A Randomized, Double-blind, Placebo-controlled Trial to Investigate the Efficacy and Safety of Cannabidiol (CBD; GWP42003-P) in Infants with Infantile Spasms Following an Initial Open-label Pilot Study

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CLINICAL PROTOCOL

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Confidentiality Statement

Investigator Agreement

I have read the attached clinical protocol entitled "A Randomized, Double-blind, Placebo-controlled Trial to Investigate the Efficacy and Safety of Cannabidiol (CBD; GWP42003 P) in Infants with Infantile Spasms Following an Initial Open-label Pilot Study", dated 20 September 2016, and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the United States (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 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.

Site No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

GW Authorization

Print name: [redacted] Date: [redacted]

Senior clinical manager (DD Month YYYY)

Signature: [redacted]

1 PROTOCOL SYNOPSIS

Trial Title	A Randomized, Double-blind, Placebo-controlled Trial to Investigate the Efficacy and Safety of Cannