusion criteria relating to mTOR inhibitors to reflect their changing regulatory approval status.
- Provision has been made to extend the open-label extension for patients in the US and Poland. Patients in other countries will be able to access continued supply of investigational medicinal product (IMP) by alternative schemes.
- Administration of cannabidiol through a gastrostomy (G)/nasogastric (NG) feeding tube has been added as an option after consultation with the medical monitor. This will allow certain patients who are unable to swallow to possibly use the G/NG tube, since *in vitro* experiments demonstrated this route of feeding to be acceptable with medical guidance.

2.2 Minor Corrections and Clarifications

- Administrative updates have been made throughout for consistency (NB. in the interest of brevity, minor changes to grammar, punctuation or formatting are not all captured in this amendment document).
- The reference list has been updated to include the current version of the investigator brochure (IB) and safety information. The IMP background section of the protocol has also been updated to reflect the current version of the IB.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 5, Date 27 June 2017. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol V4 Date 05 Dec 16** *(Deleted wording is struck through and in bold)*	**Revised Wording from Clinical Protocol Amendment 4 (Clinical Protocol Version 5, Date 27 June 2017)** *(Revised wording is underscored and in bold)*	**Rationale for the amendment**
Section 1, Protocol Synopsis Secondary Objectives p. 3–4	Blinded Phase: • To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures. • ~~**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 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. • ~~**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.**~~	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.	**Re-classification of secondary endpoints**
Section 1, Protocol Synopsis	Open-label Extension: • To evaluate the long term effects of GWP42003-	Open-label Extension: • To evaluate the long term effects of	**Re-classification**

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol V4 Date 05 Dec 16 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 4 (Clinical Protocol Version 5, Date 27 June 2017) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Secondary Objectives p. 3–4 (continued)	P, as add-on therapy, on antiepileptic measures. • ~~**To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features compared with placebo.**~~ • To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old). (...)	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). (...)	**of secondary endpoints**
Section 1, Protocol Synopsis Exploratory Objectives p. 4	(NB. Not applicable-new text added)	**<u>Blinded Phase:</u>** • **<u>To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.</u>** • **<u>To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.</u>** • **<u>To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), if applicable.</u>** **<u>Open-label Extension:</u>** • **<u>To evaluate the long term effect of GWP42003-P on TAND, including cognitive and behavioral function and autistic features compared with placebo.</u>**	**Re-classification of secondary endpoints**

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol V4 Date 05 Dec 16** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Amendment 4 (Clinical Protocol Version 5, Date 27 June 2017)** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 1, Protocol Synopsis Secondary Endpoints p. 6–7 Section 1, Protocol Synopsis Secondary Endpoints p. 6–7 (continued)	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.**~~ Key: • Number of patients considered treatment responders defined as those with a ≥ 50% reduction in seizure frequency ~~**(blinded phase only)**~~. Other: • 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~~**s**~~* frequency. • ~~**Change in total seizures**~~ • ~~**Change in composite focal seizure score**~~	Blinded Phase: (...) 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	**Re-classification of secondary endpoints**

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	~~**(frequency × severity).**~~ • Change in number of TSC-associated seizure* -free days. • ~~**Change in number of seizures by subtype.**~~ • Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms). • ~~**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).**~~	seizure* -free days. • Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).	
Section 1, Protocol Synopsis Secondary Endpoints p. 6–7 (continued) Section 1, Protocol Synopsis Secondary Endpoints p. 6–7 (continued)	~~**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.**~~ Growth and Development (in patients less than 18	Growth and Development (in patients less than 18 years old): • (...) 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: (...)	**Re-classification of secondary endpoints**

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	years old): • (...) 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 Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.~~** • Change in Physician Global Impression of Change (PGIC) score. Safety and Tolerability: (...) **~~PK:~~** **~~• 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.~~**		
Section 1,	**<u>Open-label Extension:</u>**	**<u>Open-label Extension:</u>**	**Re-**

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Protocol Synopsis Secondary Endpoints p. 7–8 Section 1, Protocol Synopsis Secondary Endpoints p. 7–8 (continued)	The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase: (...) • Percentage change in number of TSC-associated seizures* (average per 28 days). • 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 total seizures~~ ~~• **Change in composite focal seizure score (frequency × severity).**~~ • Change in number of TSC-associated seizure*-free days. ~~• **Change in number of seizures by subtype.**~~ • Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms). ~~• **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**	The following endpoints will be assessed relative to the pre-randomization baseline of the blinded phase: (...) **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:** • **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).	**classification of secondary endpoints**

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	~~**assessed by the SGIC SD or the CGIC-SD.**~~		
Section 1, Protocol Synopsis Secondary Endpoints p. 7–8 (continued)	~~**TAND:**~~ ~~**Cognitive and Behavioral Function:**~~ ~~**• Changes in Vineland-II.**~~ ~~**• Changes in Wechsler Scales (pre-school, primary, children, adult).**~~ ~~**• Changes in CBCL or ABCL.**~~ ~~**Autistic Features:**~~ ~~**• Changes in SCQ score.**~~ Growth and Development (patients less than 18 years): (...) Quality of Life: • Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score. ~~**• Change in CGIC or SGIC score.**~~ • Change in PGIC score. (...)	Growth and Development (patients less than 18 years): (...) 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. (...)	**Re-classification of secondary endpoints**
Section 1, Protocol Synopsis Exploratory Endpoints p. 8–9	(NB. Not applicable-new text added)	**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).**	**Re-classification of secondary endpoints**

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Section 1, Protocol Synopsis Exploratory Endpoints p. 8–9 (continued)		• **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.**	

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		• **Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available**.	
Section 1, Protocol Synopsis Summary of Patient Eligibility Criteria p. 10	Exclusion: (...) • Patient has received an IMP **~~as part of a clinical trial~~** less than 12 weeks prior to the screening visit. (...)	Exclusion: (...) • Patient has received an IMP less than 12 weeks prior to the screening visit. (...)	**Clarified to reflect the changing regulatory status of mTOR inhibitors**
Section 1, Protocol Synopsis Criteria for Withdrawal p. 12-13	The patient must be withdrawn from the study if any of the following apply: (...) • General anesthesia (blinded phase only).	The patient must be withdrawn from the study if any of the following apply: (...) • General anesthesia (blinded phase only). • **Addition of a new AED (Blinded Phase only).**	**New criteria added to provide additional guidance to investigators**
Section 1, Protocol Synopsis Procedures p. 17–18	**Post Randomization Assessments** (...) • Clinical Laboratory samples (blood and urine) will be taken for: ○ Hematology ○ (...) ○ Serum IGF-1 ○ PK (Visit 10) ○ AED concentrations	**Post Randomization Assessments** (...) • Clinical Laboratory samples (blood and urine) will be taken for: ○ Hematology ○ (...) ○ Serum IGF-1 **(Visit 10)** ○ PK (Visit 10) ○ AED concentrations **(Visits 5, 7, 9 and**	**Clarified for consistency**

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	(...)	**10)** (...)	
Section 1, Protocol Synopsis Procedures p. 18–19	**Open-label Extension Transition and Open-label Extension:** (…) **~~In countries where local law requires controlled drugs only be dispensed for a maximum of 28 days, the visit schedule in the OLE period will include additional visits or expanded visit windows for patients seen in those countries.~~** 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): (…)	**Open-label Extension Transition and Open-label Extension:** (…) 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): (…)	**Text removed because it does not apply in selected countries**
Section 1, Protocol Synopsis Procedures p. 19	**Open-label Extension Transition and Open-label Extension:** (...) • Clinical Laboratory samples (blood and urine) will be taken for: ○ Hematology ○ (...) ○ Serum IGF-1 (Visit B10) ○ AED concentrations (...)	**Open-label Extension Transition and Open-label Extension:** (...) • Clinical Laboratory samples (blood and urine) will be taken for: ○ Hematology ○ (...) ○ Serum IGF-1 (Visit**s B6 and** B10) ○ AED concentrations (...)	**Clarified for consistency**
Section 1, Protocol Synopsis Statistical	**Blinded Phase:** (…)	**Blinded Phase:**	**Amended to reflect the re-**

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Considerations p. 20	~~**To control the type I error, a step-up Hochberg's procedure will be used for the primary endpoint. If both of the observed p-values from the 25 mg/kg/day and 50 mg/kg/day GWP42003-P comparisons with placebo are < 0.050 in favor of the GWP42003--P treatment groups, then both groups would be declared statistically significantly better than placebo. However, if the observed p-value is ≥ 0.050 for one GWP42003-P treatment group but < 0.025 in favor of the other GWP42003-P treatment group, then only the latter GWP42003-P treatment group will be declared statistically significantly better than placebo.**~~	(…) **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.**	**classification of secondary endpoints**
Section 1, Protocol Synopsis, Statistical Considerations p. 20	**Blinded Phase:** (...) The secondary endpoints will be tested hierarchically, starting with the key secondary endpoint followed by all other secondary endpoints.	**Blinded Phase:** (...) The secondary endpoints will be tested hierarchically, starting with the key secondary endpoint**s** followed by all other **and exploratory** secondary endpoints.	**Amended to reflect the re-classification of secondary endpoints**
Section 2.2, Secondary	**Blinded Phase:** • To evaluate the effect of GWP42003-P	**Blinded Phase:** • To evaluate the effect of GWP42003-P	**Re-classification**

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p. 38 Section 2.2, Secondary p. 38 (continued)	compared with placebo on antiepileptic measures. • **~~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 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. • **~~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.~~**	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.	**of secondary endpoints**
Section 2.2, Secondary p. 38 (continued)	**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 TAND, including cognitive and behavioral function and autistic features compared with placebo.~~** • To evaluate the long term effect of GWP42003-P	**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). (...)	**Re-classification of secondary endpoints**

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	on growth and development (in patients less than 18 years old). (...)		
Section 2.3, Exploratory p. 39 Section 2.3, Exploratory p. 39 (continued)	(NB. Not applicable-new text added)	**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 compared with placebo.**	**Re-classification of secondary endpoints**
Section 3.2, GWP42003-P Background p. 43	(...) Extracts from these plants are processed to yield purified (~~>~~ **95**%) CBD that typically contains less than ~~**0.5**~~% (w/w) THC. (...)	(...) Extracts from these plants are processed to yield purified (**≥ 98**%) CBD that typically contains less than **0.15**% (w/w) THC **(for oral formulations)**. (...)	**Amended for clarity**

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Section 4.1, Study Design Blinded Phase p. 47	**Blinded Phase:** (...) 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 and 85 until the end of treatment (Day 113). (...)	**Blinded Phase:** (...) 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). (...)	**Amended to match text in protocol synopsis**
Section 4.1, Study Design Open Label Extension p. 48	The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. The OLE period will last for a maximum of 1 year.	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.	**Minor amendment to reflect the extension of OLE in the US and Poland**
Section 4.1.2, Secondary Endpoint(s) p. 49–50	**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.~~**	**Blinded Phase:** (...) **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.**	**Re-classification of secondary endpoints**

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Section 4.1.2, Secondary Endpoint(s) p. 49–50 (continued)	**Key:** • Number of patients considered treatment responders defined as those with a ≥ 50% reduction in seizure frequency **~~(blinded phase only).~~** **Other:** • 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 total seizures.~~** • **~~Change in composite focal seizure score (frequency × severity).~~** • Change in number of TSC-associated seizure**~~s~~***-free days. • **~~Change in number of seizures by subtype.~~** • Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms). • **~~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~~**	**Other:** **<u>Antiepileptic Efficacy Measures:</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).	

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	~~**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).**~~		
Section 4.1.2, Secondary Endpoint(s) p. 49–50 (continued) Secondary Endpoint(s) p. 49–50 (continued)	~~**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.**~~ Growth and Development (in patients less than 18 years old): • (...) 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 Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.**~~ • Change in Physician Global Impression of	Growth and Development (in patients less than 18 years old): • (...) 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: (...)	**Re-classification of secondary endpoints**

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Secondary Endpoint(s) p. 49–50 (continued)	Change (PGIC) score. Safety and Tolerability: (...)**~~Pharmacokinetics:~~** • **~~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.~~**		
Section 4.1.2, Secondary Endpoint(s) p. 50–51	**Open-label Extension:** The following endpoints will be assessed relative to the pre randomization baseline of the blinded phase: (...) • Percentage change in number of TSC-associated seizures* (average per 28 days). • 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%	**Open-label Extension:** The following endpoints will be assessed relative to the pre randomization baseline of the blinded phase: (...) **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.**	**Re-classification of secondary endpoints**

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Section 4.1.2, Secondary Endpoint(s) p. 50–51 (continued)	improvement in TSC-associated seizure* frequency. • Change in total seizures. • ~~**Change in composite focal seizure score (frequency × severity).**~~ • Change in number of TSC-associated seizure* -free days. • ~~**Change in number of seizures by subtype.**~~ • Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms). • ~~**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 SGIC SD or the CGIC SD.**~~	**<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).	
Section 4.1.2, Secondary Endpoint(s) p. 50–51 (continued)	~~**TAND:**~~ ~~**Cognitive and Behavioral Function:**~~ • ~~**Changes in Vineland-II.**~~ • ~~**Changes in Wechsler Scales (pre-school, primary, children, adult).**~~ • ~~**Changes in CBCL or ABCL.**~~ ~~**Autistic Features:**~~ • ~~**Changes in SCQ score.**~~ Growth and Development (patients less than 18 years): (...) Quality of Life:	Growth and Development (patients less than 18 years): (...)	**Re-classification of secondary endpoints**

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Section 4.1.2, Secondary Endpoint(s) p. 50–51 (continued)	• Changes from baseline in the QOLCE (patients 2–18 years) or QOLIE-31-P (patients 19+ years) score. • **~~Change in CGIC or SGIC score.~~** • Change in PGIC score. (...)	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. (...)	
Section 4.1.2, Secondary Endpoint(s) p. 51–52	(NB. Not applicable-new text added)	**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**	**Re-classification of secondary endpoints**

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Section 4.1.2, Secondary Endpoint(s) p. 51–52 (continued)		**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**.	
Section 4.3 Number of Patients p. 52	A total of 210 patients will be targeted to be enrolled. The 210 patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, 70 patients per group). Patients in the placebo group will be split into two cohorts (35 patients receiving 25 mg/kg/day dosing	A total of 210 patients will be targeted to be enrolled. The 210 patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, 70 patients per group). Patients in the placebo group will be split into two cohorts (35 patients receiving	**Amended for consistency**

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Section 4.3 Number of Patients p. 52 (continued)	volumes and 35 patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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), this sample size of 70 patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and 90% power.~~**	25 mg/kg/day dosing volumes and 35 patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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.**	
Section 5.3.1 Packaging and Labeling p. 53	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. **~~For patients in countries where local law states that controlled drugs can~~**	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	**Text removed because it does not apply in selected countries**

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	~~**only be dispensed for a maximum of 28 days, the maximum duration of prescription of IMP will be 28 days.**~~ A unique identification number will be used to identify each box and the IMP it contains. (…)	IMP it contains. (…)	
Section 6.2, Exclusion Criteria p. 59	**Exclusion Criteria:** (...) 6.2.18 Patient has received an IMP ~~**as part of a clinical trial**~~ less than 12 weeks prior to the screening visit. (...)	**Exclusion Criteria:** (...) 6.2.18 Patient has received an IMP less than 12 weeks prior to the screening visit. (...)	**Amended to reflect the changing approval status of mTOR inhibitors**
Section 8.1.1, Dose Administration p. 61	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.	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. **<u>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.</u>**	**Amended to provide additional guidance to investigators**
Section 8.1.2, Dose Escalation and Dose Adjustments	Table 8.1.2-3 OLE Titration Schedule OLE Day | ~~**Blinded**~~ Dose (mg/kg/day)	Table 8.1.2-3 OLE Titration Schedule OLE Day | **<u>Daily</u>** Dose (mg/kg/day)	**Amended for clarity**

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p. 63–64	(...) (...)	(...) (...)	
Section 8.2, Concomitant Therapy p. 64–65	(...) If plasma concentrations of concomitant AEDs are found to be altered following administration of IMP then the dosage of concomitant AEDs may be modified, depending on the clinical need, following discussion with the GW medical ~~**advisor**~~. However, it is encouraged that management of possible interactions be on emerging clinical symptoms with discussion with the GW medical ~~**advisor**~~. (...) 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). (...)	(...) If 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,** then the dosage of concomitant AEDs may be modified, depending on the clinical need, following discussion with the GW medical **monitor**. However, it is encouraged that management of possible interactions be on emerging clinical symptoms with discussion with the GW medical **monitor**. (...) **Additional new AEDs are not allowed to be added during the randomized phase of the trial, but may be considered on a case-by-case basis after consultation with the GW medical monitor for the OLE phase of the trial**. 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). (...)	**Amended to provide additional guidance to investigators**
Section 9.1.2.3, Visit B3 (Day 36)	~~**9.1.2.3 Open-label Extension Visit Schedules in Countries Where Local Law Requires Controlled**~~	**9.1.2.3** Visit B3 (Day 36) (...)	**Text removed**

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p. 77–78 Section 9.1.2.3, Visit B3 (Day 36) p. 77–78 (continued)	~~**Drugs Are Dispensed For a Maximum of 28 Days The visit schedules to follow in the OLE period will include additional visits or slightly amended visit windows for patients seen in countries where local law requires that a controlled drug is dispensed for a maximum of 28 days. The '†' symbol denotes where scheduling of extra dispensing visits/review of visit windows is required in order to comply with this. Arrangements must be made with patients for them to attend the clinic every 4 weeks in order to be dispensed further GWP42003-P and return used/unused GWP42003-P.**~~ ~~**9.1.2.4**~~ Visit B3† (Day 36) (...) (NB. All subsequent section numbering has been updated due to the deletion of the original Section 9.1.2.3.)		**because it does not apply in selected countries**
Section 9.1.2.6 , Visit B6 (Day 183) p. 79	(...) The following observations will be made at Visit B6: concomitant medications, (including AEDs), physical examination (including height and body weight), ~~**details of menstruation (for females),**~~ ECG, vital signs, epilepsy-related hospitalizations and AEs. (...)	(...) 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. (...)	**Amended for consistency**

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Section 9.1.2.8, Visit B8 (Day 274) p. 80	~~**9.1.2.9**~~ Visit B8‡ (Day 274) (...) Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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. (...)	**9.1.2.8** Visit B8 (Day 274) (...) Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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. (...)	**Amended for consistency**
Section 9.1.2.9, Visit B9 (Day 323, Re-supply Visit) p. 81	~~**9.1.2.10**~~ Visit B9‡ (Day 323, Re-supply 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.	**9.1.2.9** Visit B9 (Day 323, Re-supply 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 enter a second year of OLE. Please refer to Protocol Annex 1 (US based patients) or Protocol Annex 2 (Poland based patients) for the remaining visit schedule.**	**Reference to OLE year 2 added**
Section 9.1.2.10 Visit B10 (Day 365, End of Treatment/ Withdrawal Visit) p. 81-82	(NB. Not applicable-new text added)	(…) **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).**	**Reference to OLE year 2 added**

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<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Section 9.2.9, Clinical Laboratory Sampling
p. 87</td><td>(...)
Table 9.2.9-1 Biochemistry, Hematology, Urinalysis and THC Screen
<table><tr><td>Biochemistry (Serum)[1]</td><td>Hematology (Whole Blood)[1]</td><td>(...)</td></tr><tr><td>Alanine aminotransferase (ALT)</td><td>(...)</td><td>(...)</td></tr><tr><td>(...)</td><td>(...)</td><td>(...)</td></tr><tr><td><s>Insulin-like growth factor-1 (IGF-1)</s></td><td></td><td></td></tr><tr><td>(...)</td><td></td><td></td></tr></table>[1]Analyzed at a central laboratory. (...)</td><td>(...)
Table 9.2.9-1 Biochemistry, Hematology, Urinalysis and THC Screen
<table><tr><td>Biochemistry (Serum)[1]</td><td><u>Biochemistry (Serum)[1, 3]</u></td><td>Hematology (Whole Blood)[1]</td><td>(...)</td></tr><tr><td>Alanine aminotransferase (ALT)</td><td><u>Insulin-like growth factor-1 (IGF-1)</u></td><td>(...)</td><td></td></tr><tr><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td></tr></table>[1]Analyzed at a central laboratory.
(...)
<u>[3]Only analyzed at Visits 3, 10/B1, B6 and B10).</u></td><td>Amended for clarity</td></tr>
<tr><td>Section 9.2.9.1 Pharmacokinetic Blood Sampling
p. 88-89</td><td>There must be a minimum period of at least two hours between each of the three 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.
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.</td><td>There must be a minimum period of at least two hours between each of the three 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.
<u>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).</u>
Analysis of all pharmacokinetic samples will be conducted at a central clinical laboratory. Sample volume requirements and processing procedures</td><td>Text added to allow assessment of relationship between food intake and PK</td></tr>
</table>

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Section 9.2.9.1 Pharmacokinetic Blood Sampling p. 88-89 (continued)		will also be detailed in a separate laboratory manual.	
Section 10, WITHDRAWAL p. 101–102	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. (...) • ALT or AST > 3 × ULN **and** (TBL* > 2 × ULN **or** INR > 1.5) **~~(*TBL > 2 × ULN)~~** (...) Patients may also be withdrawn from the study for any of the following: (...) • General anesthesia (Blinded Phase only). Should a patient request or decide to withdraw from the study, all efforts must be made to complete **~~and report the observations~~** as thoroughly as possible up to the date of withdrawal.	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. (...) • ALT or AST > 3 × ULN **and** (TBL* > 2 × ULN **or** INR > 1.5)**.** (...) Patients may also be withdrawn from the study for any of the following: (...) • 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.	**New criteria added to provide additional guidance to investigators**

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Section 13.6, Endpoints and Statistical Methods p. 114-115 Section 13.6,	**Blinded Phase:** Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. **~~Since there is a single primary analysis endpoint, no formal adjustment of statistical significance for multiple testing on multiple endpoints is required, although such multiplicity should be allowed for when interpreting the results for secondary endpoints. However, there are three treatments, so multiple significance testing will occur when making comparisons between the treatments. To control the type I error, a step-up Hochberg's procedure will be used for the primary endpoint. If both of the observed p-values from the 25 mg/kg/day and 50 mg/kg/day GWP42003-P comparisons with placebo are < 0.050 in favor of the GWP42003-P treatment groups, then both groups would be declared statistically significantly better than placebo. However, if the observed p-value is ≥ 0.050 for one GWP42003-P treatment group but < 0.025 in favor of the other GWP42003-P treatment group, then only the latter GWP42003-~~**	**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 3. 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 3 Hierarchy for Analysis**	**Amended to reflect the re-classification of secondary endpoints**

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<tr><td>Endpoints and Statistical Methods
p. 114-115
(continued)

Section 13.6, Endpoints and</td><td><s>P treatment group will be declared statistically significantly better than placebo.</s>

<s>The secondary endpoints will be tested hierarchically, starting with key secondary endpoint followed by all other secondary endpoints. No multiplicity adjustments will be made for all other secondary endpoints.</s></td><td>
<table>
<tr><th>Test</th><th>Endpoint</th><th>Treatment Comparison</th></tr>
<tr><td>1</td><td>Change from baseline in number of TSC-associated seizures</td><td>25 mg/kg/day GWP42003-P vs. Placebo</td></tr>
<tr><td>2</td><td>50% responder analysis</td><td>25 mg/kg/day GWP42003-P vs. Placebo</td></tr>
<tr><td>3</td><td>Change in CGIC/SGIC</td><td>25 mg/kg/day GWP42003-P vs. Placebo</td></tr>
<tr><td>4</td><td>Change from baseline in total seizures</td><td>25 mg/kg/day GWP42003-P vs. Placebo</td></tr>
<tr><td>5</td><td>Change from baseline in number of TSC-associated seizures</td><td>50 mg/kg/day GWP42003-P vs. Placebo</td></tr>
<tr><td>6</td><td>50% responder analysis</td><td>50 mg/kg/day GWP42003-P vs.</td></tr>
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</table>

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol V4 Date 05 Dec 16 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 4 (Clinical Protocol Version 5, Date 27 June 2017) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Statistical Methods p. 114-115 (continued)		<table><tr><td></td><td></td><td>Placebo</td></tr><tr><td>7</td><td>Change in CGIC/SGIC</td><td>50 mg/kg/day GWP42003-P vs. Placebo</td></tr><tr><td>8</td><td>Change from baseline in total seizures</td><td>50 mg/kg/day GWP42003-P vs. Placebo</td></tr></table>	
Section 13.6.2 Primary Endpoint(s) Blinded Phase p. 116 Section 13.6.2 Primary Endpoint(s)	Data will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference between each GWP42003-P group and placebo, together with approximate 95% confidence intervals (CI), will be calculated using the Hodges-Lehmann approach. ~~**A step up Hochberg's procedure will be used to control**~~ the Type I error ~~**as per**~~ Section 13.6. If a patient withdraws from the study, then the primary analysis variable will be calculated from the available data, during the treatment period, prior to the patient withdrawing.	Data will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference between each GWP42003-P group and placebo, together with approximate 95% confidence intervals (CI), will be calculated using the Hodges-Lehmann approach. **The hypothesis testing approach for controlling** the Type I error **is described in** Section 13.6 **and Table 3.** 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.	**Amended to reflect the re-classification of secondary endpoints**

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol V4 Date 05 Dec 16 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 4 (Clinical Protocol Version 5, Date 27 June 2017) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Blinded Phase p. 116 (continued)			
Section 13.6.3 Secondary Endpoint(s) p. 118-121 Section 13.6.3 Secondary Endpoint(s)	**Antiepileptic Efficacy Measures:** Key: • Number of patients considered treatment responders defined as those with a ≥ 50% reduction in seizure frequency (blinded phase only). 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 total seizures.**~~ • ~~**Change in focal composite seizure score (frequency x severity).**~~ • Change in number of seizure-free days. • ~~**Change in number of seizures by subtype.**~~ • Change in number of 'other' seizures (absence,	**Antiepileptic Efficacy Measures:** Key: • Number of patients considered treatment responders defined as those with a ≥ 50% reduction in seizure frequency (blinded phase only). • <u>**Change in CGIC or SGIC score.**</u> • <u>**Change in total seizures.**</u> <u>**The hypothesis testing approach for controlling the Type I error for these endpoints are described in Section 13.6 and Table 3.**</u> 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.	**Amended to reflect the re-classification of secondary endpoints**

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol V4 Date 05 Dec 16 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 4 (Clinical Protocol Version 5, Date 27 June 2017) *(Revised wording is underscored and in bold)*	Rationale for the amendment
p. 118-121 (continued) Section 13.6.3 Secondary Endpoint(s) p. 118-121	myoclonic, focal sensory and infantile/epileptic spasms). • **~~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 SGIC-SD or the CGIC-SD.~~** **~~TAND:~~** **~~Cognitive and Behavioral Function:~~** • **~~Changes in Vineland-II.~~** • **~~Changes in Wechsler Scales (pre-school, primary, children, adult).~~** • **~~Changes in CBCL and ABCL.~~** **~~Autistic Features:~~** • **~~Change in SCQ score.~~** **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 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. • **~~Changes in CGIC or SGIC score.~~** • Change in PGIC score. (…) **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**	

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol V4 Date 05 Dec 16 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 4 (Clinical Protocol Version 5, Date 27 June 2017) *(Revised wording is underscored and in bold)*	Rationale for the amendment
(continued) Section 13.6.3 Secondary Endpoint(s) p. 118-121 (continued)	~~• **Changes in CGIC or SGIC score.**~~ • Change in PGIC score. (…)	**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.**	

<table>
<tr><th>Revised Protocol Section Number, Heading and Page Number</th><th>Original Wording from Clinical Protocol V4 Date 05 Dec 16
(Deleted wording is struck through and in bold)</th><th>Revised Wording from Clinical Protocol Amendment 4
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(Revised wording is underscored and in bold)</th><th>Rationale for the amendment</th></tr>
<tr><td>Section 17, References
p. 135</td><td>[51] Investigator Brochure - CBD Medicine. GW Pharma Ltd. Edition 8. September <s>2015</s>.</td><td>[51] Investigator Brochure - CBD Medicine. GW Pharma Ltd, Edition <u>9</u>. September <u>2016</u>.</td><td>Amended to reflect the updated IB</td></tr>
<tr><td>APPENDIX 1, SCHEDULE OF ASSESSMENTS
p. 137–139</td><td>Blinded Phase
<table>
<tr><td>Visit Number</td><td>(...)</td><td>3</td><td>(...)</td><td>10</td><td>(...)</td></tr>
<tr><td>(...)</td><td>(...)</td><td></td><td>(...)</td><td></td><td></td></tr>
<tr><td>Clinical laboratory blood sampling</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td></tr>
<tr><td>Clinical laboratory urine sampling (dipstick urinalysis)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td></tr>
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<tr><td>Tanner Staging (where appropriate) <s>and IGF-1 testing</s></td><td></td><td>X</td><td></td><td>X</td><td></td></tr>
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</table></td><td>Amended for consistency</td></tr>
<tr><td>APPENDIX 1, SCHEDULE OF ASSESSMENTS
p. 140–142</td><td>Open-label Extension
<table>
<tr><td>Visit Number</td><td>B1</td><td>(...)</td><td>B6</td><td>(...)</td><td>End of Treatment B10</td><td>(...)</td></tr>
<tr><td>(...)</td><td>(...)</td><td></td><td>(...)</td><td></td><td></td><td>(</td></tr>
</table></td><td>Open-label Extension
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APPENDIX 1, SCHEDULE OF ASSESSMENTS p. 140–142 (continued)	<table><tr><td></td><td></td><td></td><td></td><td></td><td></td><td>...)</td></tr><tr><td>Clinical laboratory blood sampling</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td></td></tr><tr><td>Clinical laboratory urine sampling (dipstick urinalysis)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td></td></tr><tr><td>Tanner Staging (where appropriate) ~~and IGF-1 testing~~</td><td>X</td><td></td><td></td><td></td><td>X</td><td></td></tr><tr><td>(...)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	<table><tr><td></td><td></td><td></td><td></td><td></td><td></td><td>...)</td></tr><tr><td>Clinical laboratory blood sampling</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td></td></tr><tr><td><u>Clinical laboratory IGF-1 testing</u></td><td><u>X</u></td><td></td><td><u>X</u></td><td></td><td><u>X</u></td><td></td></tr><tr><td>Clinical laboratory urine sampling (dipstick urinalysis)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td><td></td></tr><tr><td>(...)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Tanner Staging (where appropriate)</td><td>X</td><td></td><td></td><td></td><td>X</td><td></td></tr><tr><td>(...)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	

5 REFERENCES

Not Applicable.

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 3

to be incorporated into the Protocol, creating CLINICAL PROTOCOL V4 05Dec16

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Confidentiality Statement

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.
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.
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 1:1:1 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 either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients in the placebo group will be split into two equivalent cohorts; half receiving 25 mg/kg/day dosing volumes and half receiving 50 mg/kg/day dosing volumes. 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. 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 open label extension 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 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.

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Table of Contents

List of Appendices

2 RATIONALE

This Clinical Protocol Amendment 3 (will be incorporated into the Protocol creating Clinical Protocol V4 05Dec16) addresses the following issue(s):

2.1 Exclusion and Withdrawal Criteria

- The exclusion criterion wording in section 6 of the protocol pertaining to liver enzyme monitoring has been updated to not repeat two conflicting exclusions.
- The withdrawal criteria wording in section 10 of the protocol pertaining to liver enzyme monitoring now stipulates that patients with "Serum ALT or AST ≥ 3 × ULN **and** (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5)" should be withdrawn from the trial. This amendment brings the protocol back in line with the current FDA guidance on liver enzyme related withdrawal criteria.

2.2 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol:

- Minor corrections made throughout – see table below and tracked changes
- Updated wording for the Clinical Hypothesis
- Additional wording regarding the different colored labels on the double-blind and open-label IMP
- Further clarification of the mechanism for simultaneous tapering down blinded IMP and titrating up OLE IMP.
- Deletion of the Tanner staging examination at Visit B6
- Addition of Creatine Kinase to the laboratory assessments

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol V4 05Dec16. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Version 3 Date 25 Aug 2015** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol V4 05Dec16)** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 1 Protocol Synopsis p. 12 (Summary of Patient Eligibility Criteria)	• 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). • ~~**Serum ALT or AST ≥ 3 x ULN or**~~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%).	• 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*	**Previous wording was contradictory.**

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 3 Date 25 Aug 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol V4 05Dec16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	This criterion can only be confirmed once the laboratory results are available.	*the laboratory results are available.*	
Section 1 Protocol Synopsis p. 13 (Criteria for Withdrawal)	• ALT or AST > 3 × ULN ~~**or**~~ (TBL* > 2 × ULN **or** INR > 1.5). (*TBL > 2 × ULN exclusion will not apply for patients diagnosed with Gilbert's disease).	• ALT or AST > 3 × ULN **and** (TBL* > 2 × ULN **or** INR > 1.5). (*TBL > 2 × ULN exclusion will not apply for patients diagnosed with Gilbert's disease).	**Wording amended to reflect the FDA DILI guidelines accurately**
Definition of Terms p. 37	Baseline The 28-day (~~±~~3 days) period from screening to randomization	Baseline The 28-day (±3 days) period from screening to randomization	**Error, there is no -3 day window for this visit**
Section 3.4 Clinical Hypothesis p. 45-46	The primary clinical hypothesis is that there will be a difference between ~~**50 mg/kg/day GWP42003-P and placebo in their effect on mean focal seizure frequency as measured by analysis of covariance (ANCOVA). The mean treatment difference would need to be at least 35% in order to achieve a clinically relevant decrease in focal seizure**~~	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.**	**More concise**

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 3 Date 25 Aug 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol V4 05Dec16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	~~**frequency**~~[50]**.**		
Section 5.3.1 Packaging and Labeling p. 55		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.	**Additional text added for clarity**
Section 6.2 Exclusion Criteria p. 59	• 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). • ~~**Serum ALT or AST ≥ 3 x ULN or**~~TBL* [serum total bilirubin] ≥ 2 × ULN **or** international normalized ratio [INR] > 1.5 (*TBL ≥ 2 × ULN exclusion will not apply	• 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	**Previous wording was contradictory.**

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 3 Date 25 Aug 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol V4 05Dec16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	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.*	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.*	
Section 8.1.2 Dose Escalation and Dose Adjustments p. 64-66		**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** (see amended figures and tables, page 26) **Following completion of the blinded transition patients may complete a three-week titration up to a**	**Additional text added to clarify how the transition between the double-blind phase and the Open-label phase works**

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		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** (see amended figures and tables, page 26)	
Section 9.1.2.7 Visit B6 (Day 183) p. 80	The following observations will be made at Visit B6: concomitant medications, (including AEDs), physical examination (including height and body weight), **~~Tanner Staging (for patient aged 10-17 yeas [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.	The following observations will be made at Visit B6: concomitant medications, (including AEDs), physical examination (including height and body weight), details of menstruation (for females), ECG, vital signs, epilepsy-related hospitalizations and AEs.	**Error, this assessment is not done at Visit B6**

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 3 Date 25 Aug 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 3 (Clinical Protocol V4 05Dec16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 9.2.9 Clinical Laboratory Sampling Table 9.2.9-1 Biochemistry, Hematology, Urinalysis and THC Screen p. 88		**Creatine Kinase (CK)**	**CK has been added to the battery of serum biochemistry tests**
Section 10 Withdrawal p. 102	• ALT or AST > 3 × ULN **~~or~~** (TBL* > 2 × ULN **or** INR > 1.5) (*TBL > 2 × ULN **~~exclusions will not apply for patients diagnosed with Gilbert's disease~~**)	• ALT or AST > 3 × ULN **and** (TBL* > 2 × ULN **or** INR > 1.5) (*TBL > 2 × ULN)	**Wording amended to reflect the FDA DILI guidelines accurately**
Section 12.8 Potential Cases of Drug-induced Liver Injury p. 110	• ALT or AST > 3 × ULN **~~or~~** (TBL* > 2 × ULN **or** INR > 1.5) (*TBL > 2 × ULN **~~exclusions will not apply for patients diagnosed with Gilbert's disease~~**)	• ALT or AST > 3 × ULN **and** (TBL* > 2 × ULN **or** INR > 1.5) (*TBL > 2 × ULN)	**Wording amended to reflect the FDA DILI guidelines accurately**

5 REFERENCES

Not Applicable.

APPENDIX 1 AMENDED FIGURES AND TABLES

Amended Figure from Clinical Protocol V4 05Dec16

(Deleted wording is struck through and in bold; amended wording is underlined and in bold)

Table 8.1.2-2

Table 8.1.2-2 Blinded Transition						
	Patients randomised to 25 mg/kg/day group		Patients randomised to 50 mg/kg/day group		Patients randomised to placebo group	
Day Blinded Transition/OLE	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

Table 8.1.2 – 3 OLE Titration Schedule

OLE Day	Blinded Dose (mg/kg/day)
15 (Visit B2)	26.25
16	27.5
17	30
18	30
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

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 2

to be incorporated into the Protocol, creating CLINICAL PROTOCOL V3 25Aug16

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Confidentiality Statement

1 PROTOCOL SYNOPSIS

Trial 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.
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.
Trial 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 1:1:1 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 either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients in the placebo group will be split into two equivalent cohorts; half receiving 25 mg/kg/day dosing volumes and half receiving 50 mg/kg/day dosing volumes. 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. 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 open label extension 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 OLE treatment 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.

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2 RATIONALE

This Clinical Protocol Amendment 2 (will be incorporated into the Protocol creating Clinical Protocol V3 25Aug16) addresses the following issue(s):**Duration of Open-label Extension Phase**

The open-label extension (OLE) phase of the trial will last for a maximum of 1 year in all cases as GWP42003-P will continue to be supplied irrespective of marketing authorization.

2.2 Change to Frequency of Assessment Measures

- In order to reduce the overall burden of the study, the frequency of assessments (QOLCE/QOLIE-31P, PGIC, SGIC/CGIC, Weschler Tests, CBCL/ABCL, SCQ and the Vineland II) have been reduced.
- The Physician Global Impression of Change (PGIC) scale has now been described, which was omitted in the original protocol.

2.3 Change to Statistical Considerations

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.

- The primary analysis has been updated from an analysis of covariance to a Wilcoxon rank-sum test and the assumptions for this test require more patients. The target sample size has therefore increased to 210.
- A modified description has been included to describe how type I error will be controlled. Equal standing is to be given to 25 mg and 50 mg groups. An adjusted p value for significance ($p<0.025$) will be required if one of the comparisons is >0.05.

2.4 Pharmacokinetics Analysis

The timings for the PK blood samplings have been changed to try to capture the C_{max} time point within the time/concentration curve. In addition, the description of the pharmacokinetic parameters that will be described has been changed to better reflect the low number of blood samples that are likely to be available.

THC will no longer be included, since the PK parameters of this minor constituent of GWP42003-P have been investigated thoroughly in previous GW sponsored studies.

2.5 Withdrawal Criteria

The "Did not meet eligibility criteria" bullet has been moved from must to may be withdrawn from the study, providing clarification that once a patient has been enrolled onto the study, they are in the intention to treat group and will stay in the study unless there is a safety concern.

2.6 Endpoint Definitions

The primary and secondary endpoints have been more clearly defined:

- Confirmation that the primary endpoint is focused on TSC-associated seizures.
- Confirmation that secondary endpoints are divided into "Key" and "other" and clarity in their definitions.
- Confirmation that change in total seizures will be included in the other secondary endpoints.

2.7 Concomitant Medications

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. Therefore, the following clarifications have been made for management of possible drug-drug interactions:

- For entry to the study, if patients are taking felbamate then they must have been taking it for at least one year.
- Management of possible interactions must be on emerging clinical symptoms with discussion with the GW medical advisor.
- Care should be taken with drugs, or their metabolite, that are cytochrome P450 (CYP) 2C19 substrates or those solely or primarily metabolized by UDP-glucuronosyltransferase 1A9 and 2B7.

2.8 THC screening

A THC test is carried out at screening to assess eligibility for the study. It will no longer be used as a measure of study compliance, since:

- The urine THC test may cross-react with other (i.e., non-THC) cannabinoids meaning it could yield 'false positive' results in patients receiving CBD and therefore would not provide any useable study information.

- THC serum test has been added in, since this was always supposed to be included but was omitted in error from the original protocol.

2.9 Changes requested by the Medicines and Healthcare Products Regulatory Agency

In response to a number comments from the Medicines and Healthcare Products Regulatory Agency, the following changes have been included within this amendment:

- Amend the wording included in the exclusion and withdrawal criteria involving liver enzyme monitoring to stipulate that patients with "Serum ALT or AST ≥ 3 × ULN **or** (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5)"should be excluded from the trial and that patients with "ALT or AST > 3 × ULN **or** (TBL* > 2 × ULN or INR > 1.5)" should be withdrawn from the trial.
- For patients with Gilbert's disease, a raised TBL would be considered normal and not a cause of exclusion or withdrawal unless ALT or AST were also elevated.
- In the UK, in order to demonstrate safety before exposing the younger patients to treatment, enrolment 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.
- Monthly pregnancy tests will be included.

2.10 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol:

- Aligning language in the exclusion and withdrawal criteria to that of other protocols, taking into account recommendations from the FDA.
- Wording has been added to cover countries where local law requires controlled drugs to be dispensed for a maximum of 28 days. This is to ensure this is covered if the study is introduced to countries where this is the legislation.
- The physical description of the IMP has been updated to 'clear, colorless to yellow'.

- In the OLE phase, all scheduled visits are clarified and amended to be represented in days or weeks as per the interactive voice response system (IVRS) diary.
- Clarification of safety telephone calls to take place during OLE titration.
- Clarification that if a safety telephone call falls at a weekend then the call may be scheduled for the Friday before or the Monday after the weekend instead. This prevents the need for center staff and patients to be available for such calls at the weekend.
- Clarification of the mechanism for simultaneous taper down of blinded IMP and titration of OLE IMP.
- Clarification that a well-documented clinical history of epilepsy is sufficient without the requirement for an EEG, since EEG recordings do not always reflect the patient's seizures.
- Clarification of the definition of history of suicidal behavior or suicidal ideation.
- Clarification that any recreational or medicinal cannabis use or any other IMP are prohibited during the study, since they may confound the interpretation of study results.
- Clarification that the patient and/or their caregiver will receive training in seizure type identification.
- Clarification of bullet points and subheading in Section 4.1.2.
- Since a separate consent form is signed by the patient to allow genetic testing, the wording within the Visit 1 (screening) visit has been amended.
- Updated information on safety from the Expanded Access IND Program and clarification of the rationale for the 25 to 50 mg/kg doses within this study.
- Update on projected number of centers based on current data.
- Correction of reference to randomization visit as Visit 3.
- Clarification that patient number is only assigned at Visit 1.
- Clarification of SAE reporting in the Netherlands.
- In Section 9.1.1.3, description of when PK samples will be taken has been cross-referenced to Section 9.2.9.1 for brevity.

- Clarification of visits at which IMP should be returned and clarification of use of dose calculator.
- All visits (assessment and resupply) are now described in detail for clarity.
- Clarification of GW's expectation of *status epilepticus* reporting.
- Changes to enable more flexibility in the timing of IVRS diary calls during the period from completion/withdrawal to follow up.
- Text relating to TSC1 and TSC2 genetic screening has been moved from 9.2.4 to 9.2.9.3.
- Clarification that vital signs includes blood pressure since there is a different definition for vital signs between the US and Europe.
- Amend partial sensory seizures to focal sensory seizures to reflect accepted seizure nomenclature.
- Section numbering amended due to the addition and deletion of sections.
- Deletion of near duplicated text in sections 1, 4.1.2, 9.1.1.3, 9.1.2.2 and 9.2.12.
- Amending text to ensure that the synopsis and main body language align.
- References renumbered sequentially after number 52.
- Minor changes to the text relating to improved brevity.
- Removal of exact numbers of studies from EAP information, as these change frequently.
- Minor spelling/grammatical corrections have been made to improve consistency but these are not captured within this amendment document.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol V3 25Aug16. It will be kept in the trial master file at GW as well as in each investigational center file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 3	(...) • To evaluate the safety and tolerability of GWP42003-P compared with placebo. • To determine the pharmacokinetics (PK) of CBD, ~~**Δ9-Tetrahydrocannabinol (THC)**~~ and ~~**their**~~ major metabolites following single and multiple doses of GWP42003-P.	(...) • To evaluate the safety and tolerability of GWP42003-P compared with placebo. • To determine the pharmacokinetics (PK) of CBD, and **its** major metabolites following single and multiple doses of GWP42003-P.	See Section 2.4
Section 1 Protocol Synopsis p. 4	(...) 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.	(...) 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.**	See Section 2.10

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 5	(...) 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. ~~**Doses will be titrated up or down, as appropriate, to ensure a**~~ll patients will enter the OLE taking 25 mg/kg/day GWP42003-P: (...) Safety telephone calls will be completed every two days throughout the open label extension transition. (...) The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. (...) Safety telephone calls will be completed every two days throughout the OLE titration and one week after the end of titration.	(...) 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: (...) Safety telephone calls will be completed every two days throughout the open label extension 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.** (...) The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. **The OLE period will last for a maximum of 1 year.** (...) 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**	See Section 2.10 See Section 2.10 See Section 2.1 See Section 2.10

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 5 (Continued)	(...) ~~**If market authorization is granted for GWP42003-P in TSC, the patient will complete the study. Patients who do not immediately continue to use GWP42003-P will then commence a taper period (tapering 10% per day for 10 days).**~~	**permitted to schedule the call for the Friday before or Monday after the weekend instead.** (...)	See Section 2.1
Section 1 Protocol Synopsis p. 6	(...) The primary endpoint is the percentage change from baseline in number of seizures* (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo. *Primary endpoint 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.	(...) The primary endpoint is the percentage change from baseline in number of **TSC-associated** seizures* (average per 28 days) during the treatment period (maintenance and titration) 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.	See Section 2.10

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 6 (Continued)	(...) *~~**S**~~eizures 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. (...)	(...) ***TSC-associated s**eizures 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. **Key:** • **Number of patients considered treatment responders defined as those with a ≥50% reduction in seizure frequency (blinded phase only).** **Other:**	See Section 2.10
	• Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in seizure* frequency. • Number of patients experiencing a >25%	• 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%	See Section 2.10 See Section 2.10

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 6-7 (Continued)	worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in seizure* frequency. • Change in composite focal seizure score (frequency × severity). • Change in number of seizure*-free days. (...) • Change in number of 'other' seizures (absence, myoclonic, **~~partial~~** sensory and infantile/epileptic spasms). • **~~Change in number of infantile/epileptic spasms.~~**	improvement, 50–75% improvement or >75% improvement in **TSC-associated** seizure* frequency. • **Change in total seizures.** • Change in composite focal seizure score (frequency × severity). • Change in number of **TSC-associated** seizure*-free days. (...) • Change in number of 'other' seizures (absence, myoclonic, **focal** sensory and infantile/epileptic spasms). (...)	See Section 2.10
Section 1 Protocol Synopsis p. 8	(...) • **~~The plasma concentration/time curve of CBD, THC and their major metabolites will~~**	(...) • **The plasma concentrations will be summarized by time window for CBD and its**	See Section 2.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 8 (Continued)	~~**be described following single and multiple doses of GWP42003-P, with the aim being to estimate:**~~ ~~• **Peak plasma concentration (Cmax).**~~ ~~• **Time to peak concentration (tmax).**~~ ~~• **Area under the plasma concentration curve from time zero to infinity (AUC(0-∞)).**~~ ~~• **Terminal half-life (t½).**~~ (...) Antiepileptic Efficacy Measures:* ~~**S**~~eizures 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. • Percentage change in number of seizures* (average per 28 days). • Number of patients considered treatment	**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.** (...) 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. • Percentage change in number of **TSC-associated** seizures* (average per 28 days).	SeeSection 2.6 See Section 2.6

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 8 (Continued)	responders defined as those with a ≥25%, ≥50%, ≥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 composite focal seizure score (frequency × severity). • Change in number of seizure*-free days. • Change in number of seizures by subtype. • Change in number of 'other' seizures (absence, myoclonic, **~~partial~~** sensory and infantile/epileptic spasms). • **~~Change in number of infantile/epileptic spasms .~~**	• 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 total seizures** • Change in composite focal seizure score (frequency × severity). • Change in number of **TSC-associated** seizure*-free days. • Change in number of seizures by subtype. • Change in number of 'other' seizures (absence, myoclonic, **focal** sensory and infantile/epileptic spasms).	See Section 2.6 See Section 2.6 See Section 2.10

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 Protocol Synopsis p. 9-10	A total of ~~**192**~~ patients will be targeted to be enrolled. The ~~**192**~~ patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, ~~**64**~~ patients per group). Patients in the placebo group will be split into two cohorts (~~**32**~~ patients receiving 25 mg/kg/day dosing volumes and ~~**32**~~ patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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) this sample size of ~~**64**~~ patients per group will be sufficient to detect a difference ~~**of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in seizures)**~~. This is based on a standard deviation of 60%, using a two-sided 5% significance level and 90% power.	A total of **210** patients will be targeted to be enrolled. The **210** patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **70** patients per group). Patients in the placebo group will be split into two cohorts (**35** patients receiving 25 mg/kg/day dosing volumes and **35** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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.	See Section 2.3 See Section 2.3
Section 1	(...)	(...)	

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Protocol Synopsis p. 10	• Well-documented history of epilepsy**~~, with compatible electroencephalogram (EEG) and clinical history~~**.	• Well-documented **clinical** history of epilepsy.	See Section 2.10
Section 1 Protocol Synopsis p. 11	(...) • Patient **~~is~~** taking felbamate**~~, and they have been taking it~~** for less than one year prior to screening. (...) • **~~Active suicidal plan/intent in the past six months, or a history of suicide attempt in the last two years, or more than one lifetime suicide attempt.~~** • **~~C-SSRS grade 4 or 5 at screening.~~**	(...) • Patient has been taking felbamate for less than one year prior to screening. (...) • **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**.	See Section 2.7 See Section 2.10
Section 1 Protocol Synopsis p. 12	(...) – Serum ALT or AST ≥ 3 × ULN **~~and~~** (TBL [serum total bilirubin] ≥ 2 × ULN **or** international normalized ratio [INR] > 1.5).	(...) – Serum ALT or AST ≥ 3 × ULN **or** (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)**.	See Section 2.9

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	(...) • Patient has received an IMP within **~~the~~** 12 weeks prior to the screening visit.	(...) • Patient has received an IMP **as part of a clinical trial less than** 12 weeks prior to the screening visit.	See Section 2.10
Section 1 Protocol Synopsis p. 13 **Section 1 Protocol Synopsis p. 13 (Continued)**	(...) • **~~Patient has travel outside the country of residence planned during the study.~~**	(...) • **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.**	See Section 2.10
Section 1 Protocol Synopsis p. 13	(...) The patient must be withdrawn from the study if any of the following apply: • Administrative decision by the Investigator, GW or Regulatory Authority. • **~~Did not meet eligibility criteria.~~** • Pregnancy (...)	(...) The patient must be withdrawn from the study if any of the following apply: • Administrative decision by the Investigator, GW or Regulatory Authority. • Pregnancy (...)	See Section 2.10

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Section 1 Protocol Synopsis p. 13 (Continued)	• ALT or AST > 3 × ULN **~~and~~** (TBL > 2 × ULN **or** INR > 1.5). • Lost to follow-up. (...)	• ALT or AST > 3 × ULN **or** (TBL* > 2 × ULN **or** INR > 1.5). **(*TBL > 2 × ULN exclusion will not apply for patients diagnosed with Gilbert's disease)**. • 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.*** (...)	See Section 2.9 See Section 2.10
Section 1 Protocol Synopsis p. 13	The patient may also be withdrawn from the study for any of the following: • Patient non-compliance.	(...) The patient may also be withdrawn from the study for	See Section 2.10

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		any of the following: • **Did not meet eligibility criteria.** • Patient non-compliance.	
Section 1 Protocol Synopsis p. 15	(...) **~~Doses will be titrated up or down, as appropriate to ensure all patients enter the OLE taking 25 mg/kg/day:~~** (...)	(...) **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:** (...) **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.**	See Section 2.10 See Section 2.9
Section 1 Protocol Synopsis p. 15	(...) o Urine THC screen	(...) o Urine**/serum** THC screen	See Section 2.8
Section 1	(...)	(...)	

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Protocol Synopsis p. 16-17	• Tanner Staging (where appropriate) • ECG (including baseline and +4 hours after first dose) (...) ○ PK	• Tanner Staging (where appropriate) • **Details of menstruation (for females)** • ECG (including baseline and +4 hours after first dose) (...) ○ PK **(patients > 20 kg only)**	See Section 2.10 See Section 2.4
Section 1 Protocol Synopsis p. 17-18	o Urinalysis **o ~~Urine THC screen~~** o Serum pregnancy test (if applicable) (...) Additional safety telephone calls will be completed every two days during titration and one week after the end of titration. (...) • Tanner Staging, where appropriate (Visits **~~3~~** and **~~9~~**) (...)	o Urinalysis o Serum pregnancy test (if applicable) (...) 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.** (...) • Tanner Staging, where appropriate (Visit **10**) • **Details of menstruation (for females)**	See Section 2.8 See Section 2.10 See Section 2.2 See Section 2.10

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Section 1 Protocol Synopsis p. 17-18 (Continued)	• Vital signs (...) • Vineland-II (Visit~~s 3 and~~ 10) • Wechsler Tests (Visit~~s 3 and~~ 10) • CBCL or ABCL (Visit~~s 3 and~~ 10) • SCQ (Visit~~s 3 and~~ 10) • QOLCE or QOLIE-31-P (Visit~~s 3 and~~ 10) • CGIC or SGIC • PGIC (...) o Urinalysis o Serum pregnancy test (if applicable) (...) o PK (Visit~~s 3~~ and 10)	**(Visit 10)** (...) • Vital signs • **Postural BP (Visit 5)** (...) • 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)** (...) o Urinalysis o Serum pregnancy test (**Visit 5, 7, 9 and 10**, if applicable) (...) o PK (Visit 10)	See Section 2.2 See Section 2.9 See Section 2.10

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	(...)	(...)	
Section 1 Protocol Synopsis p. 18	Blood sample collection for PK analysis of CBD**~~, THC~~** and **~~their~~** major metabolites will be taken at the following time points: • Visit 3 (Randomization) - Pre-IMP-dose, **~~4–5~~** hours post-dose, **~~6–7~~** hours post-dose and 8–10 hours post-dose (patients 18 years and above only). • Visit 10 (End of Treatment) - Pre-IMP-dose, **~~4–5~~** hours post dose, **~~6–7~~** hours post-dose and 8–10 hours post-dose (patients 18 years and above only).	Blood sample collection for PK analysis of CBD, and **its** major metabolites will be taken at the following time points: • Visit 3 (Randomization) - Pre-IMP-dose, **2-3** hours post-dose, **4-6** hours post-dose and 8–10 hours post-dose (patients 18 years and above only). • Visit 10 (End of Treatment) - Pre-IMP-dose, **2-3** hours post dose, **4-6** hours post-dose and 8–10 hours post-dose (patients 18 years and above only).	See Section 2.4 See Section 2.4 See Section 2.4
Section 1 Protocol Synopsis p. 18 (Continued)			
Section 1 Protocol Synopsis p. 19	(...) OLE visits will occur on Day 15, Day 36, Day 92 and then every **~~three months~~** up to **~~one~~** year**~~, then every six months thereafter until the end of treatment~~**. (...)	(...) **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.	See Section 2.10 See Section 2.1

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Section 1 Protocol Synopsis p. 19 (Continued)		(...) **In countries where controlled drugs can only be dispensed for a maximum of 28 days, the visit schedule in the OLE period will include additional visits or expanded visit windows for patients seen in those countries.**	See Section 2.10
	(...) The following assessments will be completed at visits during the OLE (full listing by visit included in Section 9.1.2): • Concomitant medication review (including AEDs) • AE review • Physical examination • Tanner Staging, where appropriate (Visit ~~**B4 and subsequent Assessment Visits**~~) • ECG	(...) 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**)	See Section 2.10

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Section 1 Protocol Synopsis p. 19-20 (Continued)	• Vital signs
	• C-SSRS or Children's C-SSRS, where applicable
	• 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
	  ○ Serum pregnancy test (if applicable)
	  ○ Serum IGF-1
		• ECG
		• Vital signs
		• C-SSRS or Children's C-SSRS, where applicable
		• 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
			See Section 2.2 and Section 2.10
			
			See Section 2.10

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Section 1 Protocol Synopsis p. 19-20 (Continued)	○ ~~**AED concentrations**~~ • Review of patient diary • IMP dispensing, collection and compliance review (...)	○ Serum pregnancy test **(Visits B4,B6, B8 and B10, if applicable)** ○ Serum IGF-1 **(Visit 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.**	See Section 2.10
Section 1 Protocol Synopsis p. 20-21	(...) 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. ~~**The primary comparison of interest is 50 mg/kg/day GWP42003-P vs. placebo, but the dose-response relationship between the 25 mg/kg/day and 50-mg/kg/day doses of GWP42003-P and placebo will also be explored.**~~	(...) 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. **To control the type I error, a step-up Hochberg's procedure will be used for the primary endpoint. If both of the observed p-values from the 25 mg/kg/day and 50 mg/kg/day GWP42003-P comparisons with placebo are < 0.050 in favor of the GWP42003-P**	See Section 2.3

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Section 1 Protocol Synopsis p. 20-21 (Continued)	All statistical tests will be two-tailed and carried out at the 5% level of significance.	**treatment groups, then both groups would be declared statistically significantly better than placebo. However, if the observed p-value is ≥ 0.050 for one GWP42003-P treatment group but < 0.025 in favor of the other GWP42003-P treatment group, then only the latter GWP42003-P treatment group will be declared statistically significantly better than placebo.** **The secondary endpoints will be tested hierarchically, starting with the key secondary endpoint followed by all other 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.	See Section 2.3
Section 1 Protocol Synopsis Figure 1.1: Study Design and	< See APPENDIX 1 for changes made to the figure > (...) # Safety telephone calls must be completed every two days during titration and one week after the end of	< See APPENDIX 1 for changes made to the figure > (...) # Safety telephone calls must be completed every two days during titration and one week after the end of	See Section 2.10

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Treatment Schema: Blinded Phase **p. 22**	titration.	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.**	
Section 1 Protocol Synopsis **Figure 1.2: Study Design and Treatment Schema: Open-label Extension** **p. 23**	< See APPENDIX 1 for changes made to the figure > (...) **~~¶ 'End of Treatment' visit will occur once market authorization is granted for GWP42003-P (in TSC).~~** (...) B5, B7, B9, **~~B11, B12, B14 and B15~~** – Re-supply visits. **~~^Visits continue sequentially after B16 with assessment visits every 6 months (± 14 days) and resupply visits every 8-10 weeks between assessment visits.~~** (...)	< See APPENDIX 1 for changes made to the figure > (...) (...) **^**B5, B7 and B9 – Resupply visits. **In addition to the resupply visits, scheduling of extra dispensing visits/review of visit windows are required in order to comply with countries where controlled drugs can only be dispensed for a maximum of 28 days. Arrangements must be made with patients (or their caregivers) to come in every 4 weeks to be dispensed further GWP42003-P and return of used/unused GWP42003-P.** (...)	See Section 2.1 See Section 2.10 See Section 2.10

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Section 1 List of Abbreviations p. 34	(...) (...)	(...) **ANCOVA** **Analysis of Covariance** (...) **CI** **Confidence Interval** (...) **EAP** **Expanded Access IND Program** (...) **ITT** **Intention to treat** (...) **MAR** **Missing at Random** **MNAR** **Missing Not at Random** (...) **MI** **Multiple Imputation** (...) **PP** **Per protocol**	See Section 2.10 See Section 2.10

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Section 1 List of Abbreviations p. 34 (Continued)		(...) **SAP** **Statistical Analysis Plan** (...) **SOC** **System Organ Class** (...)	See Section 2.10
Section 2.2 Secondary p.38	(...) • To determine the pharmacokinetics (PK) of cannabidiol (CBD), ~~**Δ9 Tetrahydrocannabinol (THC)**~~ and ~~**their**~~ major metabolites following single and multiple doses of GWP42003-P.	(...) • To determine the pharmacokinetics (PK) of cannabidiol (CBD), and **its** major metabolites following single and multiple doses of GWP42003-P.	See Section 2.4
Section 3.1 Disease p. 40	(...) The onset of epilepsy in TSC commonly manifests as ~~**partial**~~ motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms[20]. (...) Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex ~~**partial**~~ seizures (with or without secondary	(...) 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]. (...) 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	See Section 2.10 See Section 2.10

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Section 3.1 Disease p. 40 (Continued)	generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences[20]. (...) The prevalence of VGB-associated VFDs in children with refractory complex ~~**partial**~~ 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].	generalization), generalized tonic–clonic seizures, atonic seizures, and atypical absences[20]. (...) 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].	See Section 2.10
Section 3.3.1 Selection of Study Dose p44-45	(...) GWEP42003-P is currently being used by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies in ~~**two**~~ open Individual Expanded Access Investigational New Drug (IND) studies and ~~**five**~~ open Intermediate Expanded Access IND studies.	(...) GWEP42003-P is currently being used by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies in **a number of** open Individual Expanded Access Investigational New Drug (IND) studies and open Intermediate Expanded Access IND studies. **In the Expanded Access IND program (EAP), clinical dosing is determined on a case by case basis, balancing seizure control with tolerability and shows that patients have tolerated doses up to**	See Section 2.10 See Section 2.10

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Section 3.3.1 Selection of Study Dose p44-45 (Continued)		**50 mg/kg/day. In the last data review of the EAP, the median dose was 25 mg/kg among 230 patients treated for at least 12 weeks (EAP; data cut Sep 15).** **The first patient was dosed on 22 Jan 2014 and at the latest data cut (Sep 2015) 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 have 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. There has been 1 patient who received a dose higher than 50 mg/kg.** **Doses of 25 and 50 mg/kg/day have been chosen for the GWEP1521 study to cover the doses of CBD oral**	See Section 2.10

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Section 3.3.1 Selection of Study Dose p44-45 (Continued)	(...) 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 is based on emerging data from the **~~Intermediate Expanded Access IND program~~**. **~~There are currently 10 open centers in this program, from which the physicians have shared data from 65 patients. Of these patients, the Sponsor has dosing data for 59. The maximum dose safely used to date is~~**	**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 is based on emerging data from the **EAP.**	See Section 2.10

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	~~**51 mg/kg/day, with a mean dose of 24 mg/kg/day and 64% of doses falling within the 20–30 mg/kg/day range.**~~		
Section 3.4 Clinical Hypothesis p45	(...) The primary clinical hypothesis is that there will be a difference between 50 mg/kg/day GWP42003-P and placebo in their effect on mean focal seizure frequency as measured by ANCOVA.	(...) The primary clinical hypothesis is that there will be a difference between 50 mg/kg/day GWP42003-P and placebo in their effect on mean focal seizure frequency as measured by **analysis of covariance (**ANCOVA**)**.	Section 2.10
Section 4.1 Study Design p. 47-48	(...) 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. (...) ~~**Doses will be titrated up or down, as appropriate, to ensure all patients**~~ enter the OLE taking 25 mg/kg/day GWP42003-P:	(...) 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 9.1.2.15 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.** (...) **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:	See Section 2.1 See Section 2.10

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Section 4.1 Study Design p. 47-48 (Continued)	(...) Safety telephone calls will be completed every two days throughout the OLE transition. (...) The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. (...) Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg every two days. **~~Safety telephone calls will be completed every two days throughout titration and one week after the end of titration.~~** 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 titration and one week after the end of titration.	(...) 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.** (...) The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. **The OLE period will last for a maximum of 1 year.** (...) 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.** (...)	See Section 2.10 See Section 2.10 See Section 2.1 See Section 2.10

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Section 4.1 **Study Design** **p. 47-48** **(Continued)**	(...) ~~**If market authorization is granted for GWP42003-P in TSC, the patient will complete the study. Patients who do not immediately continue to use GWP42003-P will then commence a taper period (tapering 10% per day for 10 days).**~~ (...) ~~**A study schema (Figure 1-1), presented at the end of Section 1, depicts the overall study design. More detailed information on treatment and study procedures is provided in Section 8 and Section 9, respectively.**~~		See Section 2.1 See Section 2.1
Section 4.1.1 **Primary Endpoint** **p.48**	(...) The primary endpoint is the percentage change from baseline in number of seizures* (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo. *Primary endpoint seizures include:	(...) The primary endpoint is the percentage change from baseline in number of **TSC-associated** seizures* (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo. *Primary endpoint **TSC-associated** seizures include:	See Section 2.6

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Section 4.1.2 Secondary Endpoints p. 49-50	(...) *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. • Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥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 composite focal seizure score (frequency × severity). • Change in number of seizure*-free days. • Change in number of seizures by subtype.	(...) ***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. **Key:** • **Number of patients considered treatment responders defined as those with a ≥50% reduction in seizure frequency (blinded phase only).** **Other:** • 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%	See Section 2.10 See Section 2.6

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Section 4.1.2 Secondary Endpoints p. 49-50 (Continued)	• Change in number of 'other' seizures (absence, myoclonic, ~~**partial**~~ sensory and infantile/epileptic spasms). • ~~**Change in number of infantile/epileptic spasms.**~~ (...) • Change in Tanner Staging score (for patients aged 10–17 [inclusive]).~~**Quality of Life:**~~ (...)	improvement, 50–75% improvement or >75% improvement in **TSC-associated** seizure* frequency. • **Change in total seizures** • Change in composite focal seizure score (frequency × severity). • Change in number of **TSC-associated** seizure*-free days. • Change in number of seizures by subtype. • Change in number of 'other' seizures (absence, myoclonic, **focal** sensory and infantile/epileptic spasms). (...) • Change in Tanner Staging score (for patients aged 10–17 [inclusive]). **Quality of Life:** (...)	See Section 2.10 See Section 2.10

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Section 4.1.2 Secondary Endpoints p. 50	(...) • **~~The plasma concentration/time curve of CBD, THC and their major metabolites will be described following single and multiple doses of GWP42003-P, with the aim being to estimate:~~** • **~~Peak plasma concentration (C_{max}).~~** • **~~Time to peak concentration (t_{max}).~~** • **~~Area under the plasma concentration curve from time zero to infinity ($AUC_{0-\infty}$).~~** • **~~Terminal half-life (t½)~~**.	(...) • **<u>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.</u>**	See Section 2.4
Section 4.1.2 Secondary Endpoints p. 51	(...) *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>TSC-associated</u>** 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.	See Section 2.6

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Section 4.1.2 Secondary Endpoints p. 51 (Continued)	• Percentage change in number of seizures* (average per 28 days). • Number of patients considered treatment responders, defined as those with a ≥25%, ≥50% %, ≥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 composite focal seizure score (frequency × severity). • Change in number of seizure*-free days. • Change in number of seizures by subtype. • Change in number of 'other' seizures (absence, myoclonic, partial sensory and infantile/epileptic spasms). • ~~**Change in number of infantile/epileptic spasms**~~	• Percentage change in number of **TSC-associated** seizure* (average per 28 days). • 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 total seizures** • Change in composite focal seizure score (frequency × severity). • Change in number of **TSC-associated** seizure*-free days. • Change in number of seizures by subtype. • Change in number of 'other' seizures (absence, myoclonic, partial sensory and	See Section 2.6 See Section 2.6 See Section 2.10

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		infantile/epileptic spasms).	
Section 4.2 Number of Centers p.52	Approximately ~~**30**~~ centers are expected to participate in this study.	Approximately **40** centers are expected to participate in this study.	See Section 2.10
Section 4.3 Number of Patients p.52	A total of ~~**192**~~ patients will be targeted to be enrolled. The ~~**192**~~ patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, ~~**64**~~ patients per group). Patients in the placebo group will be split into two cohorts (~~**32**~~ patients receiving 25 mg/kg/day dosing volumes and ~~**32**~~ patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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), this sample size of ~~**64**~~ patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50%	A total of **210** patients will be targeted to be enrolled. The **210** patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **70** patients per group). Patients in the placebo group will be split into two cohorts (**35** patients receiving 25 mg/kg/day dosing volumes and **35** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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), this sample size of **70** patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50%	See Section 2.3 See Section 2.3

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Section 4.3 Number of Patients p.52 (Continued)	reduction in seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and 90% power.	reduction in seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and 90% power.	
Section 5.1 GWP42003-P Solution p. 54	GWP42003-P solution is presented as a ~~**yellow oily**~~ solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring (Table 5.1-1).	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).	See Section 2.10
Section 5.2 Placebo Solution p. 54	Placebo solution is presented as a yellow ~~**oily**~~ solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring (Table 5.2-1).	Placebo solution is presented as a **clear, colorless to** yellow solution containing the excipients sesame oil and anhydrous ethanol **(10% v/v)** with added sweetener (sucralose) and strawberry flavoring (Table 5.2-1).	See Section 2.10
Section 5.3.1 Packaging and Labeling p. 54	(...) Sufficient IMP will be dispensed at each relevant visit considering the dose group and weight of each patient. (...)	(...) Sufficient IMP will be dispensed at each visit considering the dose group and weight of each patient. **For patients in countries where local law states that controlled drugs can only be dispensed for a maximum of 28 days, the maximum duration of**	See Section 2.8

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		prescription of IMP will be 28 days. (...)	
Section 5.3.4 Investigational Medicinal Product Accountability p. 56	(...) IMP will be dispensed at Visits 3, 4, 5, 7 and 9 during the blinded phase and Visits B1, B2, B3 **and** B4 and **every three months thereafter during the OLE.** **P**atients will be asked to return all IMP (used and unused) to each subsequent visit.	(...) 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. In countries where controlled drugs can only be dispensed for a maximum of 28 days, arrangements must be made with patients (or their caregivers) to come in every 4 weeks to be dispensed further GWP42003-P and return of used/unused GWP42003-P. All p**atients will be asked to return all IMP (used and unused) to each subsequent visit.	See Section 2.10 See Section 2.8
Section 5.3.5 Post-trial Provision p. 56	**Following completion of the blinded phase patients will be invited to continue to receive GWP42003-P in an open-label extension study. The open-label extension will continue until market authorization is granted for GWP42003-P in TSC**.		See Section 2.1
Section 6.1	(...)	(...)	

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Inclusion Criteria p. 58	6.1.4 Well-documented history of epilepsy**~~, with compatible electroencephalogram (EEG) and clinical history~~**.	6.1.4 Well-documented **clinical** history of epilepsy.	See Section 2.10
Section 6.2.7 p.59	Patient **~~is~~** taking felbamate**~~, and they have been taking it~~** for less than one year prior to screening.	Patient **has been** taking felbamate for less than one year prior to screening.	See Section 2.7
Section 6.2.11 p.59	**~~Active suicidal plan/intent in the past six months, or a history of suicide attempt in the last two years, or more than one lifetime suicide attempt.~~**	**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**.	See Section 2.10
Section 6.2.12 p. 59	**~~C-SSRS grade 4 or 5 at screening.~~**		See Section 2.10
Section 6.2.15 p. 59	Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit **~~2~~**), defined as any of the following: (...) i) Serum ALT or AST ≥ 3 × ULN **~~and~~** (TBL [serum total bilirubin] ≥ 2 × ULN **or** international normalized ratio [INR] > 1.5).	Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit **3**), defined as any of the following: (...) ii) Serum ALT or AST ≥ 3 × ULN **or** (TBL***** [serum total bilirubin] ≥ 2 × ULN **or** international normalized ratio [INR] > 1.5) **(*TBL ≥ 2 × ULN exclusion will not apply for patients**	See Section 2.10 See Section 2.9

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		diagnosed with Gilbert's disease).	
Section 6.2.18 **p. 60**	Patient has received an IMP within **~~the~~** 12 weeks prior to the screening visit.	Patient has received an IMP **as part of a clinical trial less than** 12 weeks prior to the screening visit.	See Section 2.10
Section 6.2.24 **p. 60** **Section 6.2.24** **p. 60 (Continued)**	(...) • **~~Patient has travel outside the country of residence planned during the study.~~**	(...) • **Patient has travel outside the country and/or US state of residence planned during the trial, unless the patient has confirmation that the IMP is permitted in the destination country/state.**	See Section 2.10
Section 7 **Patient Enrollment** **p. 61**	(...) 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).	(...) 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, enrolment 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**	See Section 2.9

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		issues have been observed.	
Section 8.1.2 Dose Escalation and Dose Adjustments p. 62-63	(...) All patients will be weighed during Visit 3 and the daily volumes of IMP solution to be taken during the 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. (...) It is recommended that patients with poor tolerability have their dose reduced by 10 mg/kg**~~/day~~** every seven days unless, in the Investigator's opinion, smaller or larger or more rapid dose reductions are clinically indicated. (...) Patients entering the OLE will first complete a two-week **~~open label extension~~** transition. **~~This double blind transition phase will take two weeks to complete. Doses will be titrated up or down, as appropriate, to ensure all patients enter the open label extension taking 25 mg/kg/day.~~**	(...) 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. (...) 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. (...) 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.**	Section 2.10 See Section 2.10 See Section 2.10

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Section 8.2 Concomitant Therapy p. 63	(...) Doses of any concomitant AEDs must have been stable for at least four weeks prior to screening and must remain stable throughout the study period. . If plasma concentrations of concomitant AEDs are found to be altered following administration of IMP then the dosage of concomitant AEDs may be modified, depending on the clinical need, following discussion with the GW medical advisor. (...)	(...) 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 plasma concentrations of concomitant AEDs are found to be altered following administration of IMP then the dosage of concomitant AEDs may be modified, depending on the clinical need, following discussion with the GW medical advisor. **However, it is encouraged that management of possible interactions be on emerging clinical symptoms with discussion with the GW medical advisor.**	See Section 2.7
Section 8.3 Prohibited Therapy During Study Period p. 64	(...) • Any new medications or interventions for epilepsy (including ketogenic diet and ~~**VNS**~~) or changes in dosage. • Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) ~~**within three months prior to or during the study**~~. • Any other IMP taken as part of a clinical trial	(...) • 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**	See Section 2.10 See Section 2.7

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Section 8.3 Prohibited Therapy During Study Period p. 64 (Continued)	~~**within six months or**~~ during the study.	**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.**	
Section 8.4 Compliance in Investigational Medicinal Product Administration p. 65	(...) Patients should return all IMP (used and unused) at each of visits 4, 5, 6, 7, 9 ~~**and 10**~~ during the blinded phase and at all OLE visits. The usage recorded in the diary and the usage projected in the IVRS system 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.	(...) 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 and** IVRS system 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.	See Section 2.10
Section 9.1.1.1 Visit 1 (Day-35, Screening) p. 67	(...) ~~**A**~~ blood test to determine the mutation status of *TSC1* and *TSC2* ~~**will be carried out**~~ if it is unknown. (...)	(...) **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. (...)	See Section 2.10

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Section 9.1.1.1 Visit 1 (Day-35, Screening) p. 67 (Continued)	Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen and a pregnancy test (using a serum sample, if appropriate).	Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine**/serum** THC screen and a pregnancy test (using a serum sample, if appropriate).	See Section 2.8
Section 9.1.1.2 Visit 2 (Day -28, Baseline) p. 68	(...) The investigator will review and train the caregiver to identify the patient's expected seizure types.	(...) The investigator will review and train the **patient or their** caregiver to identify the patient's expected seizure types.	See Section 2.10
Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 68-69	(...) The ECG will be repeated four hours after the first dose of IMP. **~~The investigator will verify that the ESC has confirmed the diagnosis of TSC.~~** (...) PK samples (patients >20 kg in weight only) will be taken **~~following randomization and at two hours and four hours after first dose of IMP. An additional PK sample will be taken~~** **~~six hours after the first dose for patients aged 18 years or above.~~** (...) Patients/caregivers will be asked to write a brief	(...) The ECG will be repeated four hours after the first dose of IMP. (...) PK samples (patients >20 kg in weight only) will be taken **in accordance with section 9.2.9.1.** (...) Patients/caregivers **and investigators** will be asked to	See Section 2.10 See Section 2.10 See Section 2.2

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Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 68-69 (Continued)	description of their/the patient's overall condition and assess the average duration of seizure subtypes as a memory aid for the SGIC/CGIC and SGIC-SD/CGIC-SD; these will be referred to at relevant, subsequent visits or withdrawal. (...) Patients or their caregivers will be instructed on how to record the diary information, including both the paper and IVRS diaries. **~~Provided that the risk/benefit outcome is favorable in the investigator's opinion, a blood sample will be collected prior to administration of IMP to determine plasma concentrations of concomitant AEDs.~~**	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. (...) Patients or their caregivers will be instructed on how to record the diary information, including both the paper and IVRS diaries.	See Section 2.10

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Section 9.1.1.4 Visit 4 (Day 15) p. 69	(...) ~~**The PGIC and SGIC/CGIC will also be performed.**~~ Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment. (...) Following Visit 4, during titration, safety telephone calls must be made every two days.	(...) Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment. (...) 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.**	See Section 2.2 See Section 2.10
Section 9.1.1.5 Visit 5 (Day 29) p.70	The following observations will be made at Visit 5: 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.	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 a pregnancy test if appropriate (using both a serum sample and a urine dipstick),** will be taken for hematology, biochemistry and	See Section 2.10 See Section 2.9

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Section 9.1.1.5 Visit 5 (Day 29) p.70 (Continued)	(...) ~~**The PGIC and SGIC/CGIC will also be performed.**~~ Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	urinalysis. (...) Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	See Section 2.2
Section 9.1.1.6 Visit 6 (Day 43) p. 71	(...) ~~**The PGIC and SGIC/CGIC will also be performed.**~~ Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	(...) Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	See Section 2.2
Section 9.1.1.7 Visit 7 (Day 57) p. 71-72	(...) Clinical laboratory samples (blood and urine [where possible]), will be taken for hematology, biochemistry and urinalysis. (...) ~~**The PGIC and SGIC/CGIC will also be performed.**~~	(...) Clinical laboratory samples (blood and urine [where possible]), **including a pregnancy test if appropriate (using both a serum sample and a urine dipstick),** will be taken for hematology, biochemistry and urinalysis. (...) Suicidality will be assessed using the C-SSRS/	See Section 2.9 See Section 2.2

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Section 9.1.1.7 Visit 7 (Day 57) p. 71-72 (Continued)	Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	
Section 9.1.1.9 Visit 9 (Day 85) p. 72	(...) Clinical laboratory samples (blood and urine [where possible]), will be taken for hematology, biochemistry and urinalysis. (...) **~~The PGIC and SGIC/CGIC will also be performed.~~** Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	(...) Clinical laboratory samples (blood and urine [where possible]), **<u>including a pregnancy test if appropriate (using both a serum sample and a urine dipstick),</u>** will be taken for hematology, biochemistry and urinalysis. (...) Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	See Section 2.9 See Section 2.2

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Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/Withdrawal Visit) p. 72-73	(...) 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. (...) (...) Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, **~~a urine THC screen~~**, determination of serum IGF 1 levels (for patients less than 18 years of age) and a pregnancy test (using a serum sample, if appropriate), to be performed by the central laboratory.	(...) 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. **In countries where controlled drugs can only be dispensed for a maximum of 28 days, there will not be a +3 day visit window, only a -3 day visit window. (...)** Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, determination of serum IGF 1 levels (for patients less than 18 years of age) and a pregnancy test (using a serum sample, if appropriate), to be performed by the central laboratory.	See Section 2.10 See Section 2.8
Section 9.1.2 Open Label Extension p. 74	(...) 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.	(...) 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.**	See Section 2.1

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Section 9.1.2.1 Visit B1 (Day 1) p. 75-76	(...) 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 ~~**(including THC screen)**~~, serum IGF-1 levels (patients less than 18 years of age) and pregnancy test (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, concomitant medications and/or changes to medication, suicidality, QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. ~~**A pregnancy test (if appropriate) must be conducted.**~~ (...) In addition, patients/caregivers will be instructed to complete a weekly seizure reporting diary until the ~~**'End of Treatment'/withdrawal**~~ visit using the IVRS.	(...) 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, serum IGF-1 levels (patients less than 18 years of age) and pregnancy test (if appropriate), IVRS and **patient** diary information from the blinded phase (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, IMP dosing), epilepsy-related hospitalizations, concomitant medications and/or changes to medication, suicidality, QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. (...) In addition, patients/caregivers will be instructed to complete a weekly seizure reporting diary until the **Follow-up** visit using the IVRS.	See Section 2.8 See Section 2.10

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Section 9.1.2.1 Visit B1 (Day 1) p. 75-76 (Continued)	(...) Following Visit B1, during the blinded transition, safety telephone calls must be made every two days.	(...) 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.**	See Section 2.10
Section 9.1.2.2 Visit B2 (Day 15) p. 76-77	(...) Patients **~~will~~** titrate up to the target dose of 50 mg/kg/day according to the defined titration schedule. (...) Following Visit B2, during titration, safety telephone calls must be made every two days.	(...) Patients **may** titrate up to the target dose of 50 mg/kg/day according to the defined titration schedule. (...) 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.**	See Section 2.10 See Section 2.10
Section 9.1.2.3 Open-Label Extension Visit Schedules in France	N/A	**9.1.2.3 Open-Label Extension Visit Schedules in Countries Where Local Law Requires Controlled Drugs Are Dispensed for a Maximum of 28 Days** **The visit schedules to follow in the OLE period will include additional visits or slightly amended visit**	See Section 2.10

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p. 77		**windows for patients seen in France. This is required due to local law requiring that a controlled drug is dispensed for a maximum of 28 days[52]. The '†' symbol denotes where scheduling of extra dispensing visits/review of visit windows is required in order to comply with this. Arrangements must be made with patients for them to attend the clinic every 4 weeks in order to be dispensed further GW42003-P and return used/unused GW42003-P.**	
Section 9.1.2.4 Visit B3† (Day 36) p. 77	Section ~~**9.1.2.3**~~ Visit B3 (Day 36) (...) 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: vital signs, physical examination (including height and body weight) and~~,~~ ECG~~, PGIC and SGIC/CGIC.~~	Section **9.1.2.4** Visit B3† (Day 36) (...) 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: vital signs, **postural blood pressure**, physical examination (including height and body weight) and ECG.	See Section 2.10 See Section 2.10 See Section 2.2

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Section 9.1.2.5 Visit B4† (Day 92) p. 78	Section ~~**9.1.2.4**~~ Visit B4 (Day 92) (...) 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), ~~**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]), 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. (...)	Section **9.1.2.5** Visit B4† (Day 92) (...) 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 a pregnancy test 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. (...) The following assessments will also be performed: SGIC-SD/CGIC-SD.	See Section 2.10 See Section 2.2 See Section 2.9 See Section 2.2
	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**~~.		

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Section 9.1.2.6 Visit B5† (Day 141) (Re-supply Visit) p. 79	Section ~~**9.1.2.5**~~ Visit B5 to End of Treatment (...) ~~**From Visit B5, visits will be defined as either Assessment Visits or Re-supply Visits.**~~ ~~**Assessment Visits will be scheduled every three months beginning at Visit B6 (Week 26) until patients have been enrolled in the OLE for one year. From one year to the End of Treatment, Assessment Visits will be scheduled every six months.**~~ ~~**Re-supply Visits will be scheduled to occur between Assessment Visits to ensure re supply volumes of IMP are manageable for both patients and dispensing staff. Re supply Visit dates will be calculated from the previous Assessment Visit. At each Re-supply Visit patients will be dispensed with sufficient IMP for a maximum of 11 weeks' treatment.**~~ ~~**A full visit schedule, from Visit B5 to the End of Treatment, is detailed below:**~~ ~~**Table 9.1.2.5-1 OLE Visit Schedule**~~ <See APPENDIX 1 for the details of the deleted table>	Section **9.1.2.6** 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.**	See Section 2.10 See Section 2.10

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Section 9.1.2.7 Assessment Visit B6 (Day 183) p. 79	Section **~~9.1.2.5.1~~ ~~Assessment Visits~~** (...) **~~The following observations will be made at Assessment Visits: 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]) will be taken for hematology, biochemistry, urinalysis, 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-~~**	Section **9.1.2.7** 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 a pregnancy test 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:**	See Section 2.10 See Section 2.10

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Section 9.1.2.7 Assessment Visit B6 (Day 183) p. 79 (Continued)	**~~SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment. 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 a three-month supply of IMP.~~**	**QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment. 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 for eight weeks' home dosing.**	See Section 2.10
Section 9.1.2.8 Visit B7 (Day 232, Re-supply Visit) p. 80	Section **~~9.1.2.5.2~~** Re-supply Visit~~s~~ (...) **~~Re-supply Visits will comprise a review of concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.~~**	(...) Section **9.1.2.8 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**	See Section 2.10 See Section 2.1

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Section 9.1.2.8 Visit B7 (Day 232, Re-supply Visit) p. 80 (Continued)	**~~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 IMP until the next scheduled visit.~~**	**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.**	See Section 2.10
Section 9.1.2.9 Visit B8 (Day 274) p. 80-81 Section 9.1.2.9	N/A	**9.1.2.9 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**	See Section 2.10

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Visit B8 (Day 274) p. 80-81 (Continued)		**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 a pregnancy test 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 using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment. The investigator must assess adherence to the dosing**	

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Section 9.1.2.9 Visit B8 (Day 274) p. 80-81 (Continued)		**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 for eight weeks' home dosing.**	See Section 2.10
Section 9.1.2.10 Visit B9 (Day 323, Re-supply Visit) p. 81	N/A	**9.1.2.10 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**	See Section 2.10

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Section 9.1.2.10 Visit B9 (Day 323, Re-supply Visit) p. 81 (Continued)		**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.**	
Section 9.1.2.11 Visit B10 (Day 365, End of Treatment/ Withdrawal Visit) p. 82	Section **~~9.1.2.6~~** End of Treatment/Withdrawal Visit This visit will **~~take place once market authorization is granted for GWP42003-P in TSC~~** or following early withdrawal from the study. (...) 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, serum IGF-1 levels (patients less than 18 years of age) and pregnancy test, IVRS and paper diary	Section **9.1.2.11 Visit B10 (Day 365,** End of Treatment/Withdrawal Visit**)** **This visit will occur 364 days after Visit B1**or 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, serum IGF-1 levels (patients less than 18 years of age) and pregnancy test **(using both a serum sample**	See Section 2.10 See Section 2.1 See Section 2.9

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Section 9.1.2.11 Visit B10 (Day 365, End of Treatment/ Withdrawal Visit) p. 82 (Continued)	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. (...) Following the 'End of Treatment'/Withdrawal visit, the IVRS seizure reporting diary should only be completed **~~on the day before the 'End of Taper Period' visit and on the day before~~** the Follow-up visit.	**and a urine dipstick, if appropriate)**, 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. (...) Following the 'End of Treatment'/Withdrawal visit, the IVRS seizure reporting diary should only be completed **up to** the Follow-up visit.	See Section 2.10
Section 9.1.2.12 Visit B11 (Day 375, End of Taper Period Visit) p. 83	Section **~~9.1.2.7~~** End of Taper Period Visit (...) Following the 'End of Taper Period' visit (or date of final dosing), the IVRS seizure reporting diary should **~~only~~** be completed **~~on the day before~~** the Follow-up visit.	Section **9.1.2.12 Visit B11 (Day 375,** End of Taper Period Visit) (...) Following the 'End of Taper Period' visit (or date of final dosing), the IVRS seizure reporting diary should be completed **up to** the Follow-up visit.	See Section 2.10 See Section 2.10
Section 9.1.2.13	Section **~~9.1.2.8~~** Post-taper Safety Telephone Call	Section **9.1.2.13 B12 (Day 389,** Post-taper Safety	See Section 2.10

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Post-taper Safety Telephone Call p. 83	(...) Following this call, the IVRS seizure reporting diary should ~~**only**~~ be completed ~~**on the day before**~~ the Follow-up visit.	Telephone Call) (...) Following this call, the IVRS seizure reporting diary should be completed **up to** the Follow-up visit.	See Section 2.10
Section 9.1.2.14 Follow-up Visit p. 83-84	Section ~~**9.1.2.9**~~ Follow-up Visit (...)	Section **9.1.2.14** Follow-up Visit (...)	See Section 2.10
Section 9.1.2.15 Safety Telephone Calls p. 84	Section ~~**9.1.2.10**~~ 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.	Section **9.1.2.15** 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.**	See Section 2.10 See Section 2.10
Section 9.2.4 Medical History	(...) The mutation status of the *TSC1* and *TSC2* genes, if	(...) The mutation status of the *TSC1* and *TSC2* genes, if	See Section 2.10

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p. 85	known, will be obtained through the patient's medical records. ~~**If the mutation status of TSC1 and TSC2 is unknown, genetic analysis will be carried out during the study analysis (a blood sample will be taken during Visit 1).**~~	known, will be obtained through the patient's medical records.	
Section 9.2.7 Vital Signs and Blood Pressure p. 86 **Section 9.2.7 Vital Signs and Blood Pressure p. 86 (Continued)**	**9.2.7 Vital Signs** Vital sign measurements taken in a sitting position at rest for five minutes, will be completed alongside the physical examination. Postural blood pressure should be measured after five minutes in supine position followed by two minutes in standing position, if possible. Blood pressure must be recorded using the same arm throughout the study, where possible.	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 p**ostural blood pressure is required it should be measured after five minutes in supine position followed by two minutes in standing position, if possible. Blood pressure must be recorded using the same arm throughout the study, where possible.	See Section 2.10 See Section 2.10
Section 9.2.9 Clinical Laboratory Sampling p. 86-88.	(...) Laboratory tests will include hematology, biochemistry, urinalysis (provided urine can be obtained), urine THC screening and a serum pregnancy test (if appropriate).	(...) Laboratory tests will include hematology, biochemistry, urinalysis (provided urine can be obtained), urine**/serum** THC screening and a serum pregnancy test (if appropriate).	See Section 2.8

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Section 9.2.9 Clinical Laboratory Sampling p. 86-88.	(...) The results of THC screening will be reported back to the study site to permit confirmation of eligibility **~~and to be used as a measure of study compliance (i.e., to confirm that the patient did not use cannabis during the course of the study).~~** (...) 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 results of THC screening will be reported back to the study site to permit confirmation of eligibility. (...) 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.**	See Section 2.8 See Section 2.10 See Section 2.10
Section 9.2.9.1 Pharmacokinetic Blood Sampling p. 88	The plasma concentration/time curves of CBD, **~~THC~~** and **~~their~~** 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	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	See Section 2.4

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Section 9.2.9.1 Pharmacokinetic Blood Sampling p. 88 (Continued)	IMP). • One sample between **~~four and five~~** hours post-dose. • One sample between **~~six and seven~~** hours post-dose. • One sample between **~~eight and ten~~** hours post-dose (patients 18 years and above only).	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).	
Section 9.2.9.3 Determination of Mutation Status of the TSC1 and TSC2 Genes p. 89	N/A	**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, with the patient/parent(s)/legal representative's consent, during the study analysis (a blood sample will be taken during Visit 1).**	See Section 2.10
Section 9.2.10 Interactive Voice Response System p. 89-90	(...) A member of the study team must contact the IVRS at each clinic visit in order to: • **~~Obtain a patient's screening number~~** (Visit 1). • Randomize a patient **~~and obtain their patient number~~** (Visit 3).	(...) 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).	Section 2.10

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	(...)	(...)	
Section 9.2.11 Patient Diary p. 90	(...) 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) **~~until completion of dosing (Visit 10/Withdrawal visit)~~**. (...) **~~Partial~~** sensory seizures*	(...) 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). (...) **Focal** sensory seizures	See Section 2.10 See Section 2.10
Section 9.2.12 Questionnaires and Assessments Completed at Scheduled Visits p. 91	**~~Questionnaires should be completed by the caregiver. The same person should complete/answer the questionnaires/assessments in order to maintain consistency. The C-SSRS (where applicable) will be administered by a trained rater.~~**		See Section 2.10
Section 9.2.12.2 Physician Global Impression of Change	N/A	**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**	See Section 2.2

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p. 91-92 **Section 9.2.12.2 Physician Global Impression of Change** **p. 91-92** **(Continued)**		**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.**	
Sections 9.2.12.4 - 9.2.12.9 **p. 92-94**	(...) ~~**9.2.12.3**~~ (...) ~~**9.2.12.4**~~ (...)	(...) **9.2.12.4** (...) **9.2.12.5** (...)	

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Sections 9.2.12.4 - 9.2.12.9 p. 92-94 (Continued)	~~**9.2.12.5**~~ (...) ~~**9.2.12.6**~~ (...) ~~**9.2.12.7**~~ (...) ~~**9.2.12.8**~~	**9.2.12.6** (...) **9.2.12.7** (...) **9.2.12.8** (...) **9.2.12.9**	See Section 2.10
Section 10 Withdrawal p. 101	(...) The patient must be withdrawn from the study if any of the following apply: • Administrative decision by the Investigator, GW, or a Regulatory Authority. • ~~**Did not meet eligibility criteria.**~~ (...) • ALT or AST ≥ 3 × ULN ~~**and**~~ (TBL ≥ 2 × ULN **or** INR > 1.5). (...)	(...) The patient must be withdrawn from the study if any of the following apply: • Administrative decision by the Investigator, GW, or a Regulatory Authority. (...) • ALT or AST ≥ 3 × ULN **or** (TBL***** ≥ 2 × ULN **or** INR > 1.5) **(*TBL ≥ 2 × ULN exclusion will not apply for patients diagnosed with Gilbert's disease)**. (...)	See Section 2.5 See Section 2.9

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Section 10 Withdrawal p. 101 (Continued)		***Note: Prior to withdrawal for the transaminase elevations noted above, the Investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase and alkaline phosphatase. Should the above transaminase elevation criteria be confirmed, the patient must be withdrawn from the trial.*** (...) Patients may also be withdrawn from the study for any of the following: • **Did not meet eligibility criteria.** • Patient non-compliance.	See Section 2.10
Section 12.2 Serious Adverse Events p. 104	(...) 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.	(...) 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-**	See Section 2.10

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		convulsive *status epilepticus* events to be medically significant and should be reported to the sponsor as medically significant SAEs	
Section 12.8 Potential Cases of Drug-Induced Liver Injury p. 109	(...) • ALT or AST > 3 × ULN **~~and~~** (TBL > 2 × ULN or INR > 1.5). (...) The Investigator will arrange for the patient to return to the investigational center as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL and alkaline phosphatase levels, detailed history and physical examination. Patients should be followed up in this way until all abnormalities have normalized (in the Investigator's opinion) or returned to the baseline state.	(...) ALT or AST > 3 × ULN **or** (TBL* > 2 × ULN or INR > 1.5). **(*TBL > 2 × ULN exclusion will not apply for patients diagnosed with Gilbert's disease).** (...) 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 **up** 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**.	See Section 2.9 See Section 2.5 See Section 2.5

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Section 12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees. p. 110-111 **Section 12.9 Notification of Safety Information to Investigators, Regulatory Authorities and**	(...) An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.	(...) 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**	See Section 2.10

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Ethics Committees. p. 110-111 (Continued)		**the accredited Medical Research Ethics Committee and competent authority.**	
Section 13.1 Sample Size, Power and Significance Levels p. 112	(...) A total of **~~192~~** patients will be enrolled. The **~~192~~** patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **~~64~~** patients per group). Patients in the placebo group will be split into two cohorts (**~~32~~** patients 25 mg/kg/day dosing volumes and **~~32~~** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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), **~~this sample size of 64 patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in seizures). This is based on a standard~~**	(...) A total of **210** patients will be enrolled. The **210** patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **70** patients per group). Patients in the placebo group will be split into two cohorts (**35** patients **receiving** 25 mg/kg/day dosing volumes and **35** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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**	See Section 2.3 See Section 2.3

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Section 13.1 Sample Size, Power and Significance Levels p. 112 (Continued)	**~~deviation of 60%, using a two-sided 5% significance level and 90% power.~~**	**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**.	
Section 13.6 Endpoints and Statistical Methods p. 114-115	(...) However, there are three treatments, so multiple significance testing will occur when making comparisons between the treatments**~~; the major comparisons of interest are those between each of the GWP42003-P Dose Levels and placebo and, in particular, the 50 mg/kg/day Dose Level and placebo. A step-down procedure will be used to control the type I error. The comparison of 50 mg/kg/day GWP42003-P and placebo will be tested first and only if this is statistically significant at the 5% level will the comparison of 25 mg/kg/day GWP42003-P and placebo be tested.~~**	(...) However, there are three treatments, so multiple significance testing will occur when making comparisons between the treatments. **To control the type I error, a step-up Hochberg's procedure will be used for the primary endpoint. If both of the observed p-values from the 25 mg/kg/day and 50 mg/kg/day GWP42003-P comparisons with placebo are < 0.050 in favor of the GWP42003-P treatment groups, then both groups would be declared statistically significantly better than placebo. However, if the observed p-value is ≥ 0.050 for one GWP42003-P treatment group but < 0.025 in favor of the other GWP42003-P treatment group, then**	See Section 2.3 See Section 2.3

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Section 13.6 Endpoints and Statistical Methods p. 114-115 (Continued)		**only the latter GWP42003-P treatment group will be declared statistically significantly better than placebo.** **The secondary endpoints will be tested hierarchically, starting with key secondary endpoint followed by all other secondary endpoints. No multiplicity adjustments will be made for all other secondary endpoints.**	
Section 13.6.2 Primary Endpoints p. 115	(...) **~~If the data are found to be normally distributed, they will be analyzed using an analysis of covariance (ANCOVA) approach. The model will include baseline and age group as covariates and treatment group as fixed factor.~~** **~~The treatment difference, together with the 95% confidence intervals (CIs) will be presented. A step down procedure will be used to control the type I error as per Section 13.6.~~** **~~However, due to the nature of seizure data, if a normal distribution cannot be assumed, the data will be analyzed using a Wilcoxon rank-sum test. An~~**	(...) **Data will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference between each GWP42003-P group and placebo, together with approximate 95% CI, will be calculated using the Hodges-Lehmann approach. A step-up Hochberg's procedure will be used to control the Type I error as per Section 13.6.**	See Section 2.3

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Section 13.6.2 Primary Endpoints p. 115 (Continued)	**~~estimate of the median difference between 50 mg/kg/day GWP42003-P and placebo, together with approximate 95% CI, will be calculated using the Hodges-Lehmann approach. The comparison of 25 mg/kg/day GWP42003-P and placebo will be presented, but the Wilcoxon rank-sum test only performed if the comparison of 50 mg/kg/day GWP42003-P and placebo is statistically significant at the 5% level.~~** **~~A graphical assessment of normality will be performed as well as computation of summary statistics for normality using the Shapiro-Wilk statistical test. If it is assumed that normality does hold, then a sensitivity analysis will be performed using the Wilcoxon rank-sum test as described above.~~**		See Section 2.3

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Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 116-118	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 number of seizures (average per 28 days) during the treatment period; • **~~ANCOVA~~** on percentage change from baseline in number of seizures (average per 28 days) during the maintenance period (Day **~~22~~** to the end of the evaluable period); • **~~ANCOVA~~** on percentage change from baseline in number of seizures (average per 28 days) during the treatment period, 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. (...) • **~~Mixed Effect Model Repeated Measures (MMRM) on percentage change from baseline in number of seizures (average per 28 days) during~~**	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 number of seizures (average per 28 days) during the treatment period **using the PP analysis set**; • **Wilcoxon rank-sum test** on percentage change from baseline in number of seizures (average per 28 days) during the maintenance period (Day **29** to the end of the evaluable period); • **Wilcoxon rank-sum test** on percentage change from baseline in number of seizures (average per 28 days) during the treatment period, 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. (...) • **A rank analysis of covariance (ANCOVA) on percentage change from baseline in number of**	See Section 2.3

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Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 116-118 (Continued)	~~**the treatment period:**~~ • ~~**The model will include baseline and age group as covariates and treatment group as a fixed factor. The time variable will be the assessment time point (nominal visit number, corresponding to each 21 days of the double-blind period) treated as a categorical repeated factor. The baseline-by-time and treatment-by-time interactions will also be included. The model will have an unstructured covariance matrix.**~~ • ~~**The fitted model will then be used to produce a final time point comparison, which implicitly adjusts for missing observations under the assumption of missing at random (MAR); there will be no imputations for missing values at individual time points.**~~ • ~~**The time course of the treatment effect will also be examined by estimating treatment differences, together with their 95% CIs, for each nominal visit during the randomized treatment period. A step-down procedure will be used to control the**~~	**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**	See Section 2.3

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Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 116-118 (Continued)	~~**type I error as per Section 13.6.**~~ • ~~**MMRM 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 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 21 calendar days of the treatment period. Intermittent missing values for intermediate 21-day time points before the last 21-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**~~	**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.** • **Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during 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).** **This analysis will include only patients who have at least 7 days of seizure data within each corresponding 4 week period.**	See Section 2.3

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Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 116-118 (Continued)	~~**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 21-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 21-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 21 day time point up to time point t (in chronological order) and will be performed for each GWP42003-P group**~~	• **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 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**	See Section 2.3

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Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 116-118 (Continued)	~~**separately.**~~ • ~~**ANCOVA on percentage change from baseline in number of seizures (average per 28 days) during the treatment period, using MI to impute data under the MNAR assumption.**~~ Full details for this sensitivity analysis will be provided in the SAP.	**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**	See Section 2.3

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Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 116-118 (Continued)		**separately.** Full details for this sensitivity analysis will be provided in the SAP.	See Section 2.3
Section 13.6.3 Secondary Endpoints p. 118-120	(...) (...) • 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%, ≥75% or 100% reduction in seizure frequency.	(...) **Key:** • **Number of patients considered treatment responders defined as those with a ≥50% reduction in seizure frequency (blinded phase only).** • **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	See Section 2.6 See Section 2.6

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Section 13.6.3 Secondary Endpoints p. 118-120	• 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 composite focal seizure score (frequency × severity). • Change in number of seizure-free days. • Change in number of seizures by subtype. • Change in number of 'other' seizures (absence, myoclonic, ~~**partial**~~ sensory and infantile/epileptic spasms). • ~~**Change in number of infantile/epileptic spasms.**~~ (...) Blinded Phase: The number of patient responders and the number of patients' seizure free will be summarized and analyzed using the difference in proportions and the odds ratio, together with 95% CIs, comparing the treatment groups. For changes in composite focal seizure score, number of	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 total seizures** • Change in composite focal seizure score (frequency × severity). • Change in number of seizure-free days. • Change in number of seizures by subtype. • Change in number of 'other' seizures (absence, myoclonic, **focal** sensory and infantile/epileptic spasms). (...) 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**	See Section 2.6

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Section 13.6.3 Secondary Endpoints p. 118-120 (Continued)	seizure-free days, ~~**number of seizures by subtype, number of infantile/epileptic spasms,**~~ use of rescue medication, number of episodes of status epilepticus, Vineland-II, Wechsler scales, CBCL, ABCL, SCQ, QOLCE~~**,**~~ QOLIE-31-P~~**, SGIC/CGIC and PGIC**~~ 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, ~~**as with the primary endpoint**~~ (or appropriate non-parametric methods if data are found to be not normally distributed). SGIC-SD/CGIC-SD 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	**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 changes in composite focal seizure score, 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% confidence intervals (CIs) will be presented.** **The percentage change in total seizures, the number**	See Section 2.3

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Section 13.6.3 Secondary Endpoints p. 118-120 (Continued)	and proportions. Number (%) of patients with changes in Tanner Stages will be summarized by treatment group. **~~The primary efficacy analysis uses the ITT analysis set over the evaluable period. ANCOVA analysis, using the LOCF approach, will be used to handle missing values.~~** 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. **~~Similar approaches, using the LOCF, will be applied if the data are analyzed using non-parametric methods.~~**	**of seizures (average per 28 days) by subtype and the number of 'other' seizures (average per 28 days) will be analyzed using a Wilcoxon rank-sum test as per 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.	See Section 2.3

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 13.6.4 Pharmacokinetics p. 120	Plasma concentrations for CBD**~~, THC and their~~** 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.	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.	See Section 2.4
Appendix 1 Schedules of Assessments	< Changes to the table of Schedules of Assessments (Blinded Phase and OLE) are shown in Appendix 1> (...) *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.	< Changes to the table of Schedules of Assessments (Blinded Phase and OLE) are shown in Appendix 1> (...) *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.** ∞ **In countries where controlled drugs can only be**	See Section 2.1, Section 2.2, Section 2.8, See Section 2.10

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 2 Date 21 OCT 2015 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 2 (Clinical Protocol V3 25Aug16) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Appendix 1 Schedules of Assessments (Continued)		**dispensed for a maximum of 28 days, there will not be a +3 day visit window, only a −3 day visit window.** **♦Only for patients weighing > 20 kg**	

5 REFERENCES

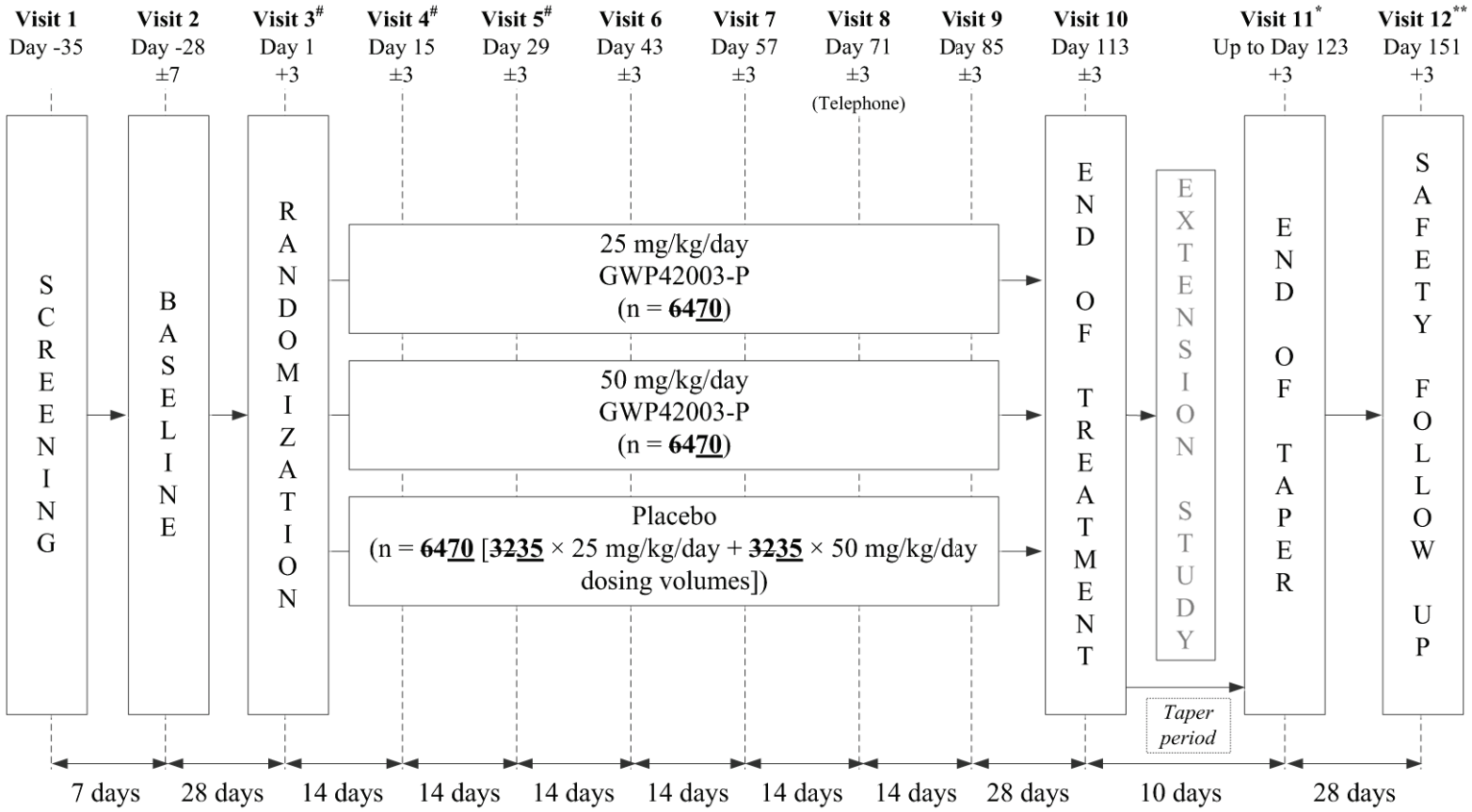
Not Applicable.

APPENDIX 1 AMENDED FIGURES AND TABLES

Amended Figure from Clinical Protocol V3 25Aug16

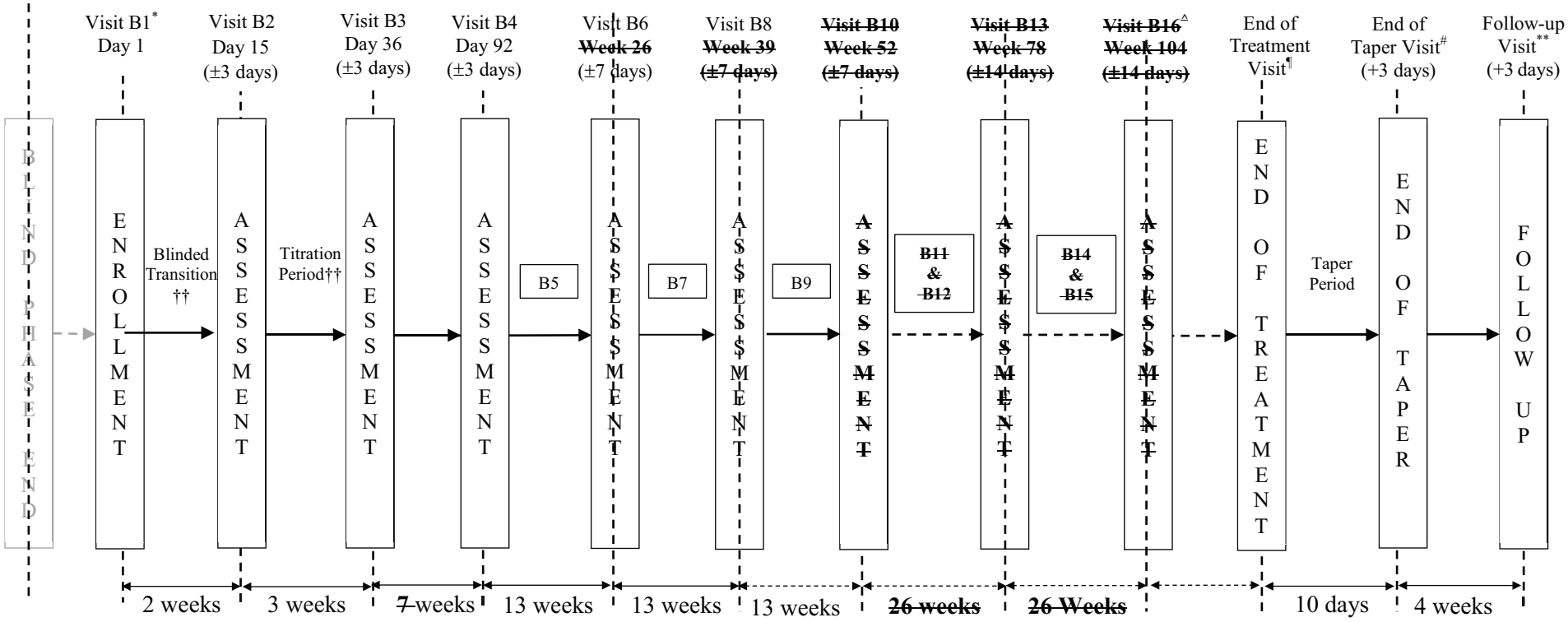
(Deleted wording is struck through and in bold; amended wording is underlined and in bold)

Amended Figure 1.1 Study Design and Treatment Schema: Blinded Phase



Original Figure from Clinical Protocol Version 2, Date 21 OCT 2015
(Deleted wording is struck through and in bold; deleted lines are in bold and dashed)

Original Figure 1.2 Study Design and Treatment Schema: Open-label Extension



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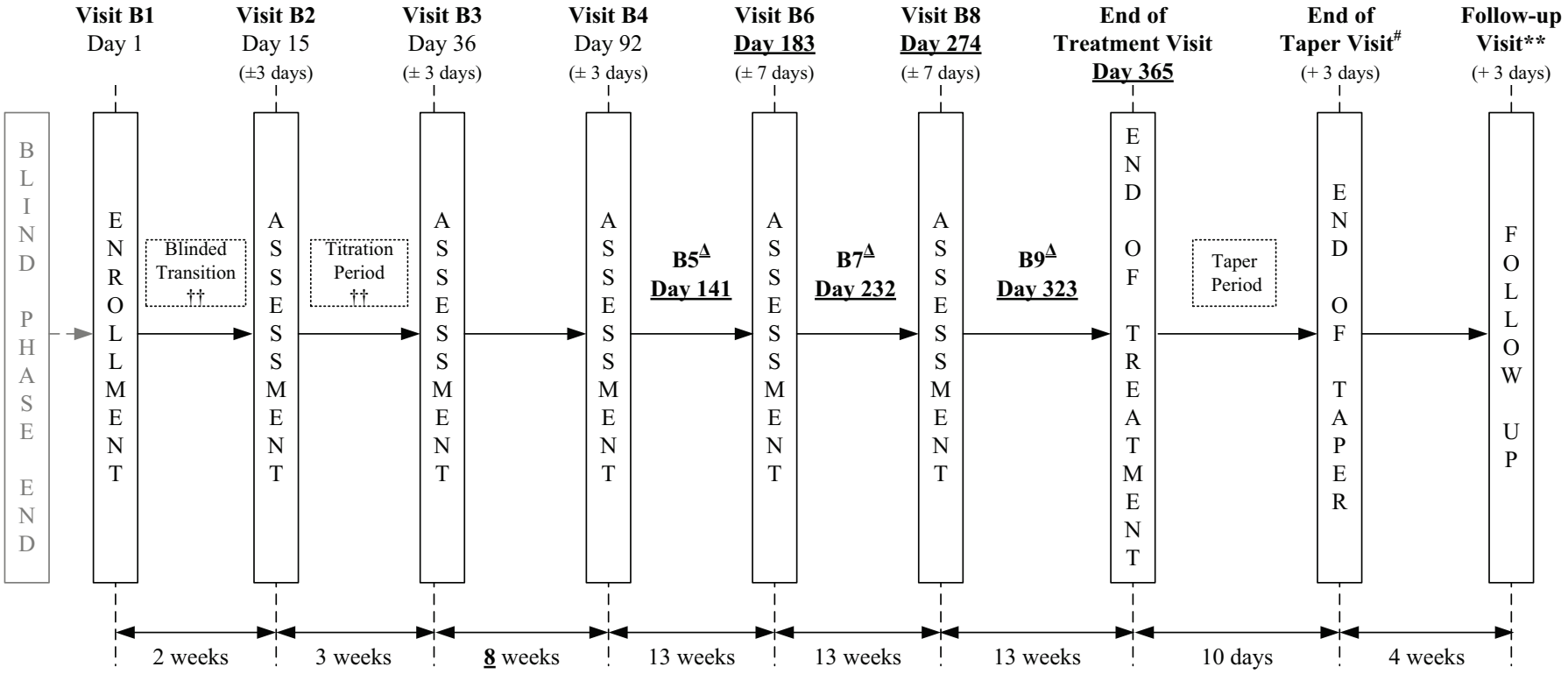
Amended Figure from Clinical Protocol V3 25Aug16
(Amended wording is underlined and in bold)

Amended Figure 1.2 Study Design and Treatment Schema: Open-label Extension



Original Table from Clinical Protocol Version 2, Date 21 OCT 2015

(Deleted wording is struck through and in bold)

~~**Table 9.1.2.6.1 OLE Visit Schedule**~~		
~~**Visit Number**~~	~~**Visit Type**~~	~~**Time from Visit B1 (except where indicated)**~~
~~**B5**~~	~~**Re-supply**~~	~~**7 weeks from B4 (±7 days)**~~
~~**B6**~~	~~**Assessment**~~	~~**26 weeks (±7 days)**~~
~~**B7**~~	~~**Re-supply**~~	~~**7 weeks from B5 (±7 days)**~~
~~**B8**~~	~~**Assessment**~~	~~**39 weeks (±7 days)**~~
~~**B9**~~	~~**Re-supply**~~	~~**7 weeks from B7 (±7 days)**~~
~~**B10**~~	~~**Assessment**~~	~~**52 weeks (±7 days)**~~
~~**B11**~~	~~**Re-supply**~~	~~**9 weeks from B9 (±14 days)**~~
~~**B12**~~	~~**Re-supply**~~	~~**18 weeks from B9 (±14 days)**~~
~~**B13**~~	~~**Assessment**~~	~~**78 weeks (±14 days)**~~
~~**B14**~~	~~**Re-supply**~~	~~**9 weeks from B12 (±14 days)**~~
~~**B15**~~	~~**Re-supply**~~	~~**18 weeks from B12 (±14 days)**~~
~~**B16**~~	~~**Assessment**~~	~~**104 weeks (±14 days)**~~
~~**Continue sequentially**~~	~~**Assessment**~~	~~**Continue every 6 months (±14 days)**~~
~~**Continue sequentially**~~	~~**Re-supply**~~	~~**Continue every 7–11 weeks between Assessment Visits**~~

Original Schedule of Assessments (Blinded Phase) from Clinical Protocol Version 2, Date 21 OCT 2015

(Deleted wording is struck through and in bold; deleted lines are in bold and dashed)

Blinded Phase

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12** (Tel.)	**Safety Calls***
Informed consent/assent	X												
Eligibility Criteria	X	X	X										
Randomization			X										
Demographics	X												
Medical history	X												
Vital signs	X		X	X	X	X	X		X	X	X		
Postural BP	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 urine sampling (dipstick urinalysis)	X		X	X	X	X	X		X	X	X		
Urine THC screen	X		~~X~~							~~X~~			
Pregnancy test (if appropriate)	X		X							X			
Pharmacokinetic blood sampling♦			X							X			
AED concentration			X		X		X		X	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		X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 (Tel.)	Safety Calls*
hospitalizations													
Suicidality / C-SSSRS/Children's C-SSSRS	X		X	X	X	X	X		X	X	X		
Vineland-II			X							X			
SGIC/CGIC			X	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	X			
PGIC			X	~~X~~	~~X~~	~~X~~	~~X~~		~~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) and IGF-1 testing			X							X			
Menstruation question (where appropriate)			X							X			
Patient 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			

Amended rows of Schedule of Assessments (Blinded Phase) from Clinical Protocol V3 25Aug16

(Amended wording is underlined and in bold)

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**$^{\infty}$	**+3**	**+3**	
(...)													
Vital signs **and BP**	X		X	X	X	X	X		X	X	X		
Postural BP	X		X		**X**								
(...)													
Urine/**serum** THC screen	X												
Pregnancy test (if appropriate)	X		X		**X**		**X**		**X**	X			
(...)													
***TSC1* and *TSC2* mutation status**	**X**												
(...)													
Inpatient epilepsy-related hospitalizations	**X**	X	X	X	X	X	X	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**	
Suicidality / C-SSRS/Children's C-SSRS	X		X	X	X	X	X		X	X	X		
(...)													
SGIC/CGIC			X							X			
PGIC			X							X			
(...)													

Original Schedule of Assessments (OLE Phase) from Clinical Protocol Version 2, Date 21 OCT 2015

(Deleted wording is struck through and in bold; deleted lines are in bold and dashed)

Visit Number	**B1**	**B2**	**B3**	**B4**	**Assessment Visits (B6, B8)**	**Re-Supply Visits (B5, B7, B9)**	**End of Treatment**	**End of Taper**	**Follow up** (Tel)	**Safety Calls***
Informed consent/assent	X									
Vital signs	X	X	X	X	X		X	X		
Physical examination (including height and body weight)	X	X	X	X	X		X	X		
ECG	X	X	X	X	X		X			
Clinical laboratory blood sampling	X	X	X	X	X		X			
Clinical laboratory urine sampling (dipstick urinalysis)	X	X	X	X	X		X			
~~**Urine THC**~~	~~**X**~~						~~**X**~~			
Pregnancy test, where appropriate	X						X			
AED concentration		X	X	X	X		X			
AEs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Inpatient epilepsy-related hospitalizations		X	X	X	X	X	X	X	X	X
Suicidality /C-SSRS/ Children's C-SSRS	X	X	X	X	X	~~**X**~~	X	X		
Vineland-II	X			~~**X**~~	~~**X**~~		X			
SGIC/CGIC	X		~~**X**~~	~~**X**~~	~~**X**~~		X			

Visit Number	B1	B2	B3	B4	Assessment Visits (B6, B8)	Re-Supply Visits (B5, B7, B9)	End of Treatment	End of Taper	Follow up (Tel)	Safety Calls*
PGIC	X		~~X~~	~~X~~	~~X~~		X			
SGIC-SD/CGIC-SD	X			~~X~~	~~X~~		X			
QOLCE/QOLIE-31-P	X			~~X~~	~~X~~		X			
Wechsler Tests	X			~~X~~	~~X~~		X			
CBCL/ABCL	X			~~X~~	~~X~~		X			
SCQ	X			~~X~~	~~X~~		X			
Tanner Staging (where appropriate) and IGF-1 testing	X			~~X~~	~~X~~		X			
Menstruation question (where appropriate)	X			~~X~~	~~X~~		X			
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)		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		
Study Medication Use and Behavior Survey							X			

Amended Schedule of Assessments (OLE Phase) from Clinical Protocol V3 25Aug16

(Amended wording is underlined and in bold)

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	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	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				
Clinical laboratory blood sampling	X	X	X	X		**X**		**X**		X				
Clinical laboratory urine sampling (dipstick urinalysis)	X	X	X	X		**X**		**X**		X				
Pregnancy test, where appropriate	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

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	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	
Inpatient epilepsy-related hospitalizations		X	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			
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) and IGF-1 testing	X									X				
Menstruation question (where appropriate)	X									X				
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)	**X**	X	X	X	**X**	**X**	**X**	**X**	**X**	X	X			
IVRS and diary training	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**	**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	
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				

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL AMENDMENT NUMBER: 1

to be incorporated into the Protocol, creating

CLINICAL PROTOCOL VERSION 2, DATE 21 OCT 15

GW Research Ltd
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Confidentiality Statement

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.
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.
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 1:1:1 randomized, double-blind, parallel-group, 16-week comparison of two doses of GWP42003-P versus placebo. Following screening and seizure classification, patients will complete a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: 1–6, 7–11, 12–17 years and 18+ years. Patients in the placebo group will be split into two equivalent cohorts; half receiving 25 mg/kg/day dosing volumes and half receiving 50 mg/kg/day dosing volumes. 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. 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. Doses will be titrated up or down, as appropriate, to ensure all patients 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 open label extension transition. **Open-label Extension:** The OLE consists of a 3-week titration period followed by a maintenance period and a 10-day taper period. 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 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 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. If market authorization is granted for GWP42003-P in TSC, the patient will complete the study. Patients who do not immediately continue to use GWP42003-P will then commence a taper period (tapering 10% per day for 10 days).
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

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List of Appendices

2 RATIONALE

This clinical protocol amendment 1 (will be incorporated into the Protocol creating Clinical Protocol Version 2, Date 21 Oct 15) addresses the following issue(s):

2.1 Compliance with U.S. Regulatory Requirements

In accordance with feedback received from the United States Food and Drug Administration, the protocol has been amended as follows:

2.1.1 Amendment to Study Title

The study title has been amended to reflect the change to indication described below.

2.1.2 Amendment to Indication

The indication has been amended to include generalized seizures where previously only focal seizures were considered. This will enable more accurate classification of seizures according to pre-defined seizure subtypes. The indication of seizures in tuberous sclerosis complex (TSC) now includes 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. Objectives have been amended to this affect.

2.1.3 Amendment to the Blinded Phase Primary Endpoint

The primary endpoint of the blinded phase of the study has been amended in parallel to reflect the change in indication. Seizures counted towards the primary endpoint now 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. Each seizure subtype will also be counted and assessed separately as secondary endpoints.

2.1.4 Insertion of New Secondary Endpoint to Blinded Phase and Open Label Extension

Absence seizures, myoclonic seizures, partial sensory seizures and infantile/epileptic spasms will now be counted towards a composite secondary endpoint measuring the change from baseline in number of ‘other’ seizures. Each seizure subtype will also be counted and assessed separately. The classification of these seizure subtypes as secondary endpoints reflects the difficulty in obtaining accurate and consistent counts.

2.1.5 Amendment to Open-label Extension Secondary Endpoint

The antiepileptic secondary endpoints of the open-label extension (OLE) phase have been amended to maintain consistency with the blinded phase indication and endpoints. Seizures counted towards this endpoint now 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. Each seizure subtype will also be counted and assessed separately.

2.1.6 Amendment to Inclusion Criteria

Inclusion criteria have been amended to remain consistent with the change to indication and endpoints. The seizure types counted towards eligibility in the baseline period have been extended and now 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.

2.1.7 Guidance on Dose Reductions

Further guidance on dose reductions in the event a patient experiences poor tolerability has been introduced. It is recommended that patients with poor tolerability have their dose reduced by 10 mg/kg/day every seven days unless, in the Investigator's opinion, smaller or larger dose reductions are clinically indicated. Where possible, the patient should be encouraged to return to the target Dose Level.

2.2 Clarification of Epilepsy Study Consortium Role and Responsibilities

The independent Epilepsy Study Consortium (ESC) will verify the seizure types of screened patients on an ongoing basis. The ESC will provide written documentation directly to the investigator and guidance on seizure types, if applicable, for inclusion in the patient file. The ESC will not review or verify TSC diagnosis. TSC diagnosis will be documented according to criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference and independent verification is not required.

2.3 Extension of Screening Period and Introduction of the 'Baseline' Visit

The screening period has been extended to ensure seizure classification has been verified and documented before baseline seizure recording begins. 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. Upon completion of this process patients will return to the clinic for the Baseline Visit to be trained on the use of the daily interactive voice response system (IVRS) diary. The 28 day baseline period will commence at this visit. This screening extension and extra visit will ensure that accurate seizure classifications and counts are recorded in the IVRS system and that seizure re-classifications do not cause discrepancies in source data. The numbering of subsequent visits has been amended as applicable.

2.4 Amendment to Secondary Objectives for Blinded and Open-label Extension Phases

The wording of secondary objectives have been amended to better reflect accepted terminology used in the treatment and care of patients with TSC and in the research community. Two existing secondary objectives have been combined to produce the following objective: To evaluate the effect of GWP42003-P on TSC Associated Neuropsychiatric Disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo. The following secondary objective has been removed: To evaluate the effect of GWP42003-P on autistic features compared with placebo. Endpoints relating to TAND have not been amended.

2.5 Amendment to Inclusion Criterion to Include One Year Old Patients

The age range for this study has been amended from 2–65 years to 1–65 years. This will ensure that the study population remains representative of the wider TSC patient population. One retrospective study of TSC patients showed that > 60% had the onset of seizures in the first year of life[1]. It also ensures consistency with the Pediatric Investigation Plan for Epidiolex.

2.6 Increase in Patient Numbers

The number of patients per treatment group has been increased from 48 to 64 (a total increase from 144 to 192 patients). The increase in patient numbers reflects an increase in power from 80% to 90% which is deemed more appropriate for a Phase Three study.

2.7 Clarification of Inclusion Criterion Relating to IVRS Diary Call Compliance

Patients are required to complete at least 90% of the daily diary calls during baseline to be considered eligible for randomization. The inclusion criterion wording has been clarified to confirm that a minimum of 25 completed daily calls out of 28 is required.

2.8 Dose Administration and Investigational Medicinal Product Description

Specific details regarding oral dosing has been removed from the protocol to allow for possible future gastrostomy tube (G-tube) administration. Specific dosing instructions will be provided to patients/caregivers.

2.9 Pharmacokinetic Blood Sampling

The timings of blood samples for pharmacokinetic (PK) blood sampling of cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC) and their major metabolites have been amended. This is in accordance with emerging data from a single ascending dose PK study in healthy volunteers which showed t_{max} to occur at approximately five hours post-dose.

Text has been amended in order to clarify that PK samples will only be taken from patients who weigh ≥ 20 kg in order to avoid multiple blood sampling (and associated risks thereof) in younger children.

2.10 Vineland Adaptive Behavior Scales

The frequency of Vineland-II assessments has been reduced during the blinded phase of the study. This assessment will be completed at the Randomization (Visit 3) and End of Treatment Visits (Visit 11) only. The relatively proximity of visits during this phase of the study means significant changes would be unlikely at interim visits. This change will also reduce the patient burden.

2.11 Administrative Changes

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

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 2, Date 21 Oct 15. It will be kept in the trial master file at GW as well as in each investigator site file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Version 1, Date 16 Jun 15** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Amendment 1 (Clinical Protocol Version 2, Date 21 Oct 15)** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Title Page p. 1	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 ~~**focal**~~ seizures (…)	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 (…)	See Section 2.1.1
Confidentiality Statement p. 1	This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board or Ethics Committee.	This document contains confidential information of GW Research Ltd (GW) that must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board or **Independent** Ethics Committee.	See Section 2.11
Investigator Agreement p. 2	(…) 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	(…) 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	See Section 2.11

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	tuberous sclerosis complex who experience inadequately-controlled **~~focal~~** seizures', dated 16 June 2015 and agree to abide by all provisions set forth therein. (…)	tuberous sclerosis complex who experience inadequately-controlled seizures', dated 21 Oct 2015 and agree to abide by all provisions set forth therein. (…)	
Section 1 PROTOCOL SYNOPSIS Study Title p. 3	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 **~~focal~~** seizures.	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.	See Section 2.1.1
Section 1 PROTOCOL SYNOPSIS Indication p. 3	**~~Focal seizures~~**~~*~~ in patients with tuberous sclerosis complex (TSC). ~~*~~**~~Focal 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.	**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**.	See Section 2.1.2
Section 1 PROTOCOL	Blinded Phase: To evaluate the efficacy of GWP42003-P as add-on	Blinded Phase: To evaluate the efficacy of GWP42003-P as add-on	See Section 2.1.2

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Section 1 SYNOPSIS Primary Objective p. 3	therapy in reducing the frequency of ~~**focal**~~ seizures when compared with placebo in patients with TSC. Open-~~**L**~~abel 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 ~~**focal**~~ seizures.	therapy in reducing the frequency of seizures when compared with placebo in patients with TSC. Open-**L**abel 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.	
Section 1 SYNOPSIS Secondary Objectives p. 3–4	Blinded Phase: (...) • To evaluate the effect of GWP42003-P on cognitive and behavioral function compared with placebo. • To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo. • ~~**To evaluate the effect of GWP42003-P on autistic features compared with placebo.**~~ (...) Open-label Extension (...) • To evaluate the effect of GWP42003-P on cognitive and behavioral function compared with placebo.	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 evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo. (...) Open-label Extension: (...) • To evaluate the effect of GWP42003-P on **TAND, including** cognitive and behavioral function **and**	See Section 2.4

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	• To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years) compared with placebo. • ~~**To evaluate the long term effect of GWP42003-P on autistic features.**~~ (...)	**autistic features** compared with placebo. • To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years **old**) compared with placebo. (...)	
Section 1 PROTOCOL SYNOPSIS Study Design p. 4–5	(…) ~~**Patients**~~ will complete a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: ~~**2–6**~~, 7–11, 12–17 years and 18+ years. (…) Clinic visits will occur for screening (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 ~~**9**~~ to Visit ~~**11**~~.	(…) **Patients** will complete **1-week screening period and** a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: **1–6**, 7–11, 12–17 years and 18+ years. (…) 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	See Section 2.3

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Section 1 PROTOCOL SYNOPSIS Study Design p. 4–5 (continued)	(…) Following completion of the blinded phase patients will be invited to continue to receive GWP42003-P in an OLE ~~**study**~~. (…) The OLE consists of a ~~**10-day**~~ titration period followed by a maintenance period and a 10-day taper period. (…) Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg every ~~**5–7**~~ days. (…)	Visit **12**. (…) Following completion of the blinded phase patients will be invited to continue to receive GWP42003-P in an OLE. (…) The OLE consists of a **3-week** titration period followed by a maintenance period and a 10-day taper period. (…) Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg every **two** days. (…)	
Section 1 PROTOCOL SYNOPSIS Primary Endpoint p. 5–6	(…) The primary endpoint is the percentage change from baseline in number of ~~**focal seizures**~~ (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.	(…) The primary endpoint is the percentage change from baseline in number of **seizures**[*] (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo. [*]**Primary endpoint seizures include: focal motor seizures without impairment of consciousness or**	See Section 2.1.3

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	(…)	**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.** (…)	
Section 1 PROTOCOL SYNOPSIS Secondary Endpoints p. 6–9	Blinded Phase: (…) Antiepileptic **e**fficacy **m**easures: • Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in **focal** seizure frequency. • Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in **focal** seizure frequency. • (…) • Change in number of **focal** seizure-free days. • (…)	Blinded Phase: (…) Antiepileptic **E**fficacy **M**easures: ***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.** • Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in seizure* frequency. • Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement,	See Section 2.11 See Section 2.1.5 See Section 2.1.4

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Section 1 PROTOCOL SYNOPSIS Secondary Endpoints p. 6–9 (continued)	(…) 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.~~** (...) Open-label Extension: Antiepileptic ~~e~~fficacy ~~m~~easures:	50–75% improvement or >75% improvement in seizure frequency.* • (…) • Change in number of seizure-free days.* • (…) • **Change in number of 'other' seizures (absence, myoclonic, partial sensory and infantile/epileptic spasms).** (…) **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.**	

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Section 1 PROTOCOL SYNOPSIS Secondary Endpoints p. 6–9 (continued)	• Percentage change in number of ~~**focal seizures**~~ (average per 28 days). (…) Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in ~~**focal**~~ seizure frequency. • Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in ~~**focal**~~ seizure frequency. • (…) • Change in number of ~~**focal**~~ seizure-free days. • Change in number of seizure subtype~~**s**~~. • (…)	(…) Open-label Extension: Antiepileptic **E**fficacy **M**easures: ***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.** • Percentage change in number of **seizures*** (average per 28 days). • Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥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. • (…)	

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Section 1 PROTOCOL SYNOPSIS Secondary Endpoints p. 6–9 (continued)	Cognitive and Behavioral Function: • Changes in Vineland-II. • Changes in Wechsler Scales (pre-school, primary, children, adult). • Changes in CBCL or ABCL. (…) ~~**Autistic Features:**~~ • ~~**Changes in SCQ score.**~~ (…)	• Change in number of seizure~~*~~-free days. • Change in number of seizure**s by** subtype. • (…) • **Change in number of 'other' seizures (absence, myoclonic, partial sensory and infantile/epileptic spasms).** • (…) **TAND:** Cognitive and Behavioral Function: • Changes in Vineland-II. • Changes in Wechsler Scales (pre-school, primary, children, adult). • Changes in CBCL or ABCL. **Autistic Features:** • **Changes in SCQ score.** (…)	
Section 1 PROTOCOL SYNOPSIS	(…) A total of ~~**144**~~ patients will be targeted to be enrolled. The ~~**144**~~ patients will be randomly allocated on a 1:1:1	(…) A total of **192** patients will be targeted to be enrolled. The **192** patients will be randomly allocated on a 1:1:1	See Section 2.6

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Sample Size p. 9 Section 1 PROTOCOL SYNOPSIS Sample Size p. 9 (continued)	basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **~~48~~** patients per group). Patients in the placebo group will be split into two cohorts (**~~24~~** patients receiving 25 mg/kg/day dosing volumes and **~~24~~** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy. If it is assumed that patients in the placebo group will experience a mean reduction in **~~focal~~** seizure frequency of 15% (from baseline), this sample size of **~~48~~** patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in **~~focal~~** seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and **~~80%~~** power. (…)	basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **64** patients per group). Patients in the placebo group will be split into two cohorts (**32** patients receiving 25 mg/kg/day dosing volumes and **32** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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), this sample size of **64** patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and **90%** power. (…)	
Section 1 PROTOCOL SYNOPSIS Summary of	(…) • Patient is male or female aged between **~~two~~** and 65 years inclusive. • (…)	(…) • Patient is male or female aged between **one** and 65 years inclusive. • (…)	See Section 2.5

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Patient Eligibility Criteria p. 10–12	• Well-documented history of ~~**focal**~~ epilepsy, with ~~**focal seizures as the primary seizure type,**~~ compatible electroencephalogram (EEG) and clinical history. • (…) • Experienced at least eight ~~**focal**~~ seizures during the first 28 days of the baseline period with at least one seizure occurring in at least three of the four weeks. • Completed at least 90% of calls to IVRS during the first 28 days of the baseline period.	• Well-documented history of epilepsy, with compatible electroencephalogram (EEG) and clinical history. • (…) • 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)**.	See Section 2.1.2 and Section 2.2 See Section 2.7
Section 1 PROTOCOL SYNOPSIS Summary of Patient Eligibility	(…) • Patient is being considered for epilepsy surgery or any procedure involving general anesthesia.	(…) • Patient is being considered for epilepsy surgery or any procedure involving general anesthesia **during the blinded phase of the study**.	See Section 2.11

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Criteria p. 10–12 (continued) Section 1 PROTOCOL SYNOPSIS Summary of Patient Eligibility Criteria p. 10–12 (continued)	• (…) Patient has significantly impaired hepatic function at the screening visit (Visit 1) or the randomization visit (Visit **~~2~~**), defined as any of the following: • Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN). • Serum ALT or AST ≥ 3 × ULN and (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5). • 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 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). • Serum ALT or AST ≥ 3 × ULN and (TBL [serum total bilirubin] ≥ 2 × ULN or international normalized ratio [INR] > 1.5). • 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. (…)	See Section 2.3
Section 1 PROTOCOL SYNOPSIS Investigational Medicinal Product:	GWP42003-P ~~**oral**~~ solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol, sweetener [sucralose] and strawberry flavoring). Placebo ~~**oral**~~ solution (sesame oil) containing the	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	See Section 2.8

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Formulation, Mode of Administration, Dose and Regimen P. 13–14	excipients anhydrous ethanol, sweetener (sucralose) and strawberry flavoring. (…) Patients will be on treatment for a total of 1~~**5**~~ weeks. (…)	anhydrous ethanol, sweetener (sucralose) and strawberry flavoring. (…) Patients will be on treatment for a total of 1**6** weeks. (…)	
Section 1 PROTOCOL SYNOPSIS Procedures p. 14–19	(…) • ~~**IVRS training**~~ • ~~**Patient diary issue and training**~~ ~~**The Diagnostic Review Form (DRF) will be completed for review and verification by the Epilepsy Study Consortium (ESC).**~~ Patients who satisfy all inclusion and none of the exclusion criteria will be assigned a unique patient number ~~**and then begin the 28-day baseline observation period**~~.	(…) 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**	See Section 2.3, Section 2.9 and Section 2.10

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Section 1 PROTOCOL SYNOPSIS Procedures p. 14–19 (continued)	(…) Patients will make a daily IVRS call to record daily seizure information including ~~**focal**~~ seizures and episodes of *status epilepticus*. Patients or their caregivers will be given a paper diary to record ~~**daily seizure information,**~~ usage of IMP, rescue medication, concomitant AEDs, and AEs and will be instructed on how to do so. (…)	**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 following assessments will be completed:** • **Concomitant medication review (including AEDs)** • **AE review** • **Epilepsy-related hospitalizations review** • **IVRS training** • **Patient diary issue and training** (…) Patients 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. (…)	

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Section 1 PROTOCOL SYNOPSIS Procedures p. 14–19 (continued)	Following the 28-day baseline observation period the investigator will assess the patient's daily number of seizures from IVRS data **~~and confirm ESC verification of diagnosis~~**. (…) Patients will then receive sufficient IMP, as assigned by IVRS, every 14 to 28 days for the **~~15~~**-week treatment period. (…) • Tanner Staging, (where appropriate) (Visits **~~2~~** and 9) (...) • SGIC-SD or CGIC-SD (Visit **~~9~~**) • Vineland II • Wechsler Tests (Visits **~~2~~** and **~~9~~**) • CBCL or ABCL (Visits **~~2~~** and **~~9~~**) • SCQ (Visits **~~2~~** and **~~9~~**) • QOLCE or QOLIE-31-P (Visits **~~2~~** and **~~9~~**) • CGIC or SGIC **~~(Visits 2 and 9)~~** • PGIC **~~(Visits 2 and 9)~~**	Following the 28-day baseline observation period the investigator will assess the patient's daily number of seizures from IVRS data. (…) Patients will then receive sufficient IMP, as assigned by IVRS, every 14 to 28 days for the **16**-week treatment period. (…) • Tanner Staging, (where appropriate) (Visits **3** and 9) (...) • SGIC-SD or CGIC-SD (Visit **10**) • Vineland II **(Visits 3 and 10)** • Wechsler Tests (Visits **3** and **10**) • CBCL or ABCL (Visits **3** and **10**) • SCQ (Visits **3** and **10**) • QOLCE or QOLIE-31-P (Visits **3** and **10**) • CGIC or SGIC • PGIC	

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Section 1 PROTOCOL SYNOPSIS Procedures p. 14–19 (continued)	• Clinical Laboratory samples (blood and urine) will be taken for: o Hematology o Biochemistry o Urinalysis o Urine THC screen o Serum pregnancy test (if applicable) o Serum IGF-1 o PK (Visits **~~2~~** and **~~9~~**) o AED concentrations (…) Blood sample collection for PK analysis of CBD, THC and their major metabolites will be taken at the **~~at the~~** following time points: • Visit **~~2~~** (Randomization) - Pre-IMP-dose **~~and 2 hours and 4 hours after IMP dose~~**. • Visit 10 (End of Treatment) - Pre-IMP-dose **~~and 2 hours and 4 hours after IMP dose~~**.	• Clinical Laboratory samples (blood and urine) will be taken for: o Hematology o Biochemistry o Urinalysis o Urine THC screen o Serum pregnancy test (if applicable) o Serum IGF-1 o PK (Visits **3** and **10**) o AED concentrations (…) Blood sample collection for PK analysis of CBD, THC and their major metabolites will be taken at the following time points: • Visit **3** (Randomization) - Pre-IMP-dose**, 4–5 hours post-dose, 6–7 hours post-dose and 8–10 hours post-dose (patients 18 years and above only).** • Visit 10 (End of Treatment) - Pre-IMP-dose**, 4–5**	See Section 2.11

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Section 1 PROTOCOL SYNOPSIS Procedures p. 14–19 (continued)	Blood samples will be collected for analysis of plasma concentrations of concomitant AEDs (if possible) ideally at the following time points: • Visit ~~**2**~~ - Pre-IMP-dose. • Visit ~~**4**~~ - Pre-IMP-dose. • Visit ~~**6**~~ - Pre-IMP-dose. • Visit ~~**8**~~ - Pre-IMP-dose. • Visit ~~**9**~~ - Pre-IMP-dose. (…) Following completion of the blinded phase of the study, patients will enter a 2-week blinded transition followed by a ~~**2**~~-week titration. Safety telephone calls will be conducted every two days during this **4**-week period and one week after the end of titration.	**<u>hours post-dose, 6–7 hours post-dose and 8–10 hours post-dose (patients 18 years and above only).</u>** Blood samples will be collected for analysis of plasma concentrations of concomitant AEDs (if possible) ideally at the following time points: • Visit **<u>3</u>** - Pre-IMP-dose. • Visit **<u>5</u>** - Pre-IMP-dose. • Visit **<u>7</u>** - Pre-IMP-dose. • Visit **<u>9</u>** - Pre-IMP-dose. • Visit **<u>10</u>** - Pre-IMP-dose. (…) Following completion of the blinded phase of the study, patients will enter a 2-week blinded transition followed by a **<u>3</u>**-week titration. Safety telephone calls will be conducted every two days during this **<u>5</u>**-week period and one week after the end of	

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Section 1 PROTOCOL SYNOPSIS Procedures p. 14–19 (continued)	OLE visits will occur on Day 15, Day ~~**29**~~, Day ~~**85**~~ and then every three months up to one year, then every six months thereafter until the end of treatment. (…) The following assessments will be completed at ~~**all**~~ visits during the OLE: • Concomitant medication review (including AEDs) • AE review • Physical examination • Tanner Staging, where appropriate (Visit~~s **B2, B5**~~ and subsequent Assessment Visits)	titration. OLE visits will occur on Day 15, Day **36**, Day **92** and then every three months up to one year, then every six months thereafter until the end of treatment. (…) The following assessments will be completed at visits during the OLE **(full listing by visit included in Section 9.1.2.)**: • Concomitant medication review (including AEDs) • AE review • Physical examination • Tanner Staging, where appropriate (Visit **B4** and subsequent Assessment Visits)	
Section 1 PROTOCOL SYNOPSIS Statistical Considerations p. 19–20	(…) Each of the primary and secondary endpoints will be described and compared between treatment groups, using appropriate statistical methods, over the ~~**15-week**~~, double-blind maintenance and titration period. (…) Where baseline data are available from the ~~**Core study**~~,	(…) 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. (…) Where baseline data are available from the **blinded**	See Section 2.11

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	changes from baseline will also be presented. (…)	**phase**, changes from baseline will also be presented. (…)	
Section 1 Figure 1-1 Study Design and Treatment Schema: Blinded Phase p. 21	• Visit **~~2~~**# Day **~~1+3~~** **~~RANDOMIZATION~~** <**~~28~~** days after Visit 1> <**~~Titration begins~~**> • Visit 3# Day **~~15±3~~** <**~~14~~** days after Visit 2> • Visit 4# Day **~~29±3~~** <**~~Titration ends~~**> • Visit **~~5~~** Day **~~43±3~~** • Visit 6 Day **~~57±3~~** • Visit 7	• Visit **2** Day **−28+7** **BASELINE** <**7** days after Visit 1> • Visit 3# Day **1+3** **RANDOMIZATION** <**28** days after Visit 2> <**Titration begins**> • Visit 4# Day **15±3** • Visit **5**# Day **29±3** <**Titration ends**> • Visit 6 Day **43±3** • Visit 7	See Section 2.3 and Section 2.11

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Section 1 Figure 1-1 Study Design and Treatment Schema: Blinded Phase p. 21 (continued)	Day ~~**71±3**~~ ~~**(Telephone)**~~ • Visit 8 Day ~~**85±3**~~ • Visit 9 Day ~~**113±3**~~ ~~**END OF TREATMENT**~~ <~~**28**~~ days after Visit 8> <~~**Taper period begins**~~> • Visit ~~**10**~~[*] ~~**Up to**~~ Day ~~**123+3**~~ ~~**END OF TAPER**~~ <~~**10**~~ days after Visit 9> <~~**Taper period ends**~~> • Visit ~~**11**~~[**] Day ~~**151**~~+3 ~~**SAFETY FOLLOW UP**~~ <~~**28**~~ days after Visit 10>	Day **57±3** • Visit 8 Day **71±3** **(Telephone)** • Visit 9 Day **85±3** <**14** days after Visit 8> • Visit **10** Day **113±3** **END OF TREATMENT** <**28** days after Visit 9> <**Taper period begins**> • Visit **11**[*] **Up to** Day **123**+3 **END OF TAPER** <**10** days after Visit 10> <**Taper period ends**> • **Visit 12**[**]	

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Section 1 Figure 1-1 Study Design and Treatment Schema: Blinded Phase p. 21 (continued)	• (…) • 25 mg/kg/day GWP42003-P (*n* = **~~48~~**) • 50 mg/kg/day GWP42003-P (*n* = **~~48~~**) • Placebo (*n* = **~~48~~** [**~~24~~** × 25 mg/kg/day + **~~24~~** × 50 mg/kg/day dosing volumes]) • (…) * For patients not entering the open label extension at Visit **~~9~~**. **~~Patients who opt not to enter the open label extension study must have weekly (±3 days) safety telephone calls until Visit 11~~**.	**Day 151+3** **SAFETY FOLLOW UP** **<28 days after Visit 11>** • (…) • 25 mg/kg/day GWP42003-P (*n* = **64**) • 50 mg/kg/day GWP42003-P (*n* = **64**) • Placebo (*n* = **64** [**32** × 25 mg/kg/day + **32** × 50 mg/kg/day dosing volumes]) • (…) * For patients not entering the open label extension at Visit **10**.	
Section 1 Figure 1-2	• Visit **~~B3~~**[§] Day **~~29~~** (±3 days)	• Visit **B3** Day **36** (±3 days)	

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Study Design and Treatment Schema: Open-label Extension p. 22	<~~**2**~~ weeks after Visit B2> • Visit ~~**B4**~~[§] Day ~~**85**~~ • <~~**8**~~ weeks after Visit B3> • Visit ~~**B6**~~[§] • Visit ~~**B8**~~[§] (…) [§,†] ~~**Between visits, safety telephone calls must be made every four weeks (§)to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.**~~ (…)	<**3** weeks after Visit B2> • Visit **B4** Day **92** • <**7** weeks after Visit B3> • Visit **B6** • Visit **B8** (…) (…)	
Section 1 List of Abbreviations p. 33	(...) SUSAR Suspected Unexpected Serious Adverse Event TBL Total Bilrubin (...)	(...) SUSAR Suspected Unexpected Serious Adverse Event **TAND** **TSC Associated Neuropsychiatric Disorders** TBL Total Bilirubin (...)	See Section 2.4
Section 2.1	Blinded Phase:	Blinded Phase:	See Section 2.1.2

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Primary Objectives p. 35	To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of ~~**focal**~~ seizures when compared with placebo in patients with TSC. Open ~~**L**~~abel 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 ~~**focal**~~ seizures.	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-**l**abel 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.	
Section 2.2 Secondary Objectives p. 35–36	Blinded Phase: (...) • To evaluate the effect of GWP42003-P on cognitive and behavioral function compared with placebo. • To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo. • ~~**To evaluate the effect of GWP42003-P on autistic features compared with placebo.**~~ (...) Open-label Extension: (...) • To evaluate the long term effect of GWP42003-P on	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 evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo. (...) Open-label Extension: (...) • To evaluate the long term effect of GWP42003-P	See Section 2.4

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	cognitive and behavioral function compared with placebo. • To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo. • **~~To evaluate the effect of GWP42003-P on autistic features compared with placebo.~~** (...)	on **TAND, including** cognitive and behavioral function **and autistic features** compared with placebo. • To evaluate the long term effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo. (...)	
Section 4.1 Study Design p. 43	(…) Patients will complete a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: **~~2–6~~**, 7–11, 12–17 years and 18+ years. (…) Clinic visits will occur for screening (Day **~~–28~~**), randomization (Day 1) and, on Days 15 and 29 during titration and on Days 43, 57 and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days	(…) Patients will complete **a 1-week screening period and** a 4-week baseline period before they are randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo. Randomization will be stratified by age according to the following ranges: **1–6**, 7–11, 12–17 years and 18+ years. (…) 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 and 85 until the end of treatment (Day 113). Safety telephone calls will be completed every two days	See Section 2.3 See Section 2.5

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Section 4.1 Study Design p. 43–44 (continued)	during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit ~~**9**~~ to Visit ~~**11**~~. (…) Following completion of the blinded phase patients will be invited to continue to receive GWP42003-P in an OLE ~~**study**~~. (…) The OLE consists of a ~~**10-day**~~ titration period followed by a maintenance period and a 10-day taper period. (…) Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg every ~~**5–7**~~ days. (…)	during titration, one week after the end of titration and, for patients not entering the OLE, weekly from Visit **10** to Visit **12**. (…) Following completion of the blinded phase patients will be invited to continue to receive GWP42003-P in an OLE. (…) The OLE consists of a **3-week** titration period followed by a maintenance period and a 10-day taper period. (…) Dose increases above 25 mg/kg/day are recommended to be done slowly, with maximum increments of 2.5 mg every **two** days. (…)	See Section 2.11
Section 4.1.1 Primary Endpoint p. 44–45	(…) The primary endpoint is the percentage change from baseline in number of ~~**focal**~~ seizures (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.	(…) The primary endpoint is the percentage change from baseline in number of seizures* (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.	See Section 2.1.3.

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Section 4.1.1 Primary Endpoint p. 44–45 (continued)	~~**Focal**~~ 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. ~~**All seizures will have focal onset in TSC but may not be discernable by patient or caregiver.**~~ ~~**All definite and probable seizures will be counted and assumed to be focal in origin**~~. (…)	[*] **Primary endpoint** 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**. (…)	
Section 4.1.2 Secondary Endpoint(s) p. 45–48	(…) (…)	(…) [*] **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.** (…)	See Section 2.1.2

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Section 4.1.2 Secondary Endpoint(s) p. 45–48 (continued)	• Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in **~~focal seizure~~** frequency. • Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in **~~focal seizure~~** frequency. • (…) • Change in number of **~~focal seizure~~**-free days. • (…) • (…) 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	• Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥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, partial sensory and infantile/epileptic spasms).** • (…) **TAND:** Cognitive and Behavioral Function: • Changes in Vineland Adaptive Behavior Scales, Second Edition (Vineland-II). • Changes in Wechsler Scales (pre-school,	See Section 2.1.4

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Section 4.1.2 Secondary Endpoint(s) p. 45–48 (continued)	(CBCL) and Adult Behavior Checklist (ABCL). • (…) **~~Autistic features~~** • **~~Change in Social Communication Questionnaire (SCQ) score.~~** • (…) (…) (…) • Percentage change in number of **~~focal seizures~~** (average per 28 days). • Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in **~~focal seizure~~** frequency.	primary, children, adult). • Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL). **Autistic Features** • **Change in Social Communication Questionnaire (SCQ) score.** • (…) (…) **~~*~~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.** (…) • Percentage change in number of **seizures~~*~~** (average per 28 days).	See Section 2.4

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Section 4.1.2 Secondary Endpoint(s) p. 45–48 (continued)	• Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in ~~**focal seizure**~~ frequency. • (…) • Change in number of ~~**focal seizure**~~-free days. • Change in number of ~~**seizure subtype**~~. • (…) Cognitive and Behavioral Function: • Changes in Vineland-II. • Changes in Wechsler Scales (pre-school, primary, children, adult). • Changes in CBCL and ABCL. (...) ~~**Autistic Features**~~ • ~~**Change in SCQ score.**~~ • (…)	• Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥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 **seizures by subtype**. • **Change in number of 'other' seizures (absence, myoclonic, partial sensory and infantile/epileptic spasms).** • (…) **TAND:** Cognitive and Behavioral Function: • Changes in Vineland-II. • Changes in Wechsler Scales (pre-school, primary, children, adult).	

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		• Changes in CBCL and ABCL. **Autistic Features** • **Change in SCQ score.** • (…)	
Section 4.2 Number of Centers P. 61	Approximately ~~**20**~~ centers are expected to participate in this study.	Approximately **30** centers are expected to participate in this study.	See Section 2.6
Section 4.3 Number of Patients p. 48 Section 4.3 Number of Patients p. 48 (continued)	(…) A total of ~~**144**~~ patients will be targeted to be enrolled. The ~~**144**~~ patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, ~~**48**~~ patients per group). Patients in the placebo group will be split into two cohorts (~~**24**~~ patients receiving 25 mg/kg/day dosing volumes and ~~**24**~~ patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy. If it is assumed that patients in the placebo group will experience a mean reduction in ~~**focal**~~ seizure frequency	(…) A total of **192** patients will be targeted to be enrolled. The **192** patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **64** patients per group). Patients in the placebo group will be split into two cohorts (**32** patients receiving 25 mg/kg/day dosing volumes and **32** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can 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%	See Section 2.6

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	of 15% (from baseline), this sample size of **~~48~~** patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in **~~focal~~** seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and **~~80%~~** power. (…)	(from baseline), this sample size of **64** patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in seizures). This is based on a standard deviation of 60%, using a two-sided 5% significance level and **90%** power. (…)	
Section 5.1 GWP42003-P Solution p. 49	5.1 GWP42003-P **~~Oral~~** Solution GWP42003-P **~~oral~~** solution is presented as a yellow oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. Table 5.1-1 Formulation of GWP42003-P **~~Oral~~** Solution 5.2 Placebo **~~Oral~~** Solution Placebo **~~oral~~** solution is presented as a yellow oily solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. Table 5.1-1 Formulation of GWP42003-P **~~Oral~~** Solution	5.1 GWP42003-P Solution GWP42003-P solution is presented as a yellow oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. Table 5.1-1 Formulation of GWP42003-P Solution 5.2 Placebo Solution Placebo solution is presented as a yellow oily solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. Table 5.1-1 Formulation of GWP42003-P Solution	See Section 2.8

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Section 5.3.4 Investigational Medicinal Product Accountability p. 51	(…) IMP will be dispensed at Visits ~~**2**~~, 3, ~~**4**~~, ~~**6**~~ and ~~**8**~~ during the blinded phase and Visits B1, B2, B3 and B4 and every three months thereafter during the OLE. (…)	(…) IMP will be dispensed at Visits **3**, **4**, **5**, **7** and **9** during the blinded phase and Visits B1, B2, B3 and B4 and every three months thereafter during the OLE. (…)	See Section 2.3
Section 6 PATIENT ELIGIBILITY p. 53	(…) After the screening visit, investigators will submit the patient's documented history of ~~**TSC**~~ directly to the Epilepsy Study Consortium (ESC) for ~~**confirmation of diagnosis by the ESC**~~. (…)	(…) 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**. (…)	See Section 2.2
Section 6.1 Inclusion Criteria p. 53–54	(…) 6.1.1 Patient is male or female aged between ~~**two**~~ and 65 years inclusive. (…) 6.1.4 Well-documented history of ~~**focal**~~ epilepsy, with ~~**focal seizures as the primary seizure type,**~~ compatible electroencephalogram (EEG) and clinical history. (…)	(…) 6.1.1 Patient is male or female aged between **one** and 65 years inclusive. (…) 6.1.4 Well-documented history of epilepsy, with compatible electroencephalogram (EEG) and clinical history. (…)	See Section 2.5

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Section 6.1 Inclusion Criteria p. 53–54 (continued)	6.1.10 Experienced at least eight **~~focal~~** seizures during the first 28 days of the baseline period with at least one seizure occurring in at least three of the four weeks. 6.1.11 Completed at least 90% of calls to IVRS during the first 28 days of the baseline period.	6.1.10 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, clonic, tonic or atonic] that are countable)**. 6.1.11 Completed at least 90% of calls to IVRS during the first 28 days of the baseline period **(a minimum of 25 completed calls)**.	See Section 2.1.6 See Section 2.11
Section 6.2 Exclusion Criteria p. 54–55	(…) 6.2.6 Patient is being considered for epilepsy surgery or any procedure involving general anesthesia. (…)	(…) 6.2.6 Patient is being considered for epilepsy surgery or any procedure involving general anesthesia **during the blinded phase of the study**. (…)	See Section 2.11

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Section 7.1 Treatment Assignment p. 56	(…) After confirmation of eligibility at Visit ~~**2**~~, patients will be randomly allocated to 25 mg/kg/day, 50 mg/kg/day or placebo using the IVRS. (…)	(…) 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. (…)	See Section 2.3
Section 7.2 Randomization p. 56	(…) The randomization will be stratified by age group (~~**2–6**~~ years, 7–11 years, 12–17 years and 18–65 years).	(…) The randomization will be stratified by age group (**1–6** years, 7–11 years, 12–17 years and 18–65 years).	See Section 2.5
Section 8.1 Investigational Medicinal Product Dosage, Administration and Schedule p. 57	(…) Patients will be assigned one of two Dose Levels of active IMP or placebo on a 1:1:1 basis (~~**48**~~ patients per treatment group). Patients in the placebo group will be split into two cohorts (~~**24**~~ receiving Low Dose Level dosing volumes and ~~**24**~~ receiving High Dose Level dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.	(…) Patients will be assigned one of two Dose Levels of active IMP or placebo on a 1:1:1 basis (**64** patients per treatment group). Patients in the placebo group will be split into two cohorts (**32** receiving Low Dose Level dosing volumes and **32** receiving High Dose Level dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.	See Section 2.6
Section 8.1.1 Dose Administration	The IMP will be administered ~~**orally**~~ by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided. ~~**The IMP will be**~~	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	See Section 2.8

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p. 57	~~**swallowed**~~ and may be taken with other concomitant medications, as directed by the investigator.	concomitant medications, as directed by the investigator.	
Section 8.1.2 Dose Escalation and Dose Adjustments p. 57–59 Section 8.1.2 Dose Escalation and Dose Adjustments p. 57–59 (continued)	All patients will be weighed during Visit ~~**2**~~ and the daily volumes of IMP solution to be taken during the 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. (…) Each patient will take their first dose of IMP at Visit ~~**2**~~ (Day 1) and their final maintenance dose of IMP at Visit ~~**9**~~ (Day 113). (…) During the maintenance period, patients should continue on a stable dosing regimen at the target Dose Level. If that dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period. ~~**However**~~, ~~**w**~~here possible, the patient should be encouraged to return to the target Dose Level.	All patients will be weighed during Visit **3** and the daily volumes of IMP solution to be taken during the 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. (…) 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). (…) During the maintenance period, patients should continue on a stable dosing regimen at the target Dose Level. If that dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period. **It is recommended that patients with poor tolerability have their dose reduced by 10 mg/kg/day every seven days unless, in the Investigator's opinion, smaller or**	See Section 2.1.7

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Section 8.1.2 Dose Escalation and Dose Adjustments p. 57–59 (continued)	(…) (…) Patients who do not enter the OLE study at Visit **~~9~~** 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 **~~10~~**.	**larger or more rapid dose reductions are clinically indicated. W**here possible, the patient should be encouraged to return to the target Dose Level. (…) **Following completion of the blinded transition patients will 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.** (…) 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**.	See Section 2.11 See Section 2.3
Section 8.4 Compliance in Investigational Medicinal Product	(…) • **~~Visit 2 (Day 1)~~** • Visit 3 (Day **~~15~~**) • Visit 4 (Day **~~29~~**)	(…) • Visit 3 (Day **1**) • Visit 4 (Day **15**)	

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Administration p. 60	• Visit 5 (Day **~~43~~**) • Visit 6 (Day **~~57~~**) • Visit **~~8~~** (Day 85) • (…) Patients should return all IMP (used and unused) at each of visits **~~3,~~** 4, **~~6, 8~~** and **~~9~~** during the blinded phase and at all OLE visits. (…)	• Visit 5 (Day **29**) • Visit 6 (Day **43**) • **Visit 7 (Day 57)** • Visit **9** (Day 85) • (…) Patients should return all IMP (used and unused) at each of visits 4, **5,** 6, **7,** 9 and **10** during the blinded phase and at all OLE visits. (…)	
Section 9.1.1.1 Visit 1 (Day −35, Screening) p.62	9.1.1.1 Visit 1 (Day **~~−28,~~** Screening) (…) The **~~Diagnostic Review Form (DRF)~~** will be sent to the ESC to confirm **~~the diagnosis of TSC~~**. (…) **~~Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 6 will be assigned a unique patient number and then begin the 28 (+3) day baseline period.~~** **~~The investigator will review and train the caregiver to identify the patient's expected seizure types.~~** **~~Patients or their caregivers will be issued with IVRS~~**	9.1.1.1 Visit 1 (Day **−35,** Screening) (…) The **patient's documented history of TSC** will be sent to the ESC to confirm **seizure classification**. (…) **The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.**	See Section 2.3

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Section 9.1.1.1 Visit 1 (Day −35, Screening) p. 62 (continued)	~~**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.**~~ ~~**The investigator must record the patient's attendance at the visit and confirm the outcome of screening on the CRF.**~~ ~~**The laboratory results will be available within 3-5 working days after Visit 1.**~~ ~~**If the results show a patient is ineligible, the patient will be withdrawn from the study.**~~		
Section 9.1.1.2 Visit 2 (Day −28, Baseline) p. 63	9.1.1.2 Visit 2 (Day ~~**1, Randomization**~~) This visit will occur ~~**28**~~ days after Visit 1. A visit window of +~~**3**~~ days from the scheduled visit ~~**date**~~ is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible. The following observations will be made at Visit 2: concomitant medications~~,~~ (including AEDs), ~~**physical**~~	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. The following observations will be made at Visit 2: **review of** concomitant medications (including	See Section 2.3

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Section 9.1.1.2 Visit 2 (Day −28, Baseline) p. 63 (continued)	**~~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 after the first dose of IMP~~**. **~~The investigator will verify that the Epilepsy Study Consortium has confirmed the diagnosis of TSC.~~** **~~Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen, determination of serum IGF-1 levels (for patients less than 18 years of age) a pregnancy test and if appropriate (using both a serum sample and a urine dipstick).~~** **~~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.~~**	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 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.**	

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Section 9.1.1.2 Visit 2 (Day −28, Baseline) p. 63 (continued)	~~**PK samples (patients >20 kg in weight only) will be taken following randomization and at two hours and four hours after first dose of IMP.**~~ ~~**An additional PK sample will be taken six hours after the first dose for patients aged 18 years or above.**~~ ~~**The investigator must assess the patient's daily number of focal 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 focal seizures during the first 28 days of the baseline period, and who meet all of the other inclusion and none of the exclusion criteria, will be eligible to continue in the study.**~~ ~~**At Visit 2 eligible patients will be randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo on a 1:1:1 basis.**~~ ~~**Following randomization at Visit 2, patients will remain at the clinic where the following baseline assessments will be performed prior to the**~~		

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Section 9.1.1.2 Visit 2 (Day −28, Baseline) p. 63 (continued)	**~~administration of study medication:~~** **~~QOLCE/QOLIE-31-P, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II.~~** **~~Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.~~** **~~Patients/caregivers 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 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 three 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 regime.~~** **~~The first dose of IMP will be administered in clinic.~~** **~~Patients or their caregivers will be instructed how to record the diary information, including both the~~**		

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	~~**paper and IVRS diaries.**~~ ~~**Provided that the risk/benefit outcome is favorable in the investigator's opinion, a blood sample will be collected prior to administration of IMP to determine plasma concentrations of concomitant AEDs.**~~ ~~**Following Visit 2, during titration, safety telephone calls must be made every two days.**~~ ~~**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.**~~		
Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 63–64	9.1.1.3 Visit 3 (Day ~~**15**~~) This visit will occur ~~**14**~~ days after Visit 2 ~~**(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 3: concomitant medications, (including AEDs), physical	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	See Section 2.3

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Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 63–64 (continued)	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. (…) ~~**The PGIC, SGIC/CGIC and Vineland-II will also be performed.**~~	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 after the first dose of IMP.** **The investigator will verify that the ESC has confirmed the diagnosis of TSC**. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry**,** urinalysis**, a urine THC screen, determination of serum IGF-1 levels (for patients less than 18 years of age) and a pregnancy test if appropriate (using both a serum sample and a urine dipstick)**. (…) **PK samples (patients >20 kg in weight only) will be taken following randomization and at two hours and**	

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Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 63–64 (continued)		**four hours after first dose of IMP.** **An additional PK sample will be taken six hours after the first dose for patients aged 18 years or above.** **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, will be eligible to continue in the study.** **At Visit 3 eligible patients will be randomized to receive either 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P or placebo on a 1:1:1 basis.** **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:**	

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Section 9.1.1.3 Visit 3 (Day 1, Randomization) p. 63–64 (continued)	(…) **~~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.~~**	**QOLCE/QOLIE-31-P, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II.** (…) **Patients/caregivers 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 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 two 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.** **Patients or their caregivers will be instructed on how to record the diary information, including both the paper and IVRS diaries.** **Provided that the risk/benefit outcome is favorable in the investigator's opinion, a blood sample will be collected prior to administration of IMP to determine**	

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	(…) (…)	**plasma concentrations of concomitant AEDs.** (…) **A further call must be completed one week after the end of titration.** (…)	
Section 9.1.1.4 Visit 4 (Day 15) p. 64–65 Section 9.1.1.4 Visit 4 (Day 15) p. 64–65 (continued)	9.1.1.4 Visit 4 (Day ~~29~~) This visit will occur ~~28~~ days after Visit ~~2~~. (…) ~~**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 PGIC~~,~~ SGIC/CGIC ~~**and Vineland-II**~~ will also be performed. Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical ~~**judgement**~~. (…)	9.1.1.4 Visit 4 (Day **15**) This visit will occur **14** days after Visit **3 (randomization)**. (…) (…) The PGIC **and** SGIC/CGIC will also be performed. Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical **judgment**. (…)	See Section 2.3

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	~~**A**~~ safety telephone ~~**call**~~ must be made ~~**one week after the end of titration (Visit 4)**~~. During ~~**this call**~~, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.	**Following Visit 4, during titration,** safety telephone **calls** must be made **every two days**. During **these calls**, caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.	
Section 9.1.1.5 Visit 5 (Day 29) p. 65–66 Section 9.1.1.5 Visit 5 (Day 29) p. 65–66 (continued)	9.1.1.5 Visit 5 (Day ~~**43**~~) This visit will occur ~~**42**~~ days after Visit ~~**2 (randomization)**~~. (…) The PGIC~~,~~ SGIC/CGIC ~~**and Vineland-II**~~ will also be performed. Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical ~~**judgement**~~. 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. (…)	9.1.1.5 Visit 5 (Day **29**) This visit will occur **28** days after Visit **3**. (…) **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 PGIC **and** SGIC/CGIC will also be performed. Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical **judgment**. 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.	See Section 2.3

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	Patients will then receive new IMP.	(…) 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.**	
Section 9.1.1.6 Visit 6 (Day 43) p. 66	9.1.1.6 Visit 6 (Day ~~57~~) This visit will occur ~~56~~ days after Visit ~~2~~ (randomization). (…) ~~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 PGIC, SGIC/CGIC ~~and Vineland II~~ will also be performed. (…)	9.1.1.6 Visit 6 (Day **43**) This visit will occur **42** days after Visit **3** (randomization). (…) The PGIC **and** SGIC/CGIC will also be performed. (…)	See Section 2.3

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Section 9.1.1.7 Visit 7 (Day 57) p. 66–67	9.1.1.7 Visit 7 (Day ~~**71**~~) This visit will occur ~~**70**~~ days after Visit ~~**2**~~ (randomization). (…) ~~**Visit 7**~~ will be ~~**completed by telephone and will comprise a review of**~~ concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.	9.1.1.7 Visit 7 (Day **57**) This visit will occur **56** days after Visit **3** (randomization). (…) **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]) 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 PGIC and SGIC/CGIC will also be performed.** **Suicidality will be assessed using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.**	See Section 2.3
Section 9.1.1.7 Visit 7 (Day 57) p. 66–67 (continued)			

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		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.**	
Section 9.1.1.8 Visit 8 (Day 71) p. 67	9.1.1.8 Visit 8 (Day **~~85~~**) This visit will occur **~~84~~** days after Visit **~~2~~** (randomization). (…) **~~The following observations~~** will be **~~made at Visit 8:~~** 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~~**	9.1.1.8 Visit 8 (Day **71**) This visit will occur **70** days after Visit **3** (randomization). (…) **Visit 8** will be **completed by telephone and will comprise a review of** concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.	See Section 2.3

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Section 9.1.1.8 Visit 8 (Day 71) p. 67 (continued) Section 9.1.1.8 Visit 8 (Day 71) p. 67 (continued)	**~~of IMP, a blood sample will be taken for analysis of plasma concentrations of concomitant AEDs.~~** **~~The PGIC, SGIC/CGIC and Vineland-II will also be performed.~~** **~~Suicidality will be assessed using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgement.~~** **~~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.~~**		
Section 9.1.1.9 Visit 9 (Day 85) p. 67	9.1.1.9 Visit 9 (Day **~~113, End of Treatment/Withdrawal Visit~~**) This visit will occur **~~112~~** days after Visit **~~2~~** (randomization) **~~or earlier if the subject withdraws from the study~~**. (…)	9.1.1.9 Visit 9 (Day **85**) This visit will occur **84** days after Visit **3** (randomization). (…)	See Section 2.3

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Section 9.1.1.9 Visit 9 (Day 85) p. 67 (continued)	~~**Patients will be instructed to record the dosing time of their concomitant AEDs in the diary.**~~ The following observations will be made at Visit 9 ~~**/ 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]) will be taken for hematology, biochemistry~~,~~ urinalysis~~**, a urine THC screen, determination of serum IGF-1 levels (for patients less than 18 years of age) and a pregnancy test (using a serum sample, if appropriate), to be performed by the central laboratory**~~. (…) ~~**PK samples (patients >20 kg in weight only) will be taken at baseline and at 2-hours and 4-hours after the last dose of IMP (taken in clinic).**~~	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]) will be taken for hematology, biochemistry **and** urinalysis. (…)	

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Section 9.1.1.9 Visit 9 (Day 85) p. 67 (continued)	~~**An additional PK sample will be taken six hours after the first dose for patients aged 18 years or above.**~~ The ~~**following assessments will also be performed: QOLCE/QOLIE-31-P,**~~ SGIC/CGIC~~,~~ ~~**SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II**~~. (…) 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**~~. (…) ~~**For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.**~~ ~~**For patients who 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**~~	The **PGIC** and SGIC/CGIC **will also be performed**. (…) 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. (…) **Patients will then receive new IMP.**	See Section 2.11

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Section 9.1.1.9 Visit 9 (Day 85) p. 67 (continued)	~~**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 should continue to complete the IVRS and paper diary and should return for Visit 10 (the 'End of Taper Period' visit), if possible.**~~ ~~**Patients who have completed all of the scheduled study visits will be offered the option of entering an OLE study.**~~ ~~**Entry is to be on the same day as Visit 9 (Day 113).**~~ ~~**Patients not entering the OLE study at this visit will be given a 10-day supply of IMP (if required) and instructions for tapering the dose, during which time IVRS and paper diary information will continue to be recorded.**~~		

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Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/ Withdrawal Visit) p. 67–69 Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/ Withdrawal Visit) p. 67–69 (continued)	9.1.1.10 Visit 10 (Day **~~123~~**, End of **~~Taper~~**) This visit **~~is required only for those patients who do not enter the OLE study on the day of Visit 9 or for those who withdraw early and taper IMP.~~** **~~For patients who complete the study but opt not to enter the OLE study, Visit 10 should occur 10 (+3) days after Visit 9 (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 10**~~:~~** **~~seizure information,~~** 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,~~**	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**	See Section 2.3

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Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/ Withdrawal Visit) p. 67–69 (continued)	**~~biochemistry and urinalysis)~~**.	**precocious puberty), details of menstruation (for females), ECG,** vital signs, **epilepsy-related hospitalizations and AEs**. **Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen, determination of serum IGF-1 levels (for patients less than 18 years of age) and a pregnancy test (using a serum sample, if appropriate), 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 at baseline and at 2-hours and 4-hours after the last dose of IMP (taken in clinic).** **An additional PK sample will be taken six hours after the first dose for patients aged 18 years or above.** **The following assessments will also be performed: QOLCE/QOLIE-31-P, PGIC, SGIC/CGIC,**	

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Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/ Withdrawal Visit) p. 67–69 (continued)	(…) (…) ~~**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.**~~	**SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II.** (…) **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 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**	

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Section 9.1.1.10 Visit 10 (Day 113, End of Treatment/ Withdrawal Visit) p. 67–69 (continued)		**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 should continue to complete the IVRS 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 and paper diary information will continue to be recorded.**	
Section 9.1.1.11 Visit 11 (Day 123, End of Taper) p. 69	9.1.1.11 Visit 11 (Day **~~151, Safety Follow-Up~~**) This visit is required for patients who do not enter the OLE **~~study~~** or who withdraw **~~from the study~~** early. **~~This visit should occur four weeks after Visit 10 (+3~~**	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**	See Section 2.3

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Section 9.1.1.11 Visit 11 (Day 123, End of Taper) p. 69 (continued)	~~**days), or date of final dosing, and can be conducted over the telephone.**~~ The following observations will be made at Visit 11: concomitant medications (including AEDs), epilepsy-related hospitalizations and AEs.	**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: **seizure information,** 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 using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.** **For patients 12 years of age and older, the trained**	

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		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.** **The patient diaries will be collected.**	
Section 9.1.1.12 Visit 12 (Day 151, Safety Follow-Up) p. 69	<N/A>	**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.**	See Section 2.3
Section 9.1.2 Open Label Extension p. 70	Patients and their parent(s)/legal representative will be invited to participate in the OLE when they reach the End of Treatment visit (Visit ~~9~~) of the Blinded Phase. (…)	Patients and their parent(s)/legal representative will be invited to participate in the OLE when they reach the End of Treatment visit (Visit **10**) of the Blinded Phase. (…)	

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	Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit ~~**1**~~ will be enrolled into the OLE.	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.	
Section 9.1.2.1 Visit B1 (Day 1) p. 70–71 Section 9.1.2.1 Visit B1 (Day 1) p. 70–71 (continued)	(…) The following data collected at the 'End of Treatment' visit of the ~~**Core Study**~~ 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 (including THC screen, serum IGF-1 levels (patients less than 18 years of age) and pregnancy test (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, concomitant medications and/or changes to medication, suicidality, QOLCE/QOLIE-31-P, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II.	(…) 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 (including THC screen**)**, serum IGF-1 levels (patients less than 18 years of age) and pregnancy test (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, concomitant medications and/or changes to medication, suicidality, QOLCE/QOLIE-31-P, **PGIC,** SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL,	See Section 2.11

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	(…) Patients will take their final dose of ~~**Core Study**~~ IMP in the morning of Visit ~~**1**~~, followed by collection of the Blinded Phase 'End of Treatment' assessments. (…)	SCQ and the Vineland-II. (…) 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. (…)	
Section 9.1.2.3 Visit B3 (Day 36) p. 72 Section 9.1.2.3 Visit B3 (Day 36) p. 72 (continued)	9.1.2.3 Visit B3 (Day ~~**29**~~) Visit B3 will take place ~~**28**~~ days after Visit B1. (…) The following assessments will be made at Visit B3: vital signs, physical examination (including height and body weight), ECG, ~~**suicidality,**~~ PGIC~~,~~ SGIC/CGIC ~~**and Vineland-II**~~.	9.1.2.3 Visit B3 (Day **36**) Visit B3 will take place **35** days after Visit B1. (…) The following assessments will be made at Visit B3: vital signs, physical examination (including height and body weight), ECG, PGIC **and** SGIC/CGIC. **Suicidality will be assessed using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.**	See Section 2.11
Section 9.1.2.4 Visit B4 (Day 92) p. 73	9.1.2.4 Visit B4 (Day ~~**85**~~) This visit will occur ~~**84**~~ days after Visit B1. (…) The following assessments will also be performed:	9.1.2.4 Visit B4 (Day **92**) This visit will occur **91** days after Visit B1. (…) The following assessments will also be performed:	

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	QOLCE/QOLIE-31-P, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment. (…) All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made.	QOLCE/QOLIE-31-P, **PGIC,** SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment. (…) 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.**	
Section 9.1.2.5 Visit B5 to End of Treatment p. 73–75	(…) Assessment Visits will be scheduled every three months beginning at Visit ~~**B5**~~ (Week 26) until patients have been enrolled in the OLE for one year. (…) At each Re-supply Visit patients will be dispensed with sufficient IMP for a maximum of ~~**10**~~ weeks' treatment. (…) <Table 9.1.2-1 OLE Visit Schedule>	(…) Assessment Visits will be scheduled every three months beginning at Visit **B6** (Week 26) until patients have been enrolled in the OLE for one year. (…) At each Re-supply Visit patients will be dispensed with sufficient IMP for a maximum of **11** weeks' treatment. (…) <Table 9.1.2**.5**-1 OLE Visit Schedule>	See Section 2.11

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	<Visit Number> | (…) | <Time from Visit B1 (except where indicated)> (…) | (…) | (…) <B13> | (…) | 78 weeks (±~~**7**~~ days) (…) | (…) | (…) *<Continue sequentially>* | (…) | *Continue every ~~**8 – 10**~~ weeks between Assessment Visits*	<Visit Number> | (…) | <Time from Visit B1 (except where indicated)> (…) | (…) | (…) <B13> | (…) | 78 weeks (±**14** days) (…) | (…) | (…) *<Continue sequentially>* | (…) | *Continue every **7–11** weeks between Assessment Visits*	
Section 9.1.2.5.1 Assessment Visits p. 75 Section 9.1.2.5.1 Assessment Visits p. 75 (continued)	The following assessments will also be performed: QOLCE/QOLIE-31-P, SGIC/CGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. Suicidality will be assessed using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	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 using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.	See Section 2.11
Section 9.1.2.6 End of Treatment / Withdrawal Visit P. 76	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 (including THC screen), serum IGF-1 levels	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 (including THC screen), serum IGF-1 levels	See Section 2.3

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Section 9.1.2.6 End of Treatment / Withdrawal Visit P. 76 (continued)	(patients less than 18 years of age) and pregnancy test (if appropriate), 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, **~~suicidality,~~** QOLCE/QOLIE-31-P, SGIC/CGIC, PGIC, SGIC-SD/CGIC-SD, Wechsler Tests, CBCL/ABCL, SCQ and the Vineland-II. 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.	(patients less than 18 years of age) and pregnancy test (if appropriate), 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 using the C-SSRS/Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.** 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.	
Section 9.2.9 Clinical Laboratory Sampling p. 82	(...) 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. **~~All laboratory results considered to represent an AE must~~**	(...) 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. (...)	See Section 2.11

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	~~be documented in the CRF.~~ (...)		
Section 9.2.9.1 Pharmacokinetic Blood Sampling p. 82	The plasma concentration/time curves of CBD, THC and their major metabolites will be assessed at Visits **~~2~~** and **~~9~~**. **~~B~~**lood samples will be taken as follows: • One sample pre-dose (i.e., prior to administration of IMP). • **~~One sample between two and three hours pose-dose.~~** • One sample between four and five hours post-dose. • One sample between six and seven hours post-dose **~~(patients 18 years and above only)~~**. (…)	The plasma concentration/time curves of CBD, THC and their major metabolites will be assessed at Visits **3** and **10 for patients weighing more than 20 kg**. **Where appropriate, b**lood samples will be taken as follows: • One sample pre-dose (i.e., prior to administration of IMP). • One sample between four and five hours post-dose. • One sample between six and seven hours post-dose. • **One sample between eight and ten hours post-dose** **~~(patients 18 years and above only)~~**. (…)	See Section 2.9
Section 9.2.9.2 Determination of Plasma Concentrations of Concomitant	Plasma concentrations of concomitant AEDs will be assessed at Visits **~~2, 4, 6, 8~~** and **~~9~~**/ the Withdrawal visit (if possible) during the blinded phase and at Visits B2, B3, B4 and all subsequent Assessment Visits during the OLE.	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.	See Section 2.3

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Antiepileptic Drugs p. 83	(…)	(…)	
Section 9.2.10 Interactive Voice Response System p. 84	(…) • Randomize a patient and obtain their patient number (Visit ~~**2**~~). • Obtain dispensing information (Visits ~~**2,**~~ 3, 4, 5, 6, ~~**8,**~~ and during OLE). • Provide completion/taper/premature termination information (Visit ~~**9**~~). (…)	(…) • Randomize a patient and obtain their patient number (Visit **3**). • Obtain dispensing information (Visits 3, 4, 5, 6, **7, 9** and during OLE). • Provide completion/taper/premature termination information (Visit **10**). (…)	See Section 2.3
Section 9.2.11 Patient Diary p. 84–85	(…) The number and type and severity of seizures as well as information on AEs, concomitant AEDs and rescue medication will be collected each day from ~~**screening**~~ (Visit ~~**1**~~) until completion of dosing (Visit ~~**9**~~/Withdrawal visit). Information on IMP intake will also be recorded each day from randomization (Visit ~~**2**~~) until completion of dosing or withdrawal (Visit ~~**9**~~/Withdrawal visit). Seizure information, including the number~~**, type**~~ and	(…) 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**) until completion of dosing (Visit **10**/Withdrawal visit). 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**	See Section 2.1.3

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Section 9.2.11 Patient Diary p. 84–5 (continued) Section 9.2.11 Patient Diary p. 84–85 (continued)	severity of focal seizures and the number of **~~infantile/epileptic spasms and~~** 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. (…)	**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. (…) **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**[#] **- Tlonic**[#] **- Clonic**[#] **- Atonic**[#] • **'Other' seizures:** **- Absence seizures**[#]	See Section 2.1.4

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 1, Date 16 Jun 15 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 1 (Clinical Protocol Version 2, Date 21 Oct 15) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	~~**The**~~ severity of seizures will be assessed according to the following criteria: (…)	**- Myoclonic seizures**[**] **- Partial 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: (…)	
Section 9.2.13 Menstruation p. 88	Caregivers will be asked if the female patient is menstruating and details will be recorded as part of their baseline (Visit ~~**2**~~); any changes in normal cycles will be captured at Visit ~~**9**~~ / the Withdrawal visit and subsequent OLE visits.	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** / the Withdrawal visit and subsequent OLE visits.	See Section 2.3
Section 12.1.1 Adverse Event p. 98	(…) 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	(…) 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	See Section 2.3

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 1, Date 16 Jun 15 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 1 (Clinical Protocol Version 2, Date 21 Oct 15) *(Revised wording is underscored and in bold)*	Rationale for the amendment
	point up to the post treatment, safety follow-up visit (Visit ~~**11**~~ and Visit OLE Follow-up), which may or may not be considered to be related to the IMP. (…)	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. (…)	
Section 12.3 Reporting Procedures for Serious Adverse Events p. 99–100	(…) The Investigator is not obliged to actively monitor for any new SAEs which occurred after the last formal follow-up observational period (Visit ~~**11**~~ or OLE Follow-up). (…) Any other problem discovered outside these time limits (Visit ~~**11**~~ 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. (…)	(…) 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). (…) 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. (…)	See Section 2.3
Section 12.6 Reporting Procedures for All Adverse Events	(…) This includes all events from the time following screening (Visit 1) up to and including the post study follow-up visit (Visit ~~**11**~~ or OLE Follow-up), whether or	(…) 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	See Section 2.3

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 1, Date 16 Jun 15 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 1 (Clinical Protocol Version 2, Date 21 Oct 15) *(Revised wording is underscored and in bold)*	Rationale for the amendment
p. 101	not attributed to IMP and observed by the Investigator or patient. (…)	not attributed to IMP and observed by the Investigator or patient. (…)	
Section 13.1 Sample Size, Power and Significance Levels p. 106	(…) A total of ~~**144**~~ patients will be enrolled. The ~~**144**~~ patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, ~~**48**~~ patients per group). Patients in the placebo group will be split into two cohorts (~~**24**~~ patients 25 mg/kg/day dosing volumes and ~~**24**~~ patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.	(…) A total of **192** patients will be enrolled. The **192** patients will be randomly allocated on a 1:1:1 basis (25 mg/kg/day GWP42003-P, 50 mg/kg/day and placebo, **64** patients per group). Patients in the placebo group will be split into two cohorts (**32** patients 25 mg/kg/day dosing volumes and **32** patients receiving 50 mg/kg/day dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.	See Section 2.6
Section 13.1 Sample Size, Power and Significance Levels p. 106 (continued)	If it is assumed that patients in the placebo group will experience a mean reduction in ~~**focal**~~ seizure frequency of 15% (from baseline), this sample size of ~~**48**~~ patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in ~~**focal**~~ seizures). This is based on a standard deviation of 60%, using a	If it is assumed that patients in the placebo group will experience a mean reduction in seizure frequency of 15% (from baseline), this sample size of **64** patients per group will be sufficient to detect a difference of 35% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in seizures). This is based on a standard deviation of 60%, using a	

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	two-sided 5% significance level and ~~**80**~~% power. (…)	two-sided 5% significance level and **90**% power. (…)	
Section 13.6.1 Evaluable Period p. 109	(…) • Day 113 of treatment for the IVRS reported efficacy data and the day of Visit ~~**9**~~ for the CRF-based efficacy data; (…)	(…) • Day 113 of treatment for the IVRS reported efficacy data and the day of Visit **10** for the CRF-based efficacy data; (…)	See Section 2.3
Section 13.6.2 Primary Endpoint(s) p. 109–110 Section 13.6.2 Primary Endpoint(s) p. 109–110 (continued)	(…) The primary endpoint is the percentage change from baseline in number of ~~**focal**~~ seizures (average per 28 days) during the treatment period (maintenance and titration) in patients taking GWP42003-P compared with placebo.	(…) The primary endpoint is the percentage change from baseline in number of seizures* (average per 28 days) during the treatment period (maintenance and titration) 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.**	See Section 2.1.3

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	(…)	(…)	
Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 110–111 Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 110–111 (continued)	(…) • Wilcoxon rank-sum test on percentage change from baseline in number of **~~focal~~** seizures (average per 28 days) during the treatment period; • ANCOVA on percentage change from baseline in number of **~~focal~~** seizures (average per 28 days) during the maintenance period (Day 22 to the end of the evaluable period); • ANCOVA on percentage change from baseline in number of **~~focal~~** seizures (average per 28 days) during the treatment period, 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 **~~focal~~** 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	(…) • Wilcoxon rank-sum test on percentage change from baseline in number of seizures (average per 28 days) during the treatment period; • ANCOVA on percentage change from baseline in number of seizures (average per 28 days) during the maintenance period (Day 22 to the end of the evaluable period); • ANCOVA on percentage change from baseline in number of seizures (average per 28 days) during the treatment period, 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	See Section 2.1.2

Revised Protocol Section Number, Heading and Page Number	Original Wording from Clinical Protocol Version 1, Date 16 Jun 15 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Amendment 1 (Clinical Protocol Version 2, Date 21 Oct 15) *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 13.6.2.1 Sensitivity Analysis for the Primary Endpoint p. 110–111 (continued)	of seizures during the treatment period based on non-missing data: (…) • Mixed Effect Model Repeated Measures (MMRM) on percentage change from baseline in number of **~~focal~~** seizures (average per 28 days) during the treatment period: – (…) • MMRM on percentage change from baseline in number of **~~focal~~** seizures (average per 28 days) during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption. – (…) – MI will be performed on the **~~focal~~** seizure frequency, based on time points corresponding to each 21 calendar days of the treatment period. (…) The imputation model will include baseline **~~focal~~** seizure frequency and each 21-day time point up to time point *t* (in chronological order).	during the treatment period based on non-missing data: (…) • Mixed Effect Model Repeated Measures (MMRM) on percentage change from baseline in number of seizures (average per 28 days) during the treatment period: – (…) • MMRM 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. – (…) – MI will be performed on the seizure frequency, based on time points corresponding to each 21 calendar days of the treatment period. (…) The imputation model will include baseline seizure frequency and each 21-day time point up to time point *t* (in chronological order).	

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	(…) The imputation model will include ~~**focal**~~ seizure frequency at baseline and each 21-day time point up to time point *t* (in chronological order) and will be performed for each GWP42003-P group separately. • ANCOVA on percentage change from baseline in number of ~~**focal**~~ seizures (average per 28 days) during the treatment period, using MI to impute data under the MNAR assumption. (…)	(…) The imputation model will include seizure frequency at baseline and each 21-day time point up to time point *t* (in chronological order) and will be performed for each GWP42003-P group separately. • ANCOVA on percentage change from baseline in number of seizures (average per 28 days) during the treatment period, using MI to impute data under the MNAR assumption. (…)	
Section 13.6.3 Secondary Endpoint(s) p. 112–113	(…) Antiepileptic ~~**e**~~fficacy ~~**m**~~easures • Percentage change from baseline in number of ~~**focal**~~ seizures (average per 28 days; ~~**open-label extension**~~ phase only). • Number of patients considered treatment responders defined as those with a ≥25%, ≥50%, ≥75% or 100% reduction in ~~**focal**~~ seizure frequency. • Number of patients experiencing a >25% worsening, −25 to +25% no change, 25–50% improvement, 50–	(…) Antiepileptic **E**fficacy **M**easures • 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%, ≥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	See Section 2.1.2

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Section 13.6.3 Secondary Endpoint(s) p. 112–113 (continued)	75% improvement or >75% improvement in ~~**focal**~~ seizure frequency. • (…) • Change in number of ~~**focal**~~ seizure-free days. • (…) • (…) Cognitive and Behavioral Function: • Changes in Vineland-II. • Changes in Wechsler Scales (pre-school, primary, children, adult). • Changes in CBCL and ABCL. 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]). ~~**Autistic Features:**~~ • ~~**Change in SCQ score.**~~ • (…)	frequency. • (…) • Change in number of seizure-free days. • (…) • **<u>Change in number of 'other' seizures (absence, myoclonic, partial sensory and infantile/epileptic spasms).</u>** • (…) **<u>TAND:</u>** Cognitive and Behavioral Function: • Changes in Vineland-II. • Changes in Wechsler Scales (pre-school, primary, children, adult). • Changes in CBCL and ABCL. **<u>Autistic Features:</u>** • **<u>Change in SCQ score.</u>** Growth and Development (patients less than 18 years): • Change in serum IGF-1 levels. • Change in Tanner Staging score (for patients aged 10–	See Section 2.4

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	For changes in composite focal seizure score, number of **~~focal~~** seizure-free days, number of seizures by subtype, number of infantile/epileptic spasms, use of rescue medication, number of episodes of status epilepticus, Vineland-II, Wechsler scales, CBCL, ABCL, SCQ, QOLCE, QOLIE-31-P, SGIC/CGIC and PGIC 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. (…)	17 [inclusive]). • (…) For changes in composite focal seizure score, number of seizure-free days, number of seizures by subtype, number of infantile/epileptic spasms, use of rescue medication, number of episodes of status epilepticus, Vineland-II, Wechsler scales, CBCL, ABCL, SCQ, QOLCE, QOLIE-31-P, SGIC/CGIC and PGIC 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. (…)	
Section 14 SAFETY MONITORING COMMITTEE p. 116	(…) Furthermore, an independent ESC will be instated to **~~monitor the TSC diagnosis and~~** verify the seizure types of screened patients on an ongoing basis **~~in order to ascertain the correct study population is randomized~~**. Investigators will submit a documented history of TSC directly to the ESC for **~~confirmation of diagnosis and~~** verification of seizure types.	(…) 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	See Section 2.2

<table>
<tr><th>Revised Protocol Section Number, Heading and Page Number</th><th>Original Wording from Clinical Protocol Version 1, Date 16 Jun 15
(Deleted wording is struck through and in bold)</th><th>Revised Wording from Clinical Protocol Amendment 1
(Clinical Protocol Version 2, Date 21 Oct 15)
(Revised wording is underscored and in bold)</th><th>Rationale for the amendment</th></tr>
<tr><td></td><td>The ESC will provide written documentation <s>of the confirmation of diagnosis</s> directly to the investigator and guidance on seizure types, if applicable, for inclusion in the patient file.
(…)</td><td>the investigator and guidance on seizure types, if applicable, for inclusion in the patient file.

(…)</td><td></td></tr>
<tr><td>APPENDIX 1
SCHEDULE OF ASSESSMENTS
p. 130–132

APPENDIX 1
SCHEDULE OF ASSESSMENTS
p. 130–132
(continued)</td><td><Blinded Phase>
<See Appendix 1 for deletions from the Blinded Phase Schedule of Assessments table>
(…)
*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 <s>9</s> to Visit <s>11</s>.
<Open-label Extension>
(…)
<table><tr><td>(...)</td><td>B1</td><td>B3</td><td>B4</td></tr><tr><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td></tr><tr><td>Vineland-II</td><td>X</td><td><s>X</s></td><td>X</td></tr><tr><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td></tr></table></td><td><Blinded Phase>
<See Appendix 1 for additions to the Blinded Phase Schedule of Assessments table>
(…)
*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 <u>10</u> to Visit <u>12</u>.
<Open-label Extension>
(…)
<table><tr><td>(...)</td><td>B1</td><td>B3</td><td>B4</td></tr><tr><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td></tr><tr><td>Vineland-II</td><td>X</td><td></td><td>X</td></tr><tr><td>(...)</td><td>(...)</td><td>(...)</td><td>(...)</td></tr></table></td><td>See Section 2.3</td></tr>
</table>

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	*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 9 to Visit 11**~~.	*Telephone safety calls will be completed every two days during **the blinded transition,** titration **and** one week after the end of titration.	

5 REFERENCES

1 Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010;51(7):1236–41.

Appendix 1 SCHEDULE OF ASSESSMENTS

Original Wording from Clinical Protocol Version 1, Date 16 Jun 15

(Deleted wording is struck through and in bold)

Blinded Phase

Visit Number	1	2	3	4	5	6	7	8	9	10	11 ~~(Tel.)~~	Safety Calls*
Informed consent/assent	X											
Eligibility Criteria	X	X										
Randomization		~~X~~										
Demographics	X											
Medical history	X											
Vital signs	X	~~X~~	X	X	X	X		~~X~~	X	X		
Postural BP	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 urine sampling (dipstick urinalysis)	X	~~X~~	X	X	X	X		~~X~~	X	X		
Urine THC screen	X	~~X~~							~~X~~			
Pregnancy test (if appropriate)	X	~~X~~							~~X~~			
Pharmacokinetic blood sampling		~~X~~							~~X~~			
AED concentration		~~X~~		~~X~~		~~X~~		~~X~~	X			
AEs	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
Inpatient epilepsy-related hospitalizations		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	X	X	X		~~X~~	X			
SGIC/CGIC			X	X	X	X		~~X~~	~~X~~			
PGIC			X	X	X	X		~~X~~	~~X~~			
SGIC-SD/CGIC-SD									~~X~~			
QOLCE/QOLIE-31-P		~~X~~							~~X~~			
Wechsler Tests		~~X~~							~~X~~			
CBCL/ABCL		~~X~~							~~X~~			
SCQ		~~X~~							~~X~~			
Tanner Staging (where appropriate) and IGF-1 testing		~~X~~							~~X~~			
Menstruation question (where appropriate)		~~X~~							~~X~~			
Patient 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~~			

Revised Wording from Clinical Protocol Amendment 1
(Clinical Protocol Version 2, Date 21 Oct 15)
(Revised wording is underscored and in bold)

Blinded Phase

Visit Number	1	2	3	4	5	6	7	8	9	10	11	**12 (Tel.)**	Safety Calls*
Informed consent/assent	X												
Eligibility Criteria	X	X	**X**										
Randomization			**X**										
Demographics	X												
Medical history	X												
Vital signs	X		X	X	X	X	**X**		X	X	**X**		
Postural BP	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 urine sampling (dipstick urinalysis)	X		X	X	X	X	**X**		X	X	**X**		
Urine THC screen	X		**X**							**X**			
Pregnancy test (if appropriate)	X		**X**							**X**			
Pharmacokinetic blood sampling			**X**							**X**			
AED concentration			**X**		**X**		**X**		X	**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	X	X	**X**		X	**X**			
SGIC/CGIC			**X**	X	X	X	**X**			**X**			
PGIC			**X**	X	X	X	**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) and IGF-1 testing			**X**							**X**			
Menstruation question (where appropriate)			**X**							**X**			
Patient 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**			

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 1

(US ONLY)

This annex outlines the assessments and procedures for years 2–4 of the open-label extension. This annex will be implemented at US sites only.

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Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol annex 1 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 15 Apr 2019 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s) the US 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 Conference for Harmonisation Tripartite Guidelines for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of patients during the trial and for all trial-related medical decisions.

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.

Centre No: _____

Print name: _____ Date: _____
Principal Investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print name: PPD _____ Date: 23-Apr-2019
Senior Clinical Manager (DD Month YYYY)

Signature: PPD _____

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List of Abbreviations

ABCL	Adult Behavior Checklist
AE	Adverse event
AED	Antiepileptic drug
CBCL	Child Behavior Checklist
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CGIC-SD	Caregiver Global Impression of Change in Seizure Duration
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	12-lead electrocardiogram
EU	European Union
FDA	US Food and Drug Administration
GCP	Good clinical practice
GW	GW Research Ltd
IGF-1	Insulin-like growth factor-1
IMP	Investigational medicinal product
IVRS	Interactive voice response system
OLE	Open-label extension
PGIC	Physician Global Impression of Change
QOLCE	Quality of Life in Childhood Epilepsy
QOLIE-31-P	Quality of Life in Epilepsy
SCQ	Social Communication Questionnaire
SGIC	Subject Global Impression of Change
SGIC-SD	Subject Global Impression of Change in Seizure Duration
TSC	Tuberous sclerosis complex

(continued)

US	United States
Vineland-II	Vineland Adaptive Behavior Scales, Second Edition

Definition of Terms

Term	Definition
End of trial	Last patient last visit or last contact, whichever occurs last.
Enrolled patient	Any patient who has provided written informed consent/assent to take part in the trial.
Investigational medicinal product	Term used to describe both investigational active product and reference therapy (placebo).
Investigator	Trial principal investigator or a formally delegated study physician.

1 RATIONALE

Trial GWEP1521 consists of a randomized, parallel-group, 16-week double-blind-phase comparing 2 doses of GWP42003-P with placebo, followed by a 1-year open-label extension (OLE) phase. To ensure continued access to GWP42003-P prior to approval, the OLE phase will be extended to a total of 4 years in duration in the United States (US). Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of 4 years of OLE treatment, whichever occurs first.

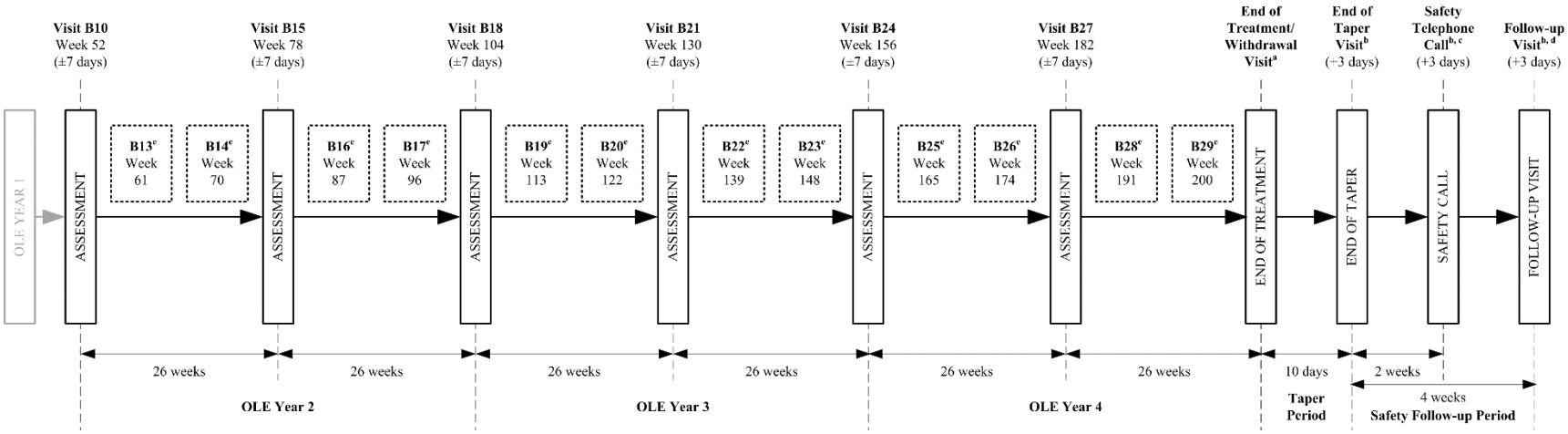
2 SUMMARY OF THE ANNEX

Patients will complete the first year of the OLE at Visit B10 and enter a second year of OLE treatment. Patients completing a second year of OLE treatment will enter a third year of OLE treatment. Patients who complete OLE year 3 may enter a fourth year of OLE treatment. Dosing will remain consistent and there is no requirement for dose adjustment or further titration upon entry into years 2, 3, or 4.

Assessment visits have been added at Week 78, Week 104, Week 130, Week 156, and Week 182 (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in years 2, 3, and 4 to ensure resupply volumes are manageable for both patients and dispensing staff. Attendance of the patient is not required for the dispensing visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 4 years of OLE treatment, whichever occurs first. Following completion of the OLE, patients who do not immediately continue to use commercial GWP42003-P will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit. A safety follow-up telephone call will be completed 2 weeks after the End of Taper visit and a safety Follow-up visit will be completed 4 weeks after the End of Taper visit.

3 TREATMENT SCHEMATIC DIAGRAM



[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 4 years of OLE treatment (i.e., 208 weeks [±7 days] from Visit B1); whichever occurs first.

[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] Visits B13, B14, B16, B17, B19, B20, B22, B23, B25, B26, B28, and B29 – Resupply visits (±7 days).

4 DESIGN AND PROCEDURES

Patients and their parent(s)/legal representative will be invited to participate in years 2, 3, and 4 of the OLE when they reach Visit B10 of the OLE phase. They will be issued with additional 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 additional visits with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit B10 will continue in the OLE.

Patients will continue to make weekly interactive voice response system (IVRS) diary calls throughout their second, third, and fourth years of OLE participation.

4.1 Visit B10 (Week 52)

In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in the US who provide written informed consent/assent (see Section 5) will receive sufficient open-label IMP for 9 weeks' home dosing and will be instructed to maintain consistent dosing. An additional dose calculator and paper diary will be issued, and patients will be trained on their appropriate use.

The Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE. The investigator must record the patient's attendance at the visit and confirm their continued participation.

4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), B23 (Week 148), B25 (Week 165), B26 (Week 174), B28 (Week 191), and B29 (Week 200)

Visits B13, B14, B16, B17, B19, B20, B22, B23, B25, B26, B28, and B29 will occur 61, 70, 87, 96, 113, 122, 139, 148, 165, 174, 191, and 200 weeks after Visit B1, respectively. 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 resupply visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Each visit will comprise a review of concomitant medications (including antiepileptic drugs [AEDs]), epilepsy-related hospitalizations and adverse events (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.

4.3 Assessment Visits B15 (Week 78), B18 (Week 104), B21 (Week 130), B24 (Week 156), and B27 (Week 182)

Visits B15, B18, B21, B24, and B27 will occur 78, 104, 130, 156, and 182 weeks after Visit B1, respectively. 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 each visit:

- Concomitant medications (including AEDs)
- Physical examination (including height and body weight)
- 12-lead electrocardiogram (ECG)
- Vital signs
- Epilepsy-related hospitalizations
- AEs
- Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

At each assessment visit, clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum insulin-like growth factor-1 (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 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 IMP until the next scheduled visit.

In addition to the above, the following assessments will be made at Visit B18 and Visit B24:

- Details of menstruation (for females)
- Tanner staging (patients aged 10–17 [inclusive] only)
- Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy (QOLIE-31-P)
- Subject Global Impression of Change (SGIC)/Caregiver Global Impression of Change (CGIC)
- Physician Global Impression of Change (PGIC)
- Wechsler Tests
- Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)
- Social Communication Questionnaire (SCQ)
- Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)

4.4 End of Treatment/Withdrawal Visit

This visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 4 years of OLE treatment (i.e., 208 weeks [±7 days] from Visit B1); whichever occurs first.

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] only)
- ECG
- IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and 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
- Vineland-II
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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, 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 trial. For patients who immediately continue to use commercial GWP42003-P following the End of Treatment visit, the IVRS will be contacted to confirm the patient's completion of this trial and the paper diaries will be collected. For patients 12 years of age and older who complete treatment and

immediately continue to use commercial GWP42003-P, or for patients 12 years of age and older who withdraw early and do not taper IMP, 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 complete treatment but do not immediately continue to use commercial GWP42003-P following the End of Treatment visit, 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.

Following the End of Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.5 End of Taper Visit

This visit is required for patients who: 1) withdraw from the trial and taper IMP; or 2) complete treatment but do not immediately continue to use commercial GWP42003-P. The End of Taper visit will take place 10 (+3) days after the End of Treatment/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 assessments will be made:

- Vital signs
- Physical examination (including height and body weight)
- IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication
- AEs
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol
- ECG

- Clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis)

The investigator must assess adherence to the dosing regimen.

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 the End of Taper visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.6 Safety Telephone Call

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Safety Telephone Call will be conducted 2 weeks (+3 days) after the patient's last dose of GWP42003-P (including final taper period dose). During this call, 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.

4.7 Follow-up Visit

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Follow-up visit will take place 4 weeks (+3 days) after the patient's last dose of GWP42003-P (including final taper period dose) and can be conducted by telephone. During this visit/call, caregivers will be asked for information on:

- AEs
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication

5 INFORMED CONSENT/ASSENT

An institutional review board/independent ethics committee-approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.

6 DATA ANALYSIS

6.1 Patients to Analyze

Patients in the US who continue to participate in years 2, 3, and 4 of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.

7 IMPLEMENTATION OF THE ANNEX

This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol. It will be kept in the trial master file at GW as well as in each US investigational center file and, if applicable, pharmacy site file.

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open-label Extension

Visit Number	B10	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
		B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23	B24	B25	B26	B27	B28	B29				
Week	52	61	70	78	87	96	104	113	122	130	139	148	156	165	174	182	191	200	See footnote[a]	10 days after End of Treatment	2 weeks after last dose	4 weeks after last dose
Visit Window	±7	±7		±7	±7		±7	±7		±7	±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		
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 urine sampling (dipstick urinalysis)	X			X			X			X			X			X			X	X		
Pregnancy test, where appropriate	X			X			X			X			X			X			X			
IGF-1 testing	X			X			X			X			X			X			X			
AED concentration	X			X			X			X			X			X			X			
AEs	X	X		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	X	X
Inpatient epilepsy-related hospitalizations	X	X		X	X		X	X		X	X		X	X		X	X		X	X	X	X
Suicidality assessment	X			X			X			X			X			X			X	X		

Visit Number	B10	Resupply B13	Resupply B14	Assess-ment B15	Resupply B16	Resupply B17	Assess-ment B18	Resupply B19	Resupply B20	Assess-ment B21	Resupply B22	Resupply B23	Assess-ment B24	Resupply B25	Resupply B26	Assess-ment B27	Resupply B28	Resupply B29	End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
Week	52	61	70	78	87	96	104	113	122	130	139	148	156	165	174	182	191	200	See footnote[a]	10 days after End of Treatment	2 weeks after last dose	4 weeks after last dose
Visit Window	±7	±7		±7	±7		±7	±7		±7	±7		±7	±7		±7	±7		±7	+3	+3	+3
Vineland-II	X						X						X						X			
SGIC/CGIC	X						X						X						X			
PGIC	X						X						X						X			
SGIC-SD/CGIC-SD	X			X			X			X			X			X			X			
QOLCE/QOLIE-31-P	X						X						X						X			
Wechsler Tests	X						X						X						X			
CBCL/ABCL	X						X						X						X			
SCQ	X						X						X						X			
Tanner Staging (where appropriate)	X						X						X						X			
Menstruation question (where appropriate)	X						X						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	X		X	X		
IMP dispensing	X	X		X	X		X	X		X	X		X	X		X	X		X			
Collection of IMP	X	X		X	X		X	X		X	X		X	X		X	X		X	X		
IMP compliance review	X	X		X	X		X	X		X	X		X	X		X	X		X	X		
Study Medication Use and Behavior Survey																			X[e]			

[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 4 years of OLE treatment (i.e., 208 weeks [±7 days] from Visit B1); whichever occurs first.

[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] 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.

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 1 (US ONLY) AMENDMENT NUMBER: 2

to be incorporated into the Protocol Annex, creating CLINICAL PROTOCOL ANNEX 1 VERSION 3 (US ONLY), DATE 15 APRIL 2019

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement

1 PROTOCOL SYNOPSIS

Trial 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.
Indication	Seizures[a] in patients with tuberous sclerosis complex (TSC).
Trial Design	Trial GWEP1521 consists of a randomized, parallel-group, 16-week double-blind phase comparing 2 doses of GWP42003-P with placebo, followed by a 1-year open-label extension (OLE) phase. Clinical Protocol Annex 1 (US Only) Version 3 extends the OLE phase by a further 3 years in the United States. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 4 years of OLE treatment, whichever occurs first.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

[a] 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.

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List of Appendices

2 RATIONALE

This Clinical Protocol Annex 1 (US only) amendment 2 (will be incorporated into the Protocol Annex creating Clinical Protocol Annex 1 [US only] Version 3, Date 15 April 2019) addresses the following issue(s):

2.1 Duration of Open-label Extension Phase

The OLE phase will be extended in duration in the US to ensure continued access to GWP42003-P prior to approval. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 4 years of OLE treatment, whichever occurs first. Procedures for each resupply visit and assessment visit have been condensed into single sections in the Annex to minimize repetition.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019. It will be kept in the trial master file at GW as well as in each investigational centre file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 2 Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Title page p. 1	(...) This annex outlines the assessments and procedures for years 2 ~~**and 3**~~ of the open-label extension. (...)	(...) This annex outlines the assessments and procedures for years 2**–4** of the open-label extension. (...)	See Section 2.1
Section 1 RATIONALE p. 6	(...) To ensure continued access to GWP42003-P prior to approval, the OLE phase will be extended to a total of ~~**3**~~ years in duration in the United States (US). (...) Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of ~~**3**~~ years~~,~~ OLE treatment, whichever occurs first. ~~**The intent is to ensure continued access**~~	(...) To ensure continued access to GWP42003-P prior to approval, the OLE phase will be extended to a total of **4** years in duration in the United States (US). (...) Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of **4** years **of** OLE treatment, whichever occurs first.	See Section 2.1

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 2 Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 1 RATIONALE p. 6 (continued)	**~~to GWP42003-P through compassionate schemes (e.g., Named Patient Supply) in other countries. However, in countries where compassionate access proves difficult prior to first approvals, the OLE duration may also be extended to include these additional countries.~~**		See Section 2.1
Section 2 SUMMARY OF THE ANNEX p. 6	(...) Dosing will remain consistent and there is no requirement for dose adjustment or further titration upon entry into years 2 **~~or~~** 3. Assessment visits have been added at Week 78, Week 104, Week 130, **~~and~~** Week 156 (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in years 2 **~~and~~** 3 to ensure resupply	(...) **Patients who complete OLE year 3 may enter a fourth year of OLE treatment.** Dosing will remain consistent and there is no requirement for dose adjustment or further titration upon entry into years 2**,** 3**, or 4**. Assessment visits have been added at Week 78, Week 104, Week 130, Week 156**, and Week 182** (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in years 2**,** 3**, and 4** to ensure resupply	See Section 2.1

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 2 Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 2 SUMMARY OF THE ANNEX p. 6 (continued)	volumes are manageable for both patients and dispensing staff. (...) Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of **~~3~~** years~~'~~ OLE treatment, whichever occurs first. (...) A safety follow-up visit will be completed 4 weeks after the End of Taper visit.	volumes are manageable for both patients and dispensing staff. (...) Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of **4** years **of** OLE treatment, whichever occurs first. (...) A safety follow-up **telephone call will be completed 2 weeks after the End of Taper visit and a safety Follow-up** visit will be completed 4 weeks after the End of Taper visit.	See Section 2.1
Section 4 DESIGN AND PROCEDURES p. 8	Patients and their parent(s)/legal representative will be invited to participate in years 2 **~~and~~** 3 of the OLE when they reach Visit B10 of the OLE phase. (...)	Patients and their parent(s)/legal representative will be invited to participate in years 2**,** 3**, and 4** of the OLE when they reach Visit B10 of the OLE phase. (...)	See Section 2.1

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 2 Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019 *(Revised wording is underscored and in bold)*	Rationale for the amendment
	Patients will continue to make weekly interactive voice response system (IVRS) diary calls throughout their second ~~**and**~~ third years of OLE participation.	Patients will continue to make weekly interactive voice response system (IVRS) diary calls throughout their second**,** third**, and fourth** years of OLE participation.	

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 2 Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), and B23 (Week 148), B25 (Week 165), B26 (Week 174), B28 (Week 191), and B29 (Week 200) p. 8	4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), **~~and~~** B23 (Week 148) Visits B13, B14, B16, B17, B19, B20, B22, **~~and~~** B23 will occur 61, 70, 87, 96, 113, 122, 139, **~~and~~** 148 weeks after Visit B1, respectively. (…)	4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), B23 (Week 148)**, B25 (Week 165), B26 (Week 174), B28 (Week 191), and B29 (Week 200)** Visits B13, B14, B16, B17, B19, B20, B22, **~~and~~** B23**, B25, B26, B28, and B29** will occur 61, 70, 87, 96, 113, 122, 139, 148**, 165, 174, 191, and 200** weeks after Visit B1, respectively. (…)	See Section 2.1

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 2 Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 4.3 Assessment Visits B15 (Week 78), B18 (Week 104), and B21 (Week 130), B24 (Week 156), and B27 (Week 182) p. 9	4.3 Assessment Visits B15 (Week 78), B18 (Week 104), ~~**and**~~ B21 (Week 130) Visits B15, B18, and B21 will occur 78, 104, ~~**and**~~ 130 weeks after Visit B1, respectively. (...) In addition to the above, the following assessments will be made at Visit B18 ~~**only**~~: (...)	4.3 Assessment Visits B15 (Week 78), B18 (Week 104), B21 (Week 130)**, B24 (Week 156), and B27 (Week 182)** Visits B15, B18, and B21**, B24, and B27** will occur 78, 104, 130**, 156, and 182** weeks after Visit B1, respectively. (...) In addition to the above, the following assessments will be made at Visit B18 **and Visit B24**: (...)	See Section 2.1
Section 4.4 End of Treatment/ Withdrawal Visit p.10	This visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of ~~**3**~~ years~~.~~ OLE treatment (i.e., ~~**156**~~ weeks [±7 days] from Visit B1); whichever occurs first. (...)	This visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of **4** years **of** OLE treatment (i.e., **208** weeks [±7 days] from Visit B1); whichever occurs first. (...)	See Section 2.1

Revised Protocol Annex Section Number, Heading and Page Number	**Original Wording from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018** ***(Deleted wording is struck through and in bold)***	**Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 2 Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019** ***(Revised wording is underscored and in bold)***	**Rationale for the amendment**
Section 6.1 Patients to Analyze p. 14	Patients in the US who continue to participate in years 2 ~~**and**~~ 3 of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.	Patients in the US who continue to participate in years 2**,** 3**, and 4** of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.	See Section 2.1

5 REFERENCES

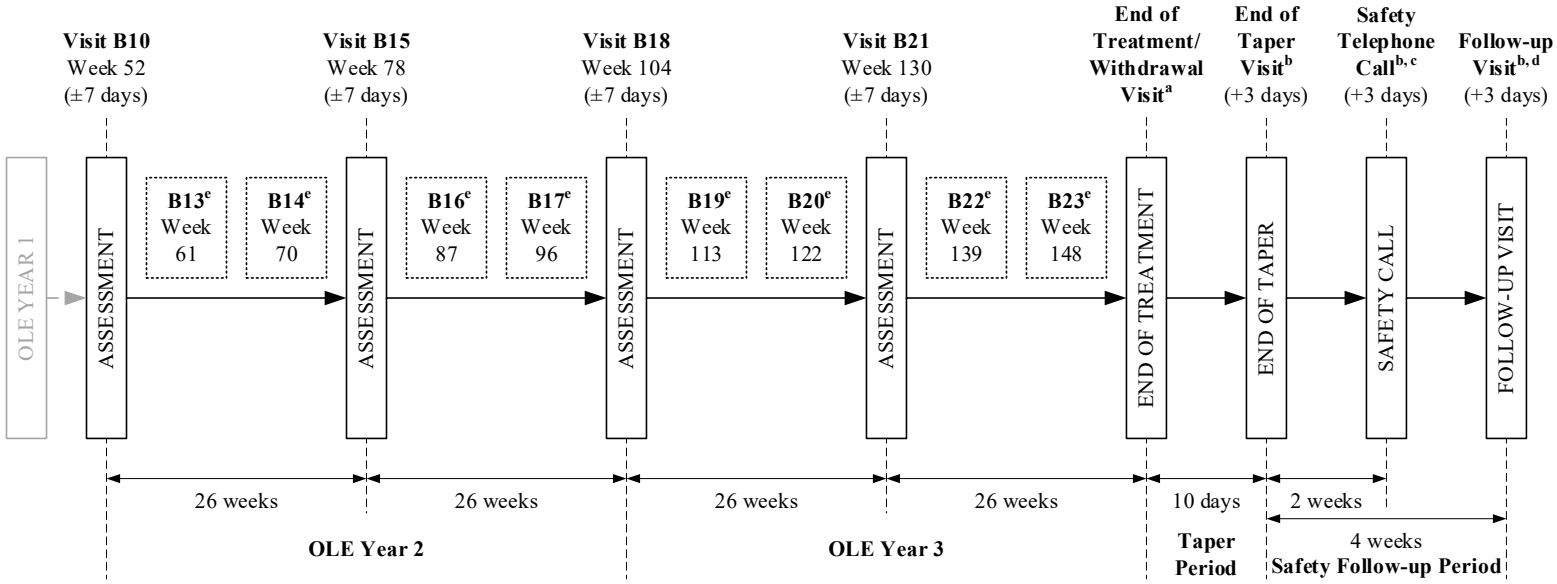
N/A

APPENDIX 1 AMENDED FIGURES AND TABLES

Original Figure from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018

(Deleted wording is struck through and in bold)

3 TREATMENT SCHEMATIC DIAGRAM



[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of **~~3~~** years~~.~~ OLE treatment (i.e., **~~156~~**-weeks [±7 days] from Visit B1); whichever occurs first.

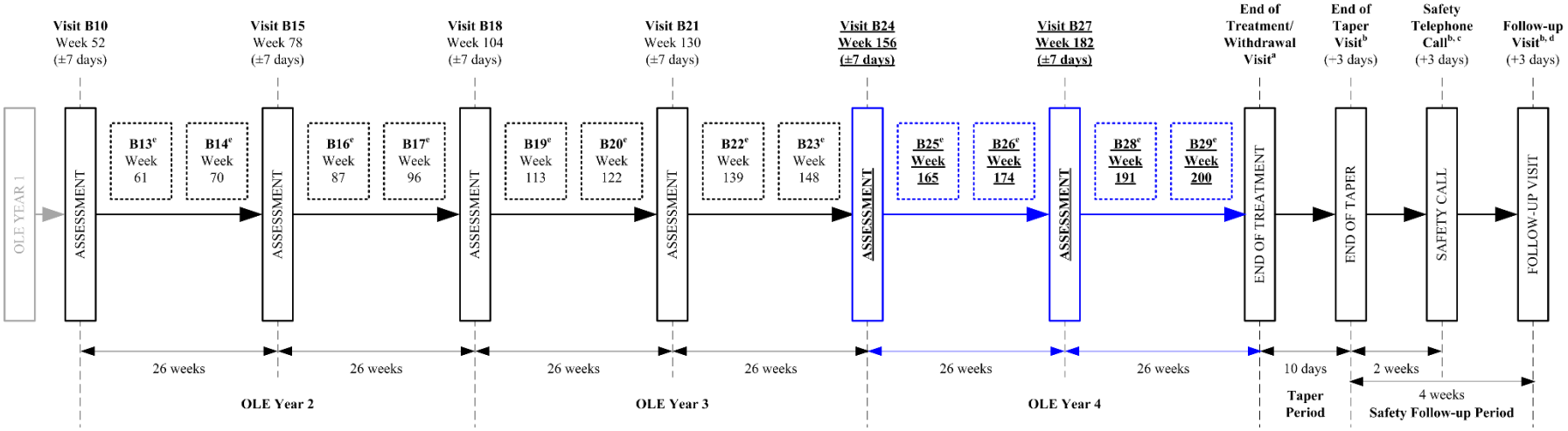
[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] Visits B13, B14, B16, B17, B19, B20, B22, B23 – Resupply visits (±7 days).

Revised Figure from Clinical Protocol Annex 1 (US Only) Amendment 2
Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019
(Additional text is underscored and in bold; new lines are blue)



[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of **4** years **of** OLE treatment (i.e., **208** weeks [±7 days] from Visit B1); whichever occurs first.

[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] Visits B13, B14, B16, B17, B19, B20, B22, B23, **B25, B26, B28, and B29** – Resupply visits (±7 days).

Original Table from Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open-label Extension

Visit Number	B10	Re-supply		Assess-ment	Re-supply		Assess-ment	Re-supply		Assess-ment	Re-supply		End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
		B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23				
Week	52	61	70	78	87	96	104	113	122	130	139	148	See footnote[a]	10 days after End of Treatment	2 weeks after last dose	4 weeks after last dose
Visit Window	±7	±7		±7	±7		±7	±7		±7	±7		±7	+3	+3	+3
Informed consent/assent	X															
Vital signs and BP	X			X			X			X			X	X		
Physical examination (including height and body weight)	X			X			X			X			X	X		
ECG	X			X			X			X			X	X		
Clinical laboratory blood sampling	X			X			X			X			X	X		
Clinical laboratory urine sampling (dipstick urinalysis)	X			X			X			X			X	X		
Pregnancy test, where appropriate	X			X			X			X			X			
IGF-1 testing	X			X			X			X			X			
AED concentration	X			X			X			X			X			
AEs	X	X		X	X		X	X		X	X		X	X	X	X

Visit Number	B10	Re-supply B13	Re-supply B14	Assess-ment B15	Re-supply B16	Re-supply B17	Assess-ment B18	Re-supply B19	Re-supply B20	Assess-ment B21	Re-supply B22	Re-supply B23	End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote[a]**	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
Concomitant medications	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 assessment	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						X			
Menstruation question (where appropriate)	X						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		
IMP dispensing	X	X		X	X		X	X		X	X		X			
Collection of IMP	X	X		X	X		X	X		X	X		X	X		

Visit Number	B10	Re-supply B13	Re-supply B14	Assess-ment B15	Re-supply B16	Re-supply B17	Assess-ment B18	Re-supply B19	Re-supply B20	Assess-ment B21	Re-supply B22	Re-supply B23	End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote[a]**	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
IMP compliance review	X	X		X	X		X	X		X	X		X	X		
Study Medication Use and Behavior Survey													X[e]			

[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of ~~3~~ years~~.~~ OLE treatment (i.e., ~~156~~ weeks [±7 days] from Visit B1); whichever occurs first.

[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] 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

Revised Table from Clinical Protocol Annex 1 (US Only) Amendment 2
Clinical Protocol Annex 1 (US Only) Version 3, Date 15 April 2019
(Additional text is underscored and in bold; new lines are blue)

Open-label Extension

Visit Number	B10	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
		B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23	**B24**	**B25**	**B26**	**B27**	**B28**	**B29**				
Week	52	61	70	78	87	96	104	113	122	130	139	148	**156**	**165**	**174**	**182**	**191**	**200**	See footnote[a]	10 days after End of Treatment	2 weeks after last dose	4 weeks after last dose
Visit Window	±7	±7		±7	±7		±7	±7		±7	±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		
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 urine sampling (dipstick urinalysis)	X			X			X			X			**X**			**X**			X	X		
Pregnancy test, where appropriate	X			X			X			X			**X**			**X**			X			
IGF-1 testing	X			X			X			X			**X**			**X**			X			

Visit Number	B10	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
		B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23	B24	B25	B26	B27	B28	B29				
Week	52	61	70	78	87	96	104	113	122	130	139	148	156	165	174	182	191	200	See footnote[a]	10 days after End of Treatment	2 weeks after last dose	4 weeks after last dose
Visit Window	±7	±7		±7	±7		±7	±7		±7	±7		±7	±7		±7	±7		±7	+3	+3	+3
AED concentration	X			X			X			X			**X**			**X**			X			
AEs	X	X		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	X	X
Inpatient epilepsy-related hospitalizations	X	X		X	X		X	X		X	X		**X**	**X**		**X**	**X**		X	X	X	X
Suicidality assessment	X			X			X			X			**X**			**X**			X	X		
Vineland-II	X						X						**X**						X			
SGIC/CGIC	X						X						**X**						X			
PGIC	X						X						**X**						X			
SGIC-SD/CGIC-SD	X			X			X			X			**X**			**X**			X			
QOLCE/QOLIE-31-P	X						X						**X**						X			
Wechsler Tests	X						X						**X**						X			
CBCL/ABCL	X						X						**X**						X			
SCQ	X						X						**X**						X			
Tanner Staging (where appropriate)	X						X						**X**						X			
Menstruation question (where appropriate)	X						X						**X**						X			

Visit Number	B10	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		Assess-ment	Resupply		End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
		B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23	B24	B25	B26	B27	B28	B29				
Week	52	61	70	78	87	96	104	113	122	130	139	148	156	165	174	182	191	200	See footnote[a]	10 days after End of Treatment	2 weeks after last dose	4 weeks after last dose
Visit Window	±7	±7		±7	±7		±7	±7		±7	±7		±7	±7		±7	±7		±7	+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		**X**	**X**		**X**	**X**		X	X		
IMP dispensing	X	X		X	X		X	X		X	X		**X**	**X**		**X**	**X**		X			
Collection of IMP	X	X		X	X		X	X		X	X		**X**	**X**		**X**	**X**		X	X		
IMP compliance review	X	X		X	X		X	X		X	X		**X**	**X**		**X**	**X**		X	X		
Study Medication Use and Behavior Survey																			X[e]			

[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of **4** years **of** OLE treatment (i.e., **208** weeks [±7 days] from Visit B1); whichever occurs first.

[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] 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.

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 1 (US ONLY) AMENDMENT NUMBER: 1

to be incorporated into the Protocol Annex, creating CLINICAL PROTOCOL ANNEX 1 VERSION 2 (US ONLY), DATE 26 APRIL 2018

GW Research Ltd
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Tel: PPD
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Confidentiality Statement

1 PROTOCOL ANNEX SYNOPSIS

Trial 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
Indication	Seizures[a] in patients with tuberous sclerosis complex (TSC).
Trial Design	Trial GWEP1521 consists of a randomized, parallel-group, 16-week double-blind phase comparing 2 doses of GWP42003-P with placebo, followed by a 1-year open-label extension (OLE) phase. Clinical Protocol Annex 1 (US Only) Version 2 extends the OLE phase by 2 further years in the United States. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

[a] 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.

Table of Contents

List of Appendices

2 RATIONALE

This clinical protocol annex 1 (US only) amendment 1 (will be incorporated into the Protocol Annex creating Clinical Protocol Annex 1 [US Only] Version 2, Date 26 April 2018) addresses the following issue(s):**Duration of Open-label Extension Phase**

The OLE phase will be extended in duration in the US to ensure continued access to GWP42003-P prior to approval. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first. Procedures for each resupply visit and assessment visit have been condensed into single sections in the Annex to minimize repetition.

2.2 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol annex:

- Clarification that the End of Taper Visit, Safety Telephone Call, and Follow-up Visit are required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. Furthermore, the timings of these visits/calls are relative to the End of Treatment/Withdrawal Visit.
- Clarification that Safety Telephone Call is still required for patients who do not taper IMP, that the call window is +3 days, and that the patient's last dose includes the final taper period dose.
- Clarification that the Follow-up Visit can be a clinic visit or can be conducted by telephone.
- Clarification that the Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE and should only be administered at the final dosing visit (End of Treatment/ Withdrawal visit or End of Taper visit, as applicable).
- Treatment days have been removed in favor of treatment weeks, as this is more compatible with the interactive voice response system.
- Collection of informed consent/assent at Visit B10 was listed in the Schedule of Assessments but was not mentioned in Section 4.1 of the Annex.

- Additional assessments for patients who withdraw early and taper IMP were listed in the End of Taper Visit section of the Annex but had not been denoted in the Schedule of Assessments.
- Abbreviations which are not used in the Annex have been removed from the List of Abbreviations, and abbreviated terms have been defined on first use.
- Terms which are not used in the Annex have been removed from the Definition of Terms.
- Bulleted lists have been used to improve readability.
- References to “the study” has been replaced with “the trial” throughout.
- Minor spelling/punctuation/grammatical corrections have been made to improve consistency and readability; however, in the interest of brevity, these changes are not captured in Section 4 of this amendment document.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 1 [Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
Title page p. 1	(…) This annex outlines the assessments and procedures for ~~**year**~~ 2 of the Open Label Extension. (…)	(…) This annex outlines the assessments and procedures for **years** 2 **and 3** of the open-label extension. (…)	See Section 2.1
List of Abbreviations p. 4–5	(…) (…) AED Antiepileptic ~~**Drugs**~~ (…) (…) (…) (…) ~~**EC**~~ ~~**Ethics Committee**~~ (…) (…) (…) (…) ~~**IEC**~~ ~~**Independent Ethics Committee**~~ (…) (…) ~~**IMP**~~ ~~**Investigational Medicinal**~~	(…) (…) AED Antiepileptic **drug** (…) (…) **CBD** **Cannabidiol** (…) (…) (…) (…) **IGF-1** **Insulin-like growth factor-1** (…) (…) (…) (…)	See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 1 [Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
List of Abbreviations p. 4–5 (continued)	~~**IRB**~~ ~~**Institutional Review Board****~~ (…) (…) SCQ ~~**Subject**~~ Communication Questionnaire (…) (…)	~~**Product**~~ (…) (…) SCQ **Social** Communication Questionnaire (…) (…) **TSC** **Tuberous sclerosis complex** **US** **United States** **Vineland-II** **Vineland Adaptive Behavior Scales, Second Edition**	
Definition of Terms p. 5	(…) (…) ~~**International normalised ratio**~~ ~~**A calculation made to standardise prothrombin time.**~~ (…) (…) ~~***Status epilepticus***~~ ~~**Any seizure lasting 30 minutes or longer**~~	(…) (…) (…) (…)	See Section 2.2
Section 1 RATIONALE p. 6	GWEP1521 ~~**includes**~~ a randomized, ~~**double-blind,**~~ parallel-group, 16-week ~~**comparison of two**~~ doses of GWP42003-P ~~**versus**~~ placebo followed by a 1 year	**Trial** GWEP1521 **consists of** a randomized, parallel-group, 16-week **double-blind phase comparing 2** doses of GWP42003-P **with** placebo,	See Section 2.2

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Section 1 RATIONALE p. 6 (continued)	Open Label Extension (OLE). ~~**In order**~~ to ensure continued access to GWP42003-P prior to approval ~~**for patients completing 1 year of OLE treatment**~~, the OLE will be extended ~~**by 1 further year**~~ in the ~~**U.S**~~. (…) However, in countries where compassionate access proves difficult prior to first approvals the OLE duration may also be extended ~~**by 1 year**~~ to include these additional countries.	followed by a 1-year open-label extension (OLE) **phase**. To ensure continued access to GWP42003-P prior to approval, the OLE **phase** will be extended **to a total of 3 years in duration** in the **United States (US)**. **Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first.** (…) However, in countries where compassionate access proves difficult prior to first approvals, the OLE duration may also be extended to include these additional countries.	See Section 2.1 and Section 2.2 See Section 2.1 and Section 2.2 See Section 2.1
Section 2 SUMMARY OF THE ANNEX p. 6	(…) Dosing will remain consistent and there is no	(…) **Patients completing a second year of OLE treatment will enter a third year of OLE treatment.** Dosing will remain consistent and there is no	See Section 2.1 See Section 2.1

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Section 2 SUMMARY OF THE ANNEX p. 6 (continued)	requirement for dose adjustment or further titration upon entry into ~~**year**~~ 2.	requirement for dose adjustment or further titration upon entry into **years** 2 **or 3**.	
	Assessment visits have been added at week 78 ~~**and**~~ week 104 (relative to Visit B1).	Assessment visits have been added at Week 78, Week 104**, Week 130, and Week 156** (relative to Visit B1).	See Section 2.1
	Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in ~~**year**~~ 2 to ensure re-supply volumes are manageable for both patients and dispensing staff.	Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in **years** 2 **and 3** to ensure resupply volumes are manageable for both patients and dispensing staff.	See Section 2.1
	(…)	(…)	
		Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first.	See Section 2.1
	Following completion ~~**of year 2**~~ of the OLE, patients who do not immediately continue to use GWP42003-P, will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit. A safety follow-up visit will be completed ~~**by**~~	Following completion of the OLE, patients who do not immediately continue to use **commercial** GWP42003-P will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit.	See Section 2.1

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	~~**telephone**~~ 4 weeks after the End of Taper ~~**(approximately 109 weeks after Visit B1)**~~.	A safety follow-up visit will be completed 4 weeks after the End of Taper **visit**.	See Section 2.2
Section 3 TREATMENT SCHEMATIC DIAGRAM p. 7	*<See Appendix 1 for changes to diagram>* ~~*** A 'Post-taper Safety telephone call' must be made two weeks after the patients last dose of IMP to collect seizure information, and to assess adverse events (AEs), epilepsy-related hospitalizations, concomitant medications and/or changes to medication.**~~	*<See Appendix 1 for changes to diagram>* **[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.**	See Section 2.1 See Section 2.1
	~~****A follow-up visit is**~~ required for patients who withdraw from the ~~**study**~~ or complete treatment but do not ~~**wish to**~~ continue to use GWP42003-P.	**[b] Only** required for patients who withdraw from the **trial** or complete treatment but do not **immediately** continue to use **commercial** GWP42003-P.	See Section 2.2
	~~**This must be made four weeks after the patients last dose of IMP to collect information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication**~~.		See Section 2.2
Section 3	~~**A Can be conducted by telephone.**~~	**[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.**	See Section 2.2

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TREATMENT SCHEMATIC DIAGRAM p. 7 (continued)	# B13, B14, B16, B17 – Resupply visits (±7 days).	[d] **This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.** [e] **Visits** B13, B14, B16, B17**, B19, B20, B22, B23** – Resupply visits (±7 days).	See Section 2.2 See Section 2.1
Section 4 DESIGN AND PROCEDURES p. 8	Patients and their parent(s)/legal representative will be invited to participate in **~~year~~** 2 of the OLE when they reach Visit B10 of the **~~Blinded~~** Phase. (…) Patients will continue to make weekly **~~IVRS~~** diary calls throughout their second **~~year~~** of OLE participation.	Patients and their parent(s)/legal representative will be invited to participate in **years** 2 **and 3** of the OLE when they reach Visit B10 of the **OLE** phase. (…) Patients will continue to make weekly **interactive voice response system (IVRS)** diary calls throughout their second **and third years** of OLE participation.	See Section 2.1 and correction of a typographical error See Section 2.1 and Section 2.2
Section 4.1 Visit B10 (Week 52) p. 8 Section 4.1 Visit B10	4.1 Visit B10 (**~~Day 365,~~** Week 52) In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in the US will receive sufficient open-label IMP for nine weeks' home dosing and instructed to maintain consistent dosing.	4.1 Visit B10 (Week 52) In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in the US **who provide written informed consent/assent (see Section 5)** will receive sufficient open-label IMP for 9 weeks' home dosing and **will be** instructed to maintain consistent dosing.	See Section 2.2 See Section 2.2

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(Week 52) p. 8 (continued)	(…) (…)	(…) **The Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE.** (…)	See Section 2.2
Section 4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), and B23 (Week 148) p. 8–9	4.2 **~~Visit B13 (Day 428, Week 61, Re-supply Visit)~~** **~~This visit~~** will occur **~~427 days~~** after Visit B1. (…) Attendance of the patient is not required for **~~this~~** re-supply **~~visit~~** provided the primary caregiver is able to attend. (…) **~~The~~** visit will comprise a review of concomitant medications (including antiepileptic drugs (AEDs),	4.2 **Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), and B23 (Week 148)** **Visits B13, B14, B16, B17, B19, B20, B22, and B23** will occur **61, 70, 87, 96, 113, 122, 139, and 148 weeks** after Visit B1**, respectively**. (…) Attendance of the patient is not required for resupply **visits** provided the primary caregiver is able to attend. (…) **Each** visit will comprise a review of concomitant medications (including antiepileptic drugs [AEDs]), epilepsy-related hospitalizations and adverse events	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.1

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	epilepsy-related hospitalizations and adverse events (AEs). The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and ~~**interactive voice response system (IVRS)**~~ data, record the patient's/caregiver's attendance at the visit and confirm the outcome of the visit. (…)	(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. (…)	See Section 2.2
Section 4.3 Assessment Visits B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 Section 4.3 Assessment Visits	*<Section 4.3 of Protocol Annex 1 Version 1 was deleted.* *The following text is revised from Section 4.4 of Protocol Annex 1 Version 1>* **4.4 ~~Visit~~** B15 (**~~Day 547,~~** Week 78) **~~This visit~~** will occur **~~546 days~~** after Visit B1. (…) The following **~~observations~~** will be made at **~~Visit B15~~**: concomitant medications, (including AEDs),	*<Section 4.3 of Protocol Annex 1 Version 1 was deleted.* *The following text is revised from Section 4.4 of Protocol Annex 1 Version 1>* **4.3 Assessment Visits** B15 (Week 78)**, B18 (Week 104), and B21 (Week 130)** **Visits B15, B18, and B21** will occur **78, 104, and 130 weeks** after Visit B1**, respectively.** (…) The following **assessments** will be made at **each visit**: • Concomitant medications (including AEDs)	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2

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B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 (continued)	physical examination (including height and body weight), 12-lead electrocardiogram (ECG), vital signs, epilepsy-related hospitalizations ~~**and**~~ AEs.	• Physical examination (including height and body weight) • 12-lead electrocardiogram (ECG) • Vital signs • Epilepsy-related hospitalizations • AEs • **Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)** • **Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol**	
Section 4.3 Assessment Visits	Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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.	**At each assessment visit,** clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum **insulin-like growth factor-1 (IGF-1)** levels (for patients less than 18 years of age) to be performed by the central laboratory. (…)	See Section 2.2

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B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 (continued)	(…) ~~**The following assessments will also be performed: Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).**~~ ~~**Suicidality will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) or Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.**~~ (…) Patients/caregivers will then receive sufficient ~~**open-label**~~ IMP ~~**for eight weeks' home dosing**~~.	(…) Patients/caregivers will then receive sufficient IMP **until the next scheduled visit**. **In addition to the above, the following assessments will be made at Visit B18 only:** • **Details of menstruation (for females)** • **Tanner staging (patients aged 10–17 [inclusive] only)** • **Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy**	See Section 2.2 See Section 2.1 See Section 2.1 See Section 2.1
Section 4.3 Assessment Visits			

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B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 (continued)		**(QOLIE-31-P)** • **Subject Global Impression of Change (SGIC)/ Caregiver Global Impression of Change (CGIC)** • **Physician Global Impression of Change (PGIC)** • **Wechsler Tests** • **Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)** • **Social Communication Questionnaire (SCQ)** • **Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)**	

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12	*<Section 4.4 of Protocol Annex 1 Version 1 was revised to create Section 4.3 of Protocol Annex 1 Version 2.* *Sections 4.5 and 4.6 of Protocol Annex 1 Version 1 were deleted.* *The following text is revised from Section 4.7 of Protocol Annex 1 Version 1>* **~~4.7~~ ~~Visit B18 (Day 729, Week 104,~~** End of Treatment/Withdrawal Visit**~~)~~** This visit will occur **~~728 days after Visit B1 or~~** 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.~~**	*<Section 4.4 of Protocol Annex 1 Version 1 was revised to create Section 4.3 of Protocol Annex 1 Version 2.* *Sections 4.5 and 4.6 of Protocol Annex 1 Version 1 were deleted.* *The following text is revised from Section 4.7 of Protocol Annex 1 Version 1>* **4.4** End of Treatment/Withdrawal Visit This visit will occur**: 1)** following early withdrawal from the **trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.**	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2 See Section 2.1 See Section 2.1

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	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 [where possible]), including a pregnancy test 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),~~** 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, **~~Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy (QOLIE-31-P)~~**, **~~Subject Global Impression of Change (SGIC)/Caregiver Global Impression of Change (CGIC)~~**, **~~Physician Global~~**	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] **only**) • ECG • IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, **and** IMP dosing) • Epilepsy-related hospitalizations • Concomitant medications and/or changes to medication • AEs • **QOLCE/QOLIE-31-P** • **SGIC/CGIC** • **PGIC** • SGIC-SD/CGIC-SD	See Section 2.2

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	~~**Impression of Change (PGIC)**~~, SGIC-SD/CGIC-SD, Wechsler Tests, ~~**Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)**~~, ~~**Social Communication Questionnaire (SCQ) and the Vineland-II.**~~	• Wechsler Tests • **CBCL/ABCL** • **SCQ** • **Vineland-II**	
	Suicidality ~~**will be**~~ assessed ~~**using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.**~~	• Suicidality, assessed **in accordance with Section 9.2.12.8 of the main protocol**	See Section 2.2
		Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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.	See Section 2.2
	(…)	(…)	
	For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the ~~**study**~~.	For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the **trial**.	See Section 2.2
	For patients who immediately continue to use	For patients who immediately continue to use **commercial** GWP42003-P following the End of	See Section 2.2

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	GWP42003-P following the 'End of Treatment' visit, the IVRS will be contacted to confirm the patient's completion of this ~~**study**~~ and the paper diaries will be collected.	Treatment visit, the IVRS will be contacted to confirm the patient's completion of this **trial** and the paper diaries will be collected. **For patients 12 years of age and older who complete treatment and immediately continue to use commercial GWP42003-P, or for patients 12 years of age and older who withdraw early and do not taper IMP, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.**	See Section 2.2
	For patients who do not immediately continue to use GWP42003-P following the 'End of Treatment' visit, IMP will be tapered at home (10% per day for 10 days).	For patients who **complete treatment but** do not immediately continue to use **commercial** GWP42003-P following the End of Treatment visit, IMP will be tapered at home (10% per day for 10 days).	See Section 2.2
	Additional IMP will be dispensed, if required.	Additional IMP will be dispensed, if required**, and instructions for tapering the dose will be provided**.	See Section 2.2
	(…)	(…) Information will continue to be recorded in the paper	

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	**~~The IVRS will generate the patient's daily IMP dosing volumes for the 10-day taper period, during which time diary~~** information will continue to be recorded in the paper diary. **~~For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.~~** Following the 'End of Treatment'/'Withdrawal' visit, the IVRS seizure reporting diary should **~~only~~** be completed up to the Follow-up visit.	diary **<u>during the taper period</u>**. Following the End of Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed up to the Follow-up visit.	See Section 2.2 See Section 2.2 Correction of a typographical error
Section 4.5 End of Taper Visit p. 12–13 Section 4.5	*<Section 4.5 of Protocol Annex 1 Version 1 was deleted.* *Section 4.6 of Protocol Annex 1 Version 1 was also deleted, and Section 4.7 was revised to create Section 4.4 of Protocol Annex 1 Version 2.* *The following text is revised from Section 4.8 of Protocol Annex 1 Version 1>* **~~4.8~~** **~~Visit B19 (Day 739, Week 105,~~** End of Taper **~~Period~~** Visit**~~)~~**	*<Section 4.5 of Protocol Annex 1 Version 1 was deleted.* *Section 4.6 of Protocol Annex 1 Version 1 was also deleted, and Section 4.7 was revised to create Section 4.4 of Protocol Annex 1 Version 2.* *The following text is revised from Section 4.8 of Protocol Annex 1 Version 1>* **<u>4.5</u>** End of Taper Visit	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2

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End of Taper Visit p. 12–13 (continued)		**This visit is required for patients who:** **1) withdraw from the trial and taper IMP; or** **2) complete treatment but do not immediately continue to use commercial GWP42003-P.**	See Section 2.2
	~~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~~**. (…)	**The End of Taper** visit will take place 10 (+3) days after the End of Treatment/Withdrawal visit. (…)	See Section 2.2
	The following assessments will be made: vital signs **~~and~~** physical examination (including height and body weight).	The following assessments will be made: • Vital signs • Physical examination (including height and body weight) • **IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)** • **Epilepsy-related hospitalizations** • **Concomitant medications and/or changes to medication** • **AEs**	See Section 2.2
Section 4.5 End of Taper Visit	Suicidality **~~will be~~** assessed **~~using the C-SSRS/~~**	• Suicidality, assessed **in accordance with**	See Section 2.2

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p. 12–13 (continued)	~~**Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.**~~ ~~**In addition, the following assessments will be made for patients who withdraw early and taper IMP (including withdrawal during the taper period):**~~ ECG ~~**and**~~ clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). ~~**The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP usage, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.**~~ (…) Following the 'End of Taper ~~**Period**~~' visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.	**<u>Section 9.2.12.8 of the main protocol</u>** • ECG • Clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis) (…) Following the End of Taper visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.	See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2

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Section 4.6 Safety Telephone Call p. 13	*<Section 4.6 of Protocol Annex 1 Version 1 was deleted.* *Sections 4.7 and 4.8 of Protocol Annex 1 Version 1 were revised to create Sections 4.4 and 4.5 of Protocol Annex 1 Version 2, respectively.* *The following text is revised from Section 4.9 of Protocol Annex 1 Version 1>* **~~4.9~~ ~~Visit B20 (Day 753, Week 107, Post-taper~~** Safety Telephone Call**~~)~~** 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~~** two 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.	*<Section 4.6 of Protocol Annex 1 Version 1 was deleted.* *Sections 4.7 and 4.8 of Protocol Annex 1 Version 1 were revised to create Sections 4.4 and 4.5 of Protocol Annex 1 Version 2, respectively.* *The following text is revised from Section 4.9 of Protocol Annex 1 Version 1>* **4.6** Safety Telephone Call This visit is required for patients who withdraw from the **trial** or complete treatment but do not **immediately** continue to use **commercial** GWP42003-P. The **Safety Telephone Call** will be **conducted** 2 weeks (+3 days) after the patient's last dose of GWP42003-P (including final taper period dose). During this call, caregivers will be asked for information on: • AEs • Epilepsy-related hospitalizations	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 1 [Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
	(…)	• Concomitant medications and/or changes to medication (…)	

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 1 [Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 4.7 Follow-up Visit p. 13	*<Section 4.7 of Protocol Annex 1 Version 1 was revised to create Section 4.4 of Protocol Annex 1 Version 2.* *Sections 4.8 and 4.9 of Protocol Annex 1 Version 1 were revised to create Sections 4.5 and 4.6 of Protocol Annex 1 Version 2, respectively.* *The following text is revised from Section 4.10 of Protocol Annex 1 Version 1>* **~~4.10~~** Follow-up Visit **~~(Telephone Call)~~** 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 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.	*<Section 4.7 of Protocol Annex 1 Version 1 was revised to create Section 4.4 of Protocol Annex 1 Version 2.* *Sections 4.8 and 4.9 of Protocol Annex 1 Version 1 were revised to create Sections 4.5 and 4.6 of Protocol Annex 1 Version 2, respectively.* *The following text is revised from Section 4.10 of Protocol Annex 1 Version 1>* **4.7** Follow-up Visit This visit is required for patients who withdraw from the **trial** or complete treatment but do not **immediately** continue to use **commercial** GWP42003-P. The Follow-up visit will **take place** 4 weeks (+3 days) after the patient's last dose of GWP42003-P **(including final taper period dose)** and can be conducted **by** telephone. During this visit/call, caregivers will be asked for information on: • AEs • Epilepsy-related hospitalizations	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 1 [Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
		• Concomitant medications and/or changes to medication	

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 1 [Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 5 INFORMED CONSENT/ ASSENT p. 14	An institutional review board **~~(IRB)~~**/independent ethics committee **~~(IEC)~~** approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.	An institutional review board/independent ethics committee-approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.	See Section 2.2
Section 6.1 Patients to Analyze p. 14	Patients in the U.S. who continue to participate in **~~year~~** 2 of the OLE will be analysed in accordance with the statistical considerations detailed in Section 13 of the main protocol.	Patients in the US who continue to participate in **years** 2 **and 3** of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.	See Section 2.1
APPENDIX 1 SCHEDULE OF ASSESSMENTS p. 15–17	*<See Appendix 1 for changes to table>*	*<See Appendix 1 for changes to table>* **[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.** **[b] Only required for patients who withdraw from**	See Section 2.1 See Section 2.1 See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 1 (US Only) Amendment 1 [Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
APPENDIX 1 SCHEDULE OF ASSESSMENTS p. 15–17 (continued)		**the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.** [c] **Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.** [d] **Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.** **This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.** [e] **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.**	See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2

5 REFERENCES

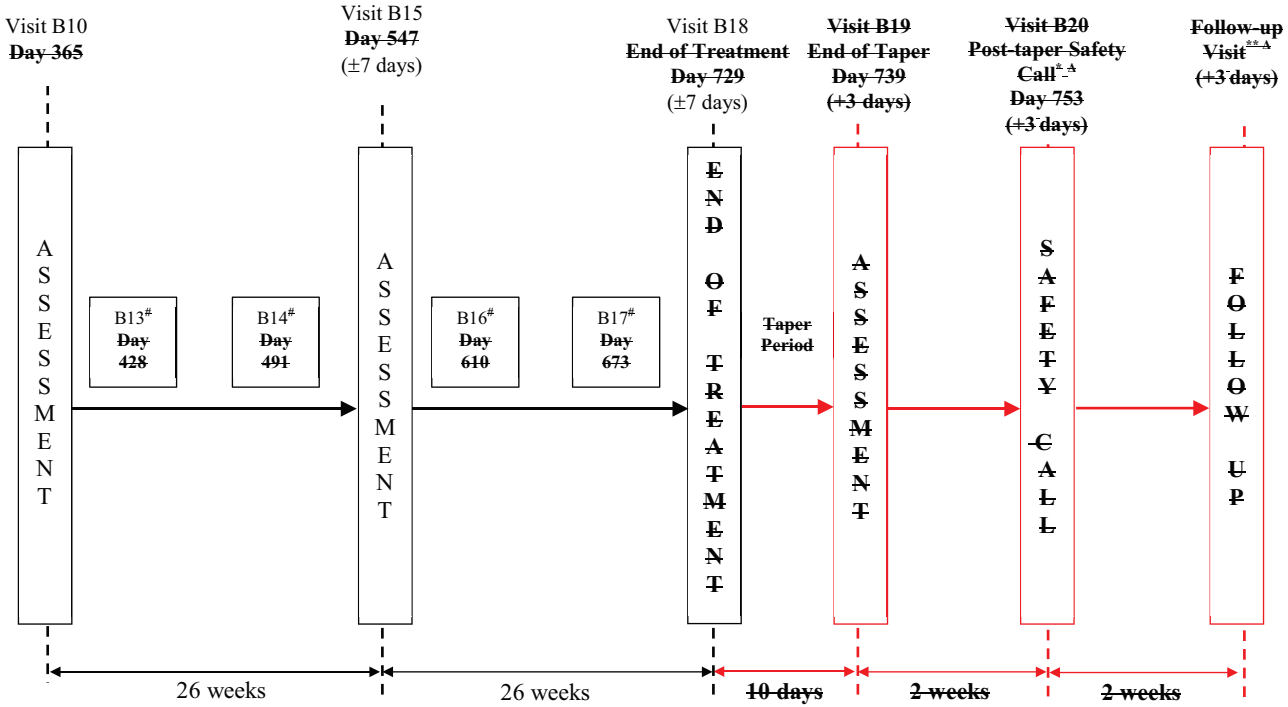
N/A

APPENDIX 1 AMENDED FIGURES AND TABLES

Original Figures from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017

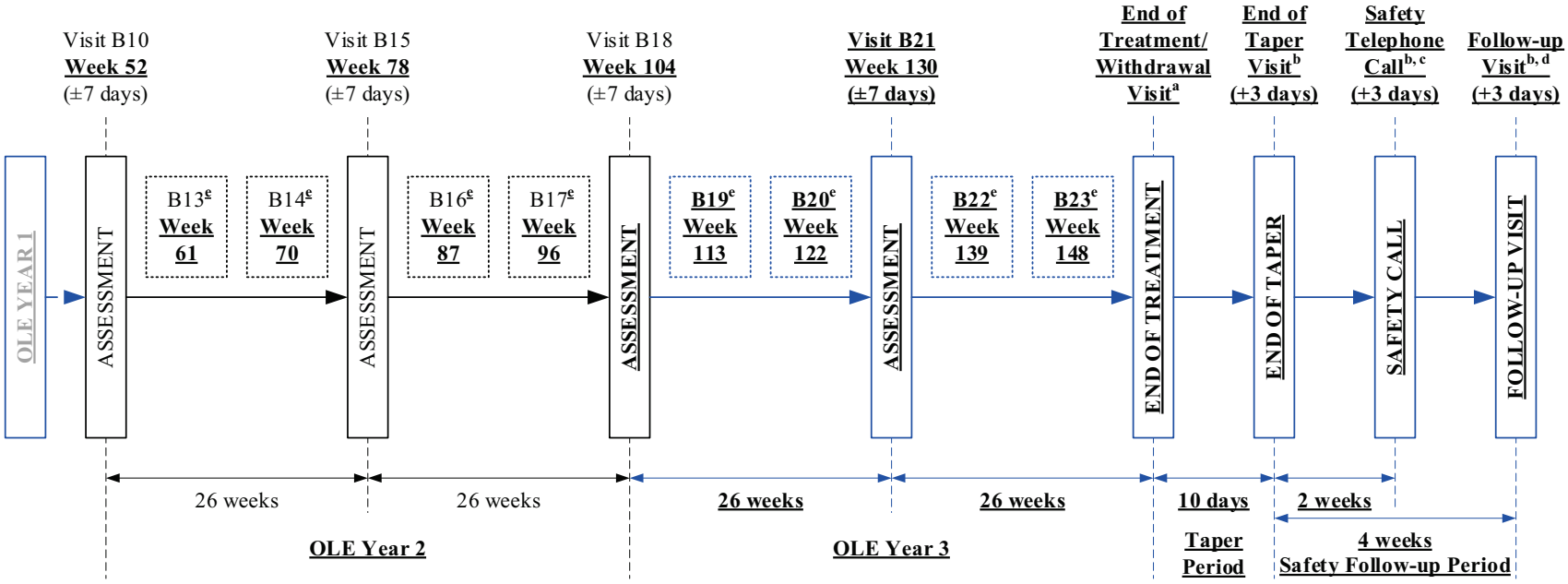
(Deleted wording is struck through and in bold; deleted lines are in red)

3 TREATMENT ~~SCHEMA~~



Revised Figures from Clinical Protocol Annex 1 (US Only) Amendment 1
[Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018]
(Revised wording is underscored and in bold; new lines are blue)

3 TREATMENT **SCHEMATIC DIAGRAM**



Original Tables from Clinical Protocol Annex 1 (US Only) Version 1, Date 27 June 2017

(Deleted wording is struck through and in bold; deleted lines are in red)

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open-label Extension

Visit Number	B10	~~**Re-Supply Visit**~~ B13	~~**Re-Supply Visit**~~ B14	B15	~~**Re-Supply Visit**~~ B16	~~**Re-Supply Visit**~~ B17	End of Treatment ~~**B18**~~	End of Taper ~~**B19**~~	~~**Post-Taper**~~ Safety Telephone Call ~~**B20**~~	Follow up ~~**Telephone Call**~~
~~**Day**~~	~~**365**~~	~~**428**~~	~~**491**~~	547	~~**610**~~	~~**673**~~	~~**729**~~	~~**739**~~	~~**753**~~	~~**767**~~
~~**Visit Window**~~	~~**±7**~~	~~**±7**~~	~~**±7**~~	~~**±7**~~		~~**±7**~~	~~**±7**~~	~~**+3**~~	~~**±3**~~	~~**+3**~~
~~**Week**~~		~~**61**~~	~~**70**~~	~~**78**~~	~~**87**~~	~~**96**~~	~~**104**~~	~~**105**~~	~~**107**~~	~~**109**~~
Informed consent/assent	X									
Vital signs	X			X			X	X		
Physical examination (including height and body weight)	X			X			X	X		
ECG	X			X			X	X		
Clinical laboratory blood sampling	X			X			X	X		
Clinical laboratory urine sampling (dipstick urinalysis)	X			X			X	X		
Pregnancy test, where	X			X			X			

Visit Number	B10	~~Re-Supply Visit~~ B13	~~Re-Supply Visit~~ B14	B15	~~Re-Supply Visit~~ B16	~~Re-Supply Visit~~ B17	End of Treatment ~~B18~~	End of Taper ~~B19~~	~~Post-Taper~~ Safety Telephone Call ~~B20~~	Follow up ~~Telephone Call~~
~~Day~~	~~365~~	~~428~~	~~491~~	547	~~610~~	~~673~~	~~729~~	~~739~~	~~753~~	~~767~~
~~Visit Window~~	~~±7~~	~~±7~~	~~±7~~	~~±7~~		~~±7~~	~~±7~~	~~+3~~	~~±3~~	~~+3~~
appropriate										
IGF-1 testing	X						X			
AED concentration	X			X			X			
AEs	X	X	~~X~~	X	X	~~X~~	X	X	X	X
Concomitant medications	X	X	~~X~~	X	X	~~X~~	X	X	X	X
Inpatient epilepsy-related hospitalizations	X	X	~~X~~	X	X	~~X~~	X	X	X	X
Suicidality /C-SSRS/ Children's C-SSRS	X			X			X	X		
Vineland-II	X						X			
SGIC/CGIC	X						X			
PGIC	X						X			
SGIC-SD/CGIC-SD	X			X			X			
QOLCE/QOLIE-31-P	X						X			
Wechsler Tests	X						X			
CBCL/ABCL	X						X			
SCQ	X						X			
Tanner Staging (where	X						X			

Visit Number	B10	~~Re-Supply Visit~~ B13	~~Re-Supply Visit~~ B14	B15	~~Re-Supply Visit~~ B16	~~Re-Supply Visit~~ B17	End of Treatment ~~B18~~	End of Taper ~~B19~~	~~Post-Taper~~ Safety Telephone Call ~~B20~~	Follow up ~~Telephone Call~~
~~Day~~	~~365~~	~~428~~	~~491~~	547	~~610~~	~~673~~	~~729~~	~~739~~	~~753~~	~~767~~
~~Visit Window~~	~~±7~~	~~±7~~	~~±7~~	~~±7~~		~~±7~~	~~±7~~	~~+3~~	~~±3~~	~~+3~~
appropriate)										
Menstruation question (where appropriate)	X						X			
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)	X	X	~~X~~	X	X	~~X~~	X	X		
IMP dispensing	X	X	~~X~~	X	X	~~X~~	X			
Collection of IMP	X	X	~~X~~	X	X	~~X~~	X	X		
IMP compliance review	X	X	~~X~~	X	X	~~X~~	X	X		
Study Medication Use and Behavior Survey							X			

Revised Tables from Clinical Protocol Annex 1 (US Only) Amendment 1

[Clinical Protocol Annex 1 (US Only) Version 2, Date 26 April 2018]

(Revised wording is underscored and in bold; new lines are blue)

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open-label Extension

Visit Number	B10	**Re-supply** B13	B14	**Assess-ment** B15	**Re-supply** B16	B17	**Assess-ment** B18	**Re-supply** **B19**	**B20**	**Assess-ment** **B21**	**Re-supply** **B22**	**B23**	End of Treatment/ **Withdrawal Visit**	End of Taper **Visit**[b]	Safety Telephone Call[b, c]	Follow-up **Visit**[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote**[a]	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
Informed consent/assent	X															
Vital signs **and BP**	X			X			X			**X**			X	X		
Physical examination (including height and body weight)	X			X			X			**X**			X	X		
ECG	X			X			X			**X**			X	X		
Clinical laboratory blood sampling	X			X			X			**X**			X	X		
Clinical laboratory urine sampling (dipstick urinalysis)	X			X			X			**X**			X	X		
Pregnancy test, where appropriate	X			X			X			**X**			X			

Visit Number	B10	Re-supply B13	Re-supply B14	Assess-ment B15	Re-supply B16	Re-supply B17	Assess-ment B18	Re-supply B19	Re-supply B20	Assess-ment B21	Re-supply B22	Re-supply B23	End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote[a]**	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
IGF-1 testing	X			X			X			**X**			X			
AED concentration	X			X			X			**X**			X			
AEs	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
Inpatient epilepsy-related hospitalizations	X	X		X	X		X	**X**		**X**	**X**		X	X	X	X
Suicidality **assessment**	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						X			
Menstruation question (where appropriate)	X						X						X			

Visit Number	B10	**Re-supply** B13	B14	**Assess-ment** B15	**Re-supply** B16	B17	**Assess-ment** B18	**Re-supply** **B19**	**B20**	**Assess-ment** **B21**	**Re-supply** **B22**	**B23**	End of Treatment/ **Withdrawal Visit**	End of Taper **Visit**[b]	Safety Telephone Call[b, c]	Follow-up **Visit**[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote**[a]	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+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**		X	X		
IMP dispensing	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[e]			

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 2

(POLAND ONLY)

This annex outlines the assessments and procedures for years 2 and 3 of the open-label extension. This annex will be implemented at Polish sites only.

GW Research Ltd
Sovereign House
Vision Park
Chivers Way
Histon
Cambridge CB24 9BZ
United Kingdom

Tel: PPD
Fax: PPD

Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol annex 2 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 26 April 2018 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s) the US 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 Conference on Harmonisation Tripartite Guidelines for GCP where the EU Clinical Trials and GCP Directives do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of patients during the trial and for all trial-related medical decisions.

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.

Centre No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print name: PPD Date: 01 MAY 2018

Senior clinical manager (DD Month YYYY)

Signature: PPD

Table of Contents

List of Abbreviations

ABCL	Adult Behavior Checklist
AE	Adverse event
AED	Antiepileptic drug
CBCL	Child Behavior Checklist
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CGIC-SD	Caregiver Global Impression of Change in Seizure Duration
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	12-lead electrocardiogram
EU	European Union
FDA	US Food and Drug Administration
GCP	Good clinical practice
GW	GW Research Ltd
IGF-1	Insulin-like growth factor-1
IMP	Investigational medicinal product
IVRS	Interactive voice response system
OLE	Open-label extension
PGIC	Physician Global Impression of Change
QOLCE	Quality of Life in Childhood Epilepsy
QOLIE-31-P	Quality of Life in Epilepsy
SCQ	Social Communication Questionnaire
SGIC	Subject Global Impression of Change
SGIC-SD	Subject Global Impression of Change in Seizure Duration
TSC	Tuberous sclerosis complex

(continued)

Vineland-II Vineland Adaptive Behavior Scales, Second Edition

Definition of Terms

Term	Definition
End of trial	Last patient last visit or last contact, whichever occurs last.
Enrolled patient	Any patient who has provided written informed consent/assent to take part in the trial.
Investigational medicinal product	Term used to describe both investigational active product and reference therapy (placebo).
Investigator	Trial principal investigator or a formally delegated study physician.

1 RATIONALE

Trial GWEP1521 consists of a randomized, parallel-group, 16-week double-blind phase comparing 2 doses of GWP42003-P with placebo, followed by a 1-year open-label extension (OLE) phase. To ensure continued access to GWP42003-P prior to approval, the OLE phase will be extended to a total of 3 years in duration in Poland. Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first. The intent is to ensure continued access to GWP42003-P through compassionate schemes (e.g., Named Patient Supply) in other countries. However, in countries where compassionate access proves difficult prior to first approvals, the OLE duration may also be extended to include these additional countries.

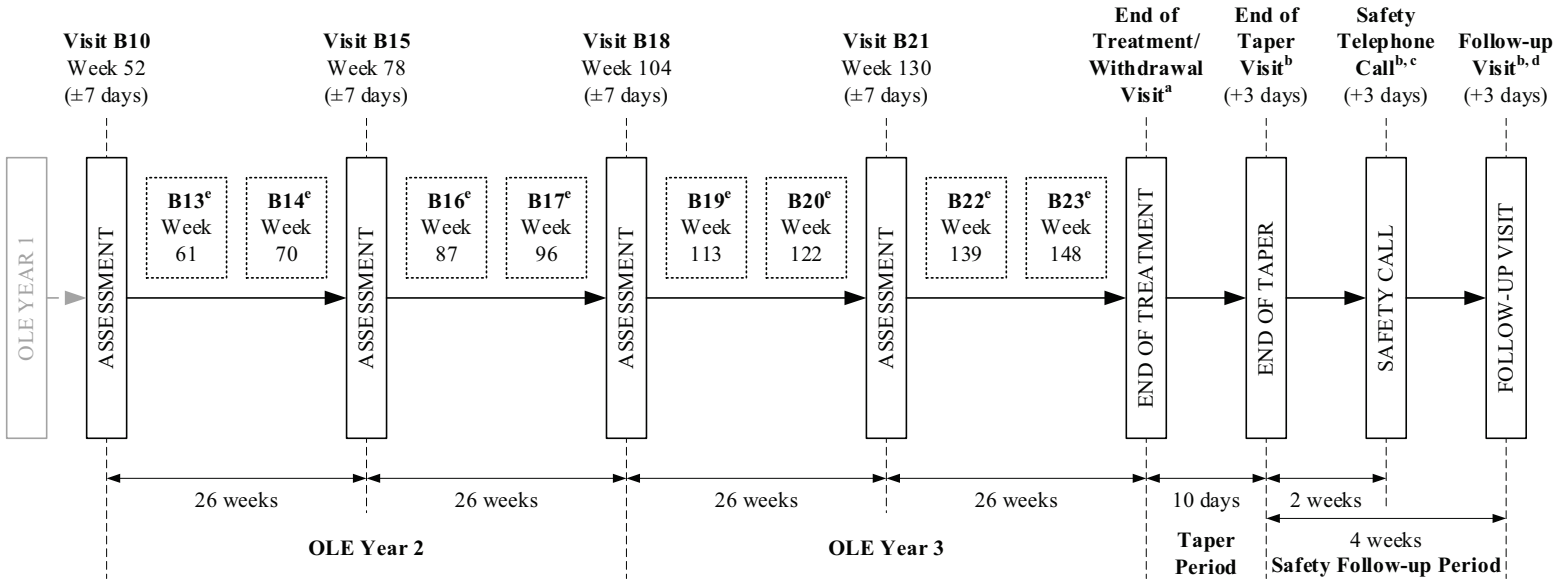
2 SUMMARY OF THE ANNEX

Patients will complete the first year of the OLE at Visit B10 and enter a second year of OLE treatment. Patients completing a second year of OLE treatment will enter a third year of OLE treatment. Dosing will remain consistent and there is no requirement for dose adjustment or further titration upon entry into years 2 or 3.

Assessment visits have been added at Week 78, Week 104, Week 130, and Week 156 (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in years 2 and 3 to ensure resupply volumes are manageable for both patients and dispensing staff. Attendance of the patient is not required for the dispensing visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first. Following completion of the OLE, patients who do not immediately continue to use commercial GWP42003-P will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit. A safety follow-up visit will be completed 4 weeks after the End of Taper visit.

3 TREATMENT SCHEMATIC DIAGRAM



[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.

[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] Visits B13, B14, B16, B17, B19, B20, B22, B23 – Resupply visits (±7 days).

4 DESIGN AND PROCEDURES

Patients and their parent(s)/legal representative will be invited to participate in years 2 and 3 of the OLE when they reach Visit B10 of the OLE phase. They will be issued with additional 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 additional visits with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit B10 will continue in the OLE.

Patients will continue to make weekly interactive voice response system (IVRS) diary calls throughout their second and third years of OLE participation.

4.1 Visit B10 (Week 52)

In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in Poland who provide written informed consent/assent (see Section 5) will receive sufficient open-label IMP for 9 weeks' home dosing and will be instructed to maintain consistent dosing. An additional dose calculator and paper diary will be issued, and patients will be trained on their appropriate use.

The Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE. The investigator must record the patient's attendance at the visit and confirm their continued participation.

4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), and B23 (Week 148)

Visits B13, B14, B16, B17, B19, B20, B22, and B23 will occur 61, 70, 87, 96, 113, 122, 139, and 148 weeks after Visit B1, respectively. 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 resupply visits provided the primary caregiver is able to attend. However, it is preferred that the patient attend where possible.

Each visit will comprise a review of concomitant medications (including antiepileptic drugs [AEDs]), epilepsy-related hospitalizations and adverse events (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.

4.3 Assessment Visits B15 (Week 78), B18 (Week 104), and B21 (Week 130)

Visits B15, B18, and B21 will occur 78, 104, and 130 weeks after Visit B1, respectively. 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 each visit:

- Concomitant medications (including AEDs)
- Physical examination (including height and body weight)
- 12-lead electrocardiogram (ECG)
- Vital signs
- Epilepsy-related hospitalizations
- AEs
- Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

At each assessment visit, clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum insulin-like growth factor-1 (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 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 IMP until the next scheduled visit.

In addition to the above, the following assessments will be made at Visit B18 only:

- Details of menstruation (for females)
- Tanner staging (patients aged 10–17 [inclusive] only)
- Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy (QOLIE-31-P)
- Subject Global Impression of Change (SGIC)/Caregiver Global Impression of Change (CGIC)
- Physician Global Impression of Change (PGIC)
- Wechsler Tests
- Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)
- Social Communication Questionnaire (SCQ)
- Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)

4.4 End of Treatment/Withdrawal Visit

This visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.

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] only)

- ECG
- IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and 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
- Vineland-II
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol

Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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, 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 trial. For patients who immediately continue to use commercial GWP42003-P following the End of Treatment visit, the IVRS will be contacted to confirm the patient's completion of this trial and the paper diaries will be collected. For patients 12 years of age and older who complete treatment and immediately continue to use commercial GWP42003-P, or for patients 12 years of age and older who withdraw early and do not taper IMP, 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 complete treatment but do not immediately continue to use commercial GWP42003-P following the End of Treatment visit, 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.

Following the End of Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.5 End of Taper Visit

This visit is required for patients who: 1) withdraw from the trial and taper IMP; or 2) complete treatment but do not immediately continue to use commercial GWP42003-P. The End of Taper visit will take place 10 (+3) days after the End of Treatment/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 assessments will be made:

- Vital signs
- Physical examination (including height and body weight)
- IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication
- AEs
- Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol
- ECG
- Clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis)

The investigator must assess adherence to the dosing regimen.

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 the End of Taper visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.

4.6 Safety Telephone Call

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Safety Telephone Call will be conducted 2 weeks (+3 days) after the patient's last dose of GWP42003-P (including final taper period dose). During this call, 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.

4.7 Follow-up Visit

This visit is required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. The Follow-up visit will take place 4 weeks (+3 days) after the patient's last dose of GWP42003-P (including final taper period dose) and can be conducted by telephone. During this visit/call, caregivers will be asked for information on:

- AEs
- Epilepsy-related hospitalizations
- Concomitant medications and/or changes to medication

5 INFORMED CONSENT/ASSENT

An institutional review board/independent ethics committee-approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.

6 DATA ANALYSIS

6.1 Patients to Analyze

Patients in Poland who continue to participate in years 2 and 3 of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.

7 IMPLEMENTATION OF THE ANNEX

This clinical protocol annex will be issued in conjunction with the current version of the main clinical trial protocol. It will be kept in the trial master file at GW as well as in each Polish investigational site file and, if applicable, pharmacy site file.

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open-label Extension

Visit Number	B10	Re-supply		Assess-ment	Re-supply		Assess-ment	Re-supply		Assess-ment	Re-supply		End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
		B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23				
Week	52	61	70	78	87	96	104	113	122	130	139	148	See footnote[a]	10 days after End of Treatment	2 weeks after last dose	4 weeks after last dose
Visit Window	±7	±7		±7	±7		±7	±7		±7	±7		±7	+3	+3	+3
Informed consent/assent	X															
Vital signs and BP	X			X			X			X			X	X		
Physical examination (including height and body weight)	X			X			X			X			X	X		
ECG	X			X			X			X			X	X		
Clinical laboratory blood sampling	X			X			X			X			X	X		
Clinical laboratory urine sampling (dipstick urinalysis)	X			X			X			X			X	X		
Pregnancy test, where appropriate	X			X			X			X			X			
IGF-1 testing	X			X			X			X			X			
AED concentration	X			X			X			X			X			
AEs	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

Visit Number	B10	Re-supply B13	Re-supply B14	Assess-ment B15	Re-supply B16	Re-supply B17	Assess-ment B18	Re-supply B19	Re-supply B20	Assess-ment B21	Re-supply B22	Re-supply B23	End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote[a]**	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
Inpatient epilepsy-related hospitalizations	X	X		X	X		X	X		X	X		X	X	X	X
Suicidality assessment	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						X			
Menstruation question (where appropriate)	X						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		

Visit Number	B10	Re-supply		Assess-ment	Re-supply		Assess-ment	Re-supply		Assess-ment	Re-supply		End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
		B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23				
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote[a]**	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
IMP dispensing	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[e]			

[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.

[b] Only required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.

[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.

[d] Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.

[e] 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.

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

EudraCT Number: 2015-002154-12

CLINICAL PROTOCOL ANNEX 2 (POLAND ONLY) AMENDMENT NUMBER: 1

to be incorporated into the Protocol Annex, creating CLINICAL PROTOCOL ANNEX 2 VERSION 2 (POLAND ONLY), DATE 26 APRIL 2018

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Confidentiality Statement

1 PROTOCOL ANNEX SYNOPSIS

Trial 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
Indication	Seizures[a] in patients with tuberous sclerosis complex (TSC).
Trial Design	Trial GWEP1521 consists of a randomized, parallel-group, 16-week double-blind phase comparing 2 doses of GWP42003-P with placebo, followed by a 1-year open-label extension (OLE) phase. Clinical Protocol Annex 2 (Poland Only) Version 2 extends the OLE phase by 2 further years in Poland. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

[a] 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.

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List of Appendices

2 RATIONALE

This clinical protocol annex 2 (Poland only) amendment 1 (will be incorporated into the Protocol Annex creating Clinical Protocol Annex 2 [Poland Only] Version 2, Date 26 April 2018) addresses the following issue(s):**Duration of Open-label Extension Phase**

The OLE phase will be extended in duration in Poland to ensure continued access to GWP42003-P prior to approval. Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first. Procedures for each resupply visit and assessment visit have been condensed into single sections in the Annex to minimize repetition.

2.2 Minor Corrections and Clarifications

The following minor corrections/clarifications have been made to the protocol annex:

- Clarification that the End of Taper Visit, Safety Telephone Call, and Follow-up Visit are required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P. Furthermore, the timings of these visits/calls are relative to the End of Treatment/Withdrawal Visit.
- Clarification that Safety Telephone Call is still required for patients who do not taper IMP, that the call window is +3 days, and that the patient's last dose includes the final taper period dose.
- Clarification that the Follow-up Visit can be a clinic visit or can be conducted by telephone.
- Clarification that the Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE and should only be administered at the final dosing visit (End of Treatment/ Withdrawal visit or End of Taper visit, as applicable).
- Treatment days have been removed in favor of treatment weeks, as this is more compatible with the interactive voice response system.
- Collection of informed consent/assent at Visit B10 was listed in the Schedule of Assessments but was not mentioned in Section 4.1 of the Annex.

- Additional assessments for patients who withdraw early and taper IMP were listed in the End of Taper Visit section of the Annex but had not been denoted in the Schedule of Assessments.
- Abbreviations which are not used in the Annex have been removed from the List of Abbreviations, and abbreviated terms have been defined on first use.
- Terms which are not used in the Annex have been removed from the Definition of Terms.
- Bulleted lists have been used to improve readability.
- References to “the study” has been replaced with “the trial” throughout.
- Minor spelling/punctuation/grammatical corrections have been made to improve consistency and readability; however, in the interest of brevity, these changes are not captured in Section 4 of this amendment document.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018. It will be kept in the trial master file at GW as well as in each investigational site file and, if applicable, pharmacy site file.

4 PRESENTATION OF AMENDED TEXT

The text will be amended as follows:

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 2 (Poland Only) Amendment 1 [Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
Title page p. 1	(…) This annex outlines the assessments and procedures for ~~**year**~~ 2 of the Open Label Extension. (…)	(…) This annex outlines the assessments and procedures for **years** 2 **and 3** of the open-label extension. (…)	See Section 2.1
List of Abbreviations p. 4–5	(…) (…) AED Antiepileptic ~~**Drugs**~~ (…) (…) (…) (…) ~~**EC**~~ ~~**Ethics Committee**~~ (…) (…) (…) (…) ~~**IEC**~~ ~~**Independent Ethics Committee**~~ (…) (…) ~~**IMP**~~ ~~**Investigational Medicinal**~~	(…) (…) AED Antiepileptic **drug** (…) (…) **CBD** **Cannabidiol** (…) (…) (…) (…) **IGF-1** **Insulin-like growth factor-1** (…) (…) (…) (…)	See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 2 (Poland Only) Amendment 1 [Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
List of Abbreviations p. 4–5 (continued)	~~**IRB**~~ ~~**Product Institutional Review Board**~~ (…) (…) SCQ ~~**Subject**~~ Communication Questionnaire (…) (…)	(…) (…) SCQ **Social** Communication Questionnaire (…) (…) **TSC Tuberous sclerosis complex** **Vineland-II Vineland Adaptive Behavior Scales, Second Edition**	
Definition of Terms p. 5	(…) (…) ~~**International normalised ratio**~~ ~~**A calculation made to standardise prothrombin time.**~~ (…) (…) ~~***Status epilepticus***~~ ~~**Any seizure lasting 30 minutes or longer**~~	(…) (…) (…) (…)	See Section 2.2
Section 1 RATIONALE p. 6	GWEP1521 ~~**includes**~~ a randomized, ~~**double-blind,**~~ parallel-group, 16-week ~~**comparison of two**~~ doses of GWP42003-P ~~**versus**~~ placebo followed by a 1 year Open Label Extension (OLE).	**Trial** GWEP1521 **consists of** a randomized, parallel-group, 16-week **double-blind phase comparing 2** doses of GWP42003-P **with** placebo, followed by a 1-year open-label extension (OLE)	See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 2 (Poland Only) Amendment 1 [Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 1 RATIONALE p. 6 (continued)	**~~In order~~** to ensure continued access to GWP42003-P prior to approval **~~for patients completing 1 year of OLE treatment~~**, the OLE will be extended **~~by 1 further year~~** in Poland. (…) However, in countries where compassionate access proves difficult prior to first approvals the OLE duration may also be extended **~~by 1 year~~** to include these additional countries.	**phase**. To ensure continued access to GWP42003-P prior to approval, the OLE **phase** will be extended **to a total of 3 years in duration** in Poland. **Patients will complete the OLE phase when GWP42003-P is approved in tuberous sclerosis complex (TSC) and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first.** (…) However, in countries where compassionate access proves difficult prior to first approvals, the OLE duration may also be extended to include these additional countries.	See Section 2.1 and Section 2.2 See Section 2.1 and Section 2.2 See Section 2.1
Section 2 SUMMARY OF THE ANNEX p. 6	(…) Dosing will remain consistent and there is no requirement for dose adjustment or further titration	(…) **Patients completing a second year of OLE treatment will enter a third year of OLE treatment.** Dosing will remain consistent and there is no requirement for dose adjustment or further titration	See Section 2.1 See Section 2.1

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 2 (Poland Only) Amendment 1 [Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
Section 2 SUMMARY OF THE ANNEX p. 6 (continued)	upon entry into ~~**year**~~ 2. Assessment visits have been added at week 78 ~~**and**~~ week 104 (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in ~~**year**~~ 2 to ensure re-supply volumes are manageable for both patients and dispensing staff. (…) Following completion ~~**of year 2**~~ of the OLE, patients who do not immediately continue to use GWP42003-P, will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit. A safety follow-up visit will be completed ~~**by telephone**~~ 4 weeks after the End of Taper	upon entry into **years** 2 **or 3**. Assessment visits have been added at Week 78, Week 104**, Week 130, and Week 156** (relative to Visit B1). Investigational medicinal product (IMP) dispensing visits have also been added between assessment visits in **years** 2 **and 3** to ensure resupply volumes are manageable for both patients and dispensing staff. (…) **Patients will complete the OLE phase when GWP42003-P is approved in TSC and is commercially available to the patient, or after a maximum of 3 years' OLE treatment, whichever occurs first.** Following completion of the OLE, patients who do not immediately continue to use **commercial** GWP42003-P will commence a 10-day taper period (tapering 10% per day) before attending an End of Taper visit. A safety follow-up visit will be completed 4 weeks	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 2 (Poland Only) Amendment 1 [Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
	~~(approximately 109 weeks after Visit B1)~~.	after the End of Taper **visit**.	
Section 3 TREATMENT SCHEMATIC DIAGRAM p. 7	*<See Appendix 1 for changes to diagram>* **~~* A 'Post-taper Safety telephone call' must be made two weeks after the patients last dose of IMP to collect seizure information, and to assess adverse events (AEs), epilepsy-related hospitalizations, concomitant medications and/or changes to medication.~~** **~~**A follow-up visit is~~** required for patients who withdraw from the **~~study~~** or complete treatment but do not **~~wish to~~** continue to use GWP42003-P. **~~This must be made four weeks after the patients last dose of IMP to collect information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication~~**. **~~A Can be conducted by telephone.~~**	*<See Appendix 1 for changes to diagram>* **[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.** **[b] Only** required for patients who withdraw from the **trial** or complete treatment but do not **immediately** continue to use **commercial** GWP42003-P. **[c] Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.** **[d] This must be made 4 weeks (+3 days) after the**	See Section 2.1 See Section 2.1 See Section 2.2 See Section 2.2 See Section 2.2
Section 3			

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 2 (Poland Only) Amendment 1 [Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
TREATMENT SCHEMATIC DIAGRAM p. 7 (continued)	# B13, B14, B16, B17 – Resupply visits (±7 days).	**patient's last dose of IMP and can be conducted by telephone.** [e] **Visits** B13, B14, B16, B17**, B19, B20, B22, B23** – Resupply visits (±7 days).	See Section 2.2 See Section 2.1
Section 4 DESIGN AND PROCEDURES p. 8	Patients and their parent(s)/legal representative will be invited to participate in ~~**year**~~ 2 of the OLE when they reach Visit B10 of the ~~**Blinded**~~ Phase. (…) Patients will continue to make weekly ~~**IVRS**~~ diary calls throughout their second ~~**year**~~ of OLE participation.	Patients and their parent(s)/legal representative will be invited to participate in **years** 2 **and 3** of the OLE when they reach Visit B10 of the **OLE** phase. (…) Patients will continue to make weekly **interactive voice response system (IVRS)** diary calls throughout their second **and third years** of OLE participation.	See Section 2.1 and correction of a typographical error See Section 2.1 and Section 2.2
Section 4.1 Visit B10 (Week 52) p. 8 Section 4.1 Visit B10	4.1 Visit B10 (~~**Day 365,**~~ Week 52) In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in Poland will receive sufficient open-label IMP for nine weeks' home dosing and instructed to maintain consistent dosing. (…)	4.1 Visit B10 (Week 52) In addition to the visit schedule outlined in Section 9.1.2.10 of the main protocol, patients treated in Poland **who provide written informed consent/assent (see Section 5)** will receive sufficient open-label IMP for 9 weeks' home dosing and **will be** instructed to maintain consistent dosing. (…)	See Section 2.2 See Section 2.2

Revised Protocol Annex Section Number, Heading and Page Number	Original Wording from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017 *(Deleted wording is struck through and in bold)*	Revised Wording from Clinical Protocol Annex 2 (Poland Only) Amendment 1 [Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018] *(Revised wording is underscored and in bold)*	Rationale for the amendment
(Week 52) p. 8 (continued)	(…)	**The Study Medication Use and Behavior Survey should not be administered at Visit B10 for patients entering the second year of the OLE.** (…)	See Section 2.2
Section 4.2 Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), and B23 (Week 148) p. 8–9	4.2 **~~Visit B13 (Day 428, Week 61, Re-supply Visit)~~** **~~This visit~~** will occur **~~427 days~~** after Visit B1. (…) Attendance of the patient is not required for **~~this~~** re-supply **~~visit~~** provided the primary caregiver is able to attend. (…) **~~The~~** visit will comprise a review of concomitant medications (including antiepileptic drugs (AEDs), epilepsy-related hospitalizations and adverse events	4.2 **Resupply Visits B13 (Week 61), B14 (Week 70), B16 (Week 87), B17 (Week 96), B19 (Week 113), B20 (Week 122), B22 (Week 139), and B23 (Week 148)** **Visits B13, B14, B16, B17, B19, B20, B22, and B23** will occur **61, 70, 87, 96, 113, 122, 139, and 148 weeks** after Visit B1**, respectively**. (…) Attendance of the patient is not required for resupply **visits** provided the primary caregiver is able to attend. (…) **Each** visit will comprise a review of concomitant medications (including antiepileptic drugs [AEDs]), epilepsy-related hospitalizations and adverse events (AEs).	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.1

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	(AEs). The investigator must assess adherence to the dosing regimen by reviewing the patient's diary and ~~**interactive voice response system (IVRS)**~~ data, record the patient's/caregiver's attendance at the visit and confirm the outcome of the visit. (…)	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. (…)	See Section 2.2
Section 4.3 Assessment Visits B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 Section 4.3 Assessment Visits	*<Section 4.3 of Protocol Annex 2 Version 1 was deleted.* *The following text is revised from Section 4.4 of Protocol Annex 2 Version 1>* ~~**4.4 Visit**~~ B15 (~~**Day 547,**~~ Week 78) ~~**This visit**~~ will occur ~~**546 days**~~ after Visit B1. (…) The following ~~**observations**~~ will be made at ~~**Visit B15**~~: concomitant medications, (including AEDs), physical examination (including height and body	*<Section 4.3 of Protocol Annex 2 Version 1 was deleted.* *The following text is revised from Section 4.4 of Protocol Annex 2 Version 1>* **4.3 Assessment Visits** B15 (Week 78)**, B18 (Week 104), and B21 (Week 130) Visits B15, B18, and B21** will occur **78, 104, and 130 weeks** after Visit B1**, respectively.** (…) The following **assessments** will be made at **each visit**: • Concomitant medications (including AEDs) • Physical examination (including height and	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2

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B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 (continued)	weight), 12-lead electrocardiogram (ECG), vital signs, epilepsy-related hospitalizations **~~and~~** AEs.	body weight) • 12-lead electrocardiogram (ECG) • Vital signs • Epilepsy-related hospitalizations • AEs • **Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)** • **Suicidality, assessed in accordance with Section 9.2.12.8 of the main protocol**	
Section 4.3 Assessment Visits	Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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. (…)	**At each assessment visit,** clinical laboratory samples (blood and urine [where possible]), including a pregnancy test if appropriate (using both a serum sample and a urine dipstick), will be taken for hematology, biochemistry, urinalysis, and determination of serum **insulin-like growth factor-1 (IGF-1)** levels (for patients less than 18 years of age) to be performed by the central laboratory. (…)	See Section 2.2

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B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 (continued) Section 4.3 Assessment Visits	**~~The following assessments will also be performed: Subject Global Impression of Change in Seizure Duration (SGIC-SD)/Caregiver Global Impression of Change in Seizure Duration (CGIC-SD).~~** **~~Suicidality will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) or Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.~~** (…) Patients/caregivers will then receive sufficient **~~open-label~~** IMP **~~for eight weeks' home dosing~~**.	(…) Patients/caregivers will then receive sufficient IMP **until the next scheduled visit**. **In addition to the above, the following assessments will be made at Visit B18 only:** • **Details of menstruation (for females)** • **Tanner staging (patients aged 10–17 [inclusive] only)** • **Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy (QOLIE-31-P)**	See Section 2.2 See Section 2.1 See Section 2.1 See Section 2.1

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B15 (Week 78), B18 (Week 104), and B21 (Week 130) p. 9–10 (continued)		• **Subject Global Impression of Change (SGIC)/ Caregiver Global Impression of Change (CGIC)** • **Physician Global Impression of Change (PGIC)** • **Wechsler Tests** • **Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)** • **Social Communication Questionnaire (SCQ)** • **Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)**	

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12	*<Section 4.4 of Protocol Annex 2 Version 1 was revised to create Section 4.3 of Protocol Annex 2 Version 2.* *Sections 4.5 and 4.6 of Protocol Annex 2 Version 1 were deleted.* *The following text is revised from Section 4.7 of Protocol Annex 2 Version 1>* **~~4.7~~ ~~Visit B18 (Day 729, Week 104,~~** End of Treatment/Withdrawal Visit**~~)~~** This visit will occur **~~728 days after Visit B1 or~~** 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.~~**	*<Section 4.4 of Protocol Annex 2 Version 1 was revised to create Section 4.3 of Protocol Annex 2 Version 2.* *Sections 4.5 and 4.6 of Protocol Annex 2 Version 1 were deleted.* *The following text is revised from Section 4.7 of Protocol Annex 2 Version 1>* **4.4** End of Treatment/Withdrawal Visit This visit will occur**: 1)** following early withdrawal from the **trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.**	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2 See Section 2.1 See Section 2.1

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	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 [where possible]), including a pregnancy test 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),~~** 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, **~~Quality of Life in Childhood Epilepsy (QOLCE)/Quality of Life in Epilepsy (QOLIE-31-P)~~**, **~~Subject Global Impression of Change (SGIC)/Caregiver Global Impression of Change (CGIC)~~**, **~~Physician Global~~**	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] **<u>only</u>**) • ECG • IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, **<u>and</u>** IMP dosing) • Epilepsy-related hospitalizations • Concomitant medications and/or changes to medication • AEs • **<u>QOLCE/QOLIE-31-P</u>** • **<u>SGIC/CGIC</u>** • **<u>PGIC</u>** • SGIC-SD/CGIC-SD	See Section 2.2

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	~~**Impression of Change (PGIC)**~~, SGIC-SD/CGIC-SD, Wechsler Tests, ~~**Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)**~~, ~~**Social Communication Questionnaire (SCQ) and the Vineland-II.**~~	• Wechsler Tests • **CBCL/ABCL** • **SCQ** • **Vineland-II**	
	Suicidality ~~**will be**~~ assessed ~~**using the C-SSRS/ Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.**~~	• Suicidality, assessed **in accordance with Section 9.2.12.8 of the main protocol**	See Section 2.2
		Clinical laboratory samples (blood and urine [where possible]), including a pregnancy test 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.	See Section 2.2
	(…)	(…)	
	For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the ~~**study**~~.	For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the **trial**.	See Section 2.2
	For patients who immediately continue to use	For patients who immediately continue to use **commercial** GWP42003-P following the End of	See Section 2.2

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	GWP42003-P following the 'End of Treatment' visit, the IVRS will be contacted to confirm the patient's completion of this ~~**study**~~ and the paper diaries will be collected.	Treatment visit, the IVRS will be contacted to confirm the patient's completion of this **trial** and the paper diaries will be collected. **For patients 12 years of age and older who complete treatment and immediately continue to use commercial GWP42003-P, or for patients 12 years of age and older who withdraw early and do not taper IMP, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.**	See Section 2.2
	For patients who do not immediately continue to use GWP42003-P following the 'End of Treatment' visit, IMP will be tapered at home (10% per day for 10 days).	For patients who **complete treatment but** do not immediately continue to use **commercial** GWP42003-P following the End of Treatment visit, IMP will be tapered at home (10% per day for 10 days).	See Section 2.2
	Additional IMP will be dispensed, if required.	Additional IMP will be dispensed, if required**, and instructions for tapering the dose will be provided**.	See Section 2.2
	(…)	(…) Information will continue to be recorded in the paper	

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Section 4.4 End of Treatment/ Withdrawal Visit p. 10–12 (continued)	**~~The IVRS will generate the patient's daily IMP dosing volumes for the 10-day taper period, during which time diary~~** information will continue to be recorded in the paper diary. **~~For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.~~** Following the 'End of Treatment'/'Withdrawal' visit, the IVRS seizure reporting diary should **~~only~~** be completed up to the Follow-up visit.	diary **<u>during the taper period</u>**. Following the End of Treatment/Withdrawal visit, the IVRS seizure reporting diary should be completed up to the Follow-up visit.	See Section 2.2 See Section 2.2 Correction of a typographical error
Section 4.5 End of Taper Visit p. 12–13 Section 4.5	*<Section 4.5 of Protocol Annex 2 Version 1 was deleted.* *Section 4.6 of Protocol Annex 2 Version 1 was also deleted, and Section 4.7 was revised to create Section 4.4 of Protocol Annex 2 Version 2.* *The following text is revised from Section 4.8 of Protocol Annex 2 Version 1>* **~~4.8~~** **~~Visit B19 (Day 739, Week 105,~~** End of Taper **~~Period~~** Visit**~~)~~**	*<Section 4.5 of Protocol Annex 2 Version 1 was deleted.* *Section 4.6 of Protocol Annex 2 Version 1 was also deleted, and Section 4.7 was revised to create Section 4.4 of Protocol Annex 2 Version 2.* *The following text is revised from Section 4.8 of Protocol Annex 2 Version 1>* **<u>4.5</u>** End of Taper Visit	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2

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End of Taper Visit p. 12–13 (continued)		**This visit is required for patients who:** **1) withdraw from the trial and taper IMP; or** **2) complete treatment but do not immediately continue to use commercial GWP42003-P.**	See Section 2.2
	~~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~~**. (…)	**The End of Taper** visit will take place 10 (+3) days after the End of Treatment/Withdrawal visit. (…)	See Section 2.2
	The following assessments will be made: vital signs **~~and~~** physical examination (including height and body weight).	The following assessments will be made: • Vital signs • Physical examination (including height and body weight) • **IVRS and paper diary information (including information regarding seizures, AEs, usage of rescue medication, concomitant AEDs, and IMP dosing)** • **Epilepsy-related hospitalizations** • **Concomitant medications and/or changes to medication** • **AEs**	See Section 2.2
Section 4.5 End of Taper Visit	Suicidality **~~will be~~** assessed **~~using the C-SSRS/~~**	• Suicidality, assessed **in accordance with**	See Section 2.2

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p. 12–13 (continued)	~~**Children's C-SSRS (Since Last Visit) or, in patients with profound cognitive impairment, by interview and clinical judgment.**~~ ~~**In addition, the following assessments will be made for patients who withdraw early and taper IMP (including withdrawal during the taper period):**~~ ECG ~~**and**~~ clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis). ~~**The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, IMP usage, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.**~~ (…) Following the 'End of Taper ~~**Period**~~' visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.	**<u>Section 9.2.12.8 of the main protocol</u>** • ECG • Clinical laboratory samples (blood and urine for hematology, biochemistry and urinalysis) (…) Following the End of Taper visit (or date of final dosing), the IVRS seizure reporting diary should be completed up to the Follow-up visit.	See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2

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Section 4.6 Safety Telephone Call p. 13	*<Section 4.6 of Protocol Annex 2 Version 1 was deleted.* *Sections 4.7 and 4.8 of Protocol Annex 2 Version 1 were revised to create Sections 4.4 and 4.5 of Protocol Annex 2 Version 2, respectively.* *The following text is revised from Section 4.9 of Protocol Annex 2 Version 1>* **~~4.9~~ ~~Visit B20 (Day 753, Week 107, Post-taper~~** Safety Telephone Call**~~)~~** 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~~** two 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.	*<Section 4.6 of Protocol Annex 2 Version 1 was deleted.* *Sections 4.7 and 4.8 of Protocol Annex 2 Version 1 were revised to create Sections 4.4 and 4.5 of Protocol Annex 2 Version 2, respectively.* *The following text is revised from Section 4.9 of Protocol Annex 2 Version 1>* **4.6** Safety Telephone Call This visit is required for patients who withdraw from the **trial** or complete treatment but do not **immediately** continue to use **commercial** GWP42003-P. The **Safety Telephone Call** will be **conducted** 2 weeks (+3 days) after the patient's last dose of GWP42003-P (including final taper period dose). During this call, caregivers will be asked for information on: • AEs • Epilepsy-related hospitalizations	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2

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	(…)	• Concomitant medications and/or changes to medication (…)	

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Section 4.7 Follow-up Visit p. 13	*<Section 4.7 of Protocol Annex 2 Version 1 was revised to create Section 4.4 of Protocol Annex 2 Version 2.* *Sections 4.8 and 4.9 of Protocol Annex 2 Version 1 were revised to create Sections 4.5 and 4.6 of Protocol Annex 2 Version 2, respectively.* *The following text is revised from Section 4.10 of Protocol Annex 2 Version 1>* **~~4.10~~** Follow-up Visit **~~(Telephone Call)~~** 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 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.	*<Section 4.7 of Protocol Annex 2 Version 1 was revised to create Section 4.4 of Protocol Annex 2 Version 2.* *Sections 4.8 and 4.9 of Protocol Annex 2 Version 1 were revised to create Sections 4.5 and 4.6 of Protocol Annex 2 Version 2, respectively.* *The following text is revised from Section 4.10 of Protocol Annex 2 Version 1>* **4.7** Follow-up Visit This visit is required for patients who withdraw from the **trial** or complete treatment but do not **immediately** continue to use **commercial** GWP42003-P. The Follow-up visit will **take place** 4 weeks (+3 days) after the patient's last dose of GWP42003-P **(including final taper period dose)** and can be conducted **by** telephone. During this visit/call, caregivers will be asked for information on: • AEs • Epilepsy-related hospitalizations	See Section 2.1 See Section 2.1 See Section 2.1 See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2 See Section 2.2

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		• Concomitant medications and/or changes to medication	

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Section 5 INFORMED CONSENT/ ASSENT p. 14	An institutional review board **~~(IRB)~~**/independent ethics committee **~~(IEC)~~** approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.	An institutional review board/independent ethics committee-approved informed consent/assent form will be given to eligible patients prior to Visit B10 of the parent trial (please refer to Section 9.1.2.11 of the main trial protocol) which will reflect the additional implications of this annex.	See Section 2.2
Section 6.1 Patients to Analyze p. 14	Patients in Poland who continue to participate in **~~year~~** 2 of the OLE will be analysed in accordance with the statistical considerations detailed in Section 13 of the main protocol.	Patients in Poland who continue to participate in **years** 2 **and 3** of the OLE will be analyzed in accordance with the statistical considerations detailed in Section 13 of the main protocol.	See Section 2.1
APPENDIX 1 SCHEDULE OF ASSESSMENTS p. 15–17	*<See Appendix 1 for changes to table>*	*<See Appendix 1 for changes to table>* **[a] End of Treatment/Withdrawal Visit will occur: 1) following early withdrawal from the trial; 2) in place of the next scheduled clinic visit (assessment or resupply) when GWP42003-P is approved in TSC and is commercially available to the patient; or 3) after a maximum of 3 years' OLE treatment (i.e., 156 weeks [±7 days] from Visit B1); whichever occurs first.** **[b] Only required for patients who withdraw from**	See Section 2.1 See Section 2.1 See Section 2.2

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APPENDIX 1 SCHEDULE OF ASSESSMENTS p. 15–17 (continued)		**the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.** [c] **Safety Telephone Call must be made 2 weeks (+3 days) after the patient's last dose of IMP.** [d] **Follow-up Visit required for patients who withdraw from the trial or complete treatment but do not immediately continue to use commercial GWP42003-P.** **This must be made 4 weeks (+3 days) after the patient's last dose of IMP and can be conducted by telephone.** [e] **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.**	See Section 2.2 See Section 2.2 See Section 2.2

5 REFERENCES

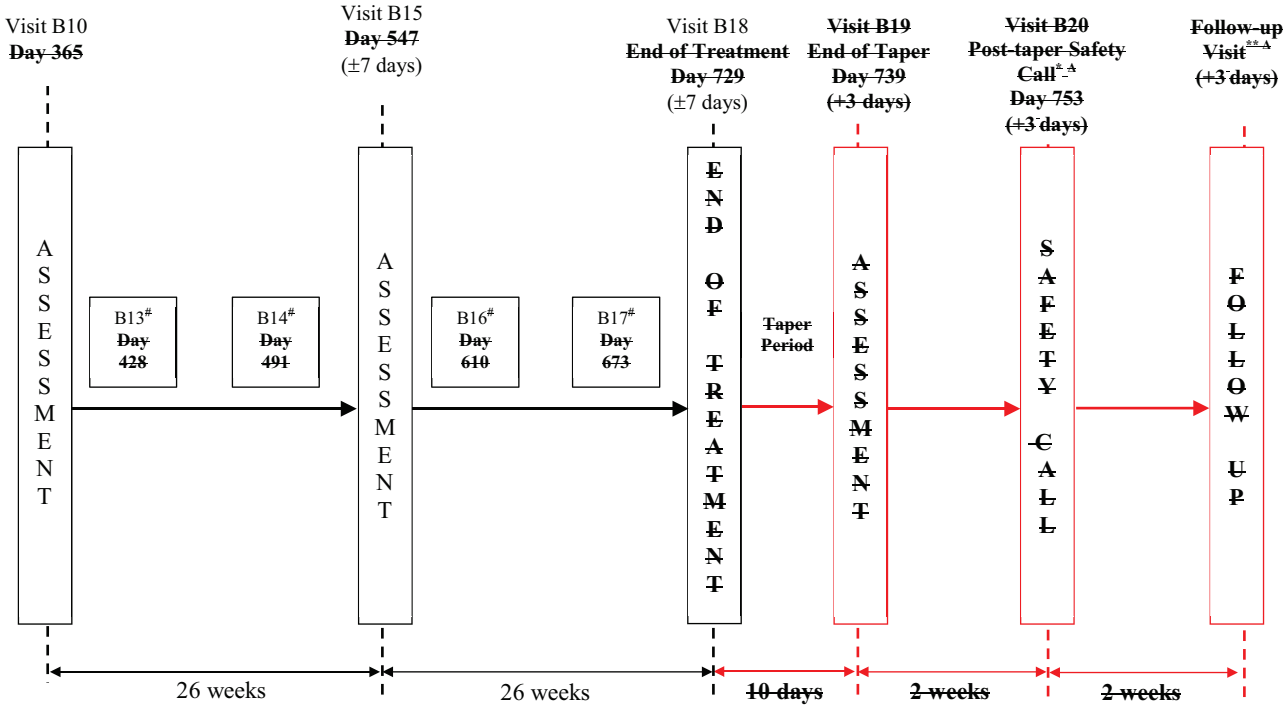
N/A

APPENDIX 1 AMENDED FIGURES AND TABLES

Original Figures from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017

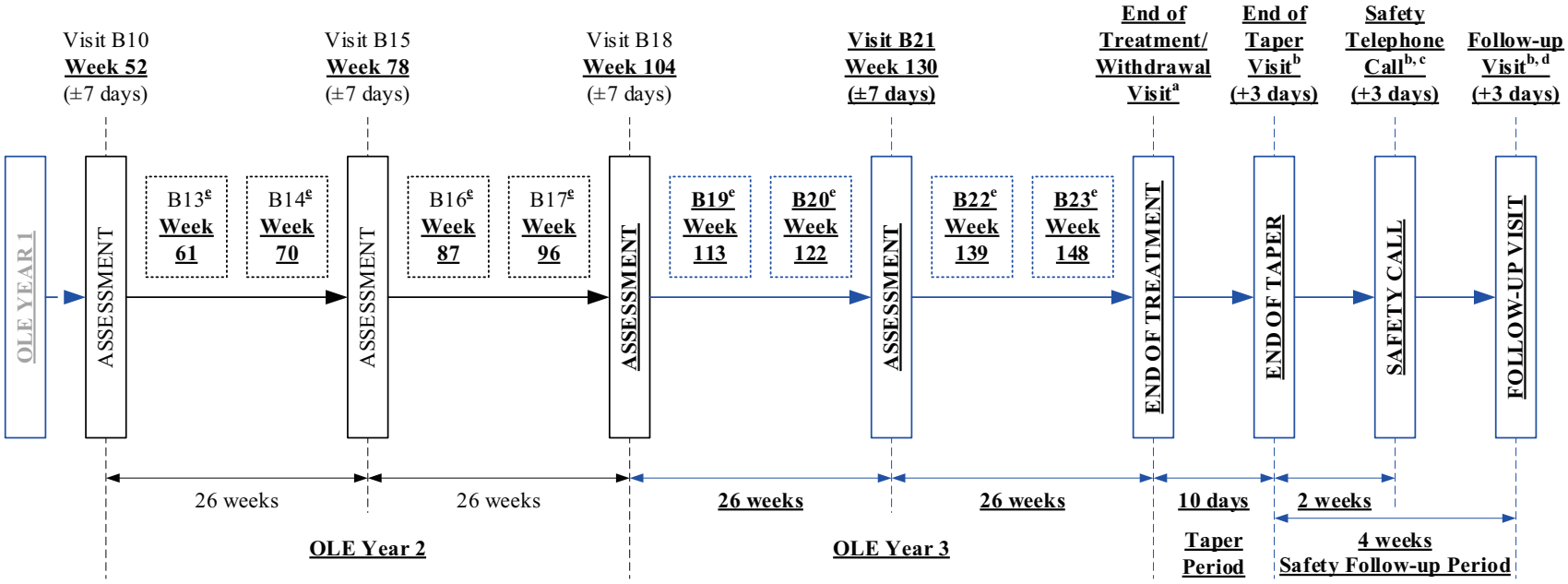
(Deleted wording is struck through and in bold; deleted lines are in red)

3 TREATMENT ~~SCHEMA~~



Revised Figures from Clinical Protocol Annex 2 (Poland Only) Amendment 1
[Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018]
(Revised wording is underscored and in bold; new lines are blue)

3 TREATMENT **SCHEMATIC DIAGRAM**



Original Tables from Clinical Protocol Annex 2 (Poland Only) Version 1, Date 27 June 2017

(Deleted wording is struck through and in bold; deleted lines are in red)

APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open-label Extension

Visit Number	B10	~~**Re-Supply Visit**~~ B13	~~**Re-Supply Visit**~~ B14	B15	~~**Re-Supply Visit**~~ B16	~~**Re-Supply Visit**~~ B17	End of Treatment ~~**B18**~~	End of Taper ~~**B19**~~	~~**Post-Taper**~~ Safety Telephone Call ~~**B20**~~	Follow up ~~**Telephone Call**~~
~~**Day**~~	~~**365**~~	~~**428**~~	~~**491**~~	547	~~**610**~~	~~**673**~~	~~**729**~~	~~**739**~~	~~**753**~~	~~**767**~~
~~**Visit Window**~~	~~**±7**~~	~~**±7**~~	~~**±7**~~	~~**±7**~~		~~**±7**~~	~~**±7**~~	~~**+3**~~	~~**±3**~~	~~**+3**~~
~~**Week**~~		~~**61**~~	~~**70**~~	~~**78**~~	~~**87**~~	~~**96**~~	~~**104**~~	~~**105**~~	~~**107**~~	~~**109**~~
Informed consent/assent	X									
Vital signs	X			X			X	X		
Physical examination (including height and body weight)	X			X			X	X		
ECG	X			X			X	X		
Clinical laboratory blood sampling	X			X			X	X		
Clinical laboratory urine sampling (dipstick urinalysis)	X			X			X	X		
Pregnancy test, where	X			X			X			

Visit Number	B10	~~Re-Supply Visit~~ B13	~~Re-Supply Visit~~ B14	B15	~~Re-Supply Visit~~ B16	~~Re-Supply Visit~~ B17	End of Treatment ~~B18~~	End of Taper ~~B19~~	~~Post-Taper~~ Safety Telephone Call ~~B20~~	Follow up ~~Telephone Call~~
~~Day~~	~~365~~	~~428~~	~~491~~	547	~~610~~	~~673~~	~~729~~	~~739~~	~~753~~	~~767~~
~~Visit Window~~	~~±7~~	~~±7~~	~~±7~~	~~±7~~		~~±7~~	~~±7~~	~~+3~~	~~±3~~	~~+3~~
appropriate										
IGF-1 testing	X						X			
AED concentration	X			X			X			
AEs	X	X	~~X~~	X	X	~~X~~	X	X	X	X
Concomitant medications	X	X	~~X~~	X	X	~~X~~	X	X	X	X
Inpatient epilepsy-related hospitalizations	X	X	~~X~~	X	X	~~X~~	X	X	X	X
Suicidality /C-SSRS/ Children's C-SSRS	X			X			X	X		
Vineland-II	X						X			
SGIC/CGIC	X						X			
PGIC	X						X			
SGIC-SD/CGIC-SD	X			X			X			
QOLCE/QOLIE-31-P	X						X			
Wechsler Tests	X						X			
CBCL/ABCL	X						X			
SCQ	X						X			
Tanner Staging (where	X						X			

Visit Number	B10	~~Re-Supply Visit~~ B13	~~Re-Supply Visit~~ B14	B15	~~Re-Supply Visit~~ B16	~~Re-Supply Visit~~ B17	End of Treatment ~~B18~~	End of Taper ~~B19~~	~~Post-Taper~~ Safety Telephone Call ~~B20~~	Follow up ~~Telephone Call~~
~~Day~~	~~365~~	~~428~~	~~491~~	547	~~610~~	~~673~~	~~729~~	~~739~~	~~753~~	~~767~~
~~Visit Window~~	~~±7~~	~~±7~~	~~±7~~	~~±7~~		~~±7~~	~~±7~~	~~+3~~	~~±3~~	~~+3~~
appropriate)										
Menstruation question (where appropriate)	X						X			
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)	X	X	~~X~~	X	X	~~X~~	X	X		
IMP dispensing	X	X	~~X~~	X	X	~~X~~	X			
Collection of IMP	X	X	~~X~~	X	X	~~X~~	X	X		
IMP compliance review	X	X	~~X~~	X	X	~~X~~	X	X		
Study Medication Use and Behavior Survey							X			

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[Clinical Protocol Annex 2 (Poland Only) Version 2, Date 26 April 2018]
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APPENDIX 1 SCHEDULE OF ASSESSMENTS

Open-label Extension

Visit Number	B10	**Re-supply** B13	B14	**Assess-ment** B15	**Re-supply** B16	B17	**Assess-ment** B18	**Re-supply** **B19**	**B20**	**Assess-ment** **B21**	**Re-supply** **B22**	**B23**	End of Treatment/ **Withdrawal Visit**	End of Taper **Visit**[b]	Safety Telephone Call[b, c]	Follow-up **Visit**[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote**[a]	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
Informed consent/assent	X															
Vital signs **and BP**	X			X			X			**X**			X	X		
Physical examination (including height and body weight)	X			X			X			**X**			X	X		
ECG	X			X			X			**X**			X	X		
Clinical laboratory blood sampling	X			X			X			**X**			X	X		
Clinical laboratory urine sampling (dipstick urinalysis)	X			X			X			**X**			X	X		
Pregnancy test, where appropriate	X			X			X			**X**			X			

Visit Number	B10	Re-supply B13	Re-supply B14	Assess-ment B15	Re-supply B16	Re-supply B17	Assess-ment B18	Re-supply B19	Re-supply B20	Assess-ment B21	Re-supply B22	Re-supply B23	End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote[a]**	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+3**	**+3**	**+3**
IGF-1 testing	X			X			X			**X**			X			
AED concentration	X			X			X			**X**			X			
AEs	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
Inpatient epilepsy-related hospitalizations	X	X		X	X		X	**X**		**X**	**X**		X	X	X	X
Suicidality **assessment**	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						X			
Menstruation question (where appropriate)	X						X						X			

Visit Number	B10	Re-supply B13	Re-supply B14	Assess-ment B15	Re-supply B16	Re-supply B17	Assess-ment B18	Re-supply B19	Re-supply B20	Assess-ment B21	Re-supply B22	Re-supply B23	End of Treatment/ Withdrawal Visit	End of Taper Visit[b]	Safety Telephone Call[b, c]	Follow-up Visit[b, d]
Week	**52**	**61**	**70**	**78**	**87**	**96**	**104**	**113**	**122**	**130**	**139**	**148**	**See footnote[a]**	**10 days after End of Treatment**	**2 weeks after last dose**	**4 weeks after last dose**
Visit Window	**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**±7**		**±7**	**+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**		X	X		
IMP dispensing	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[e]			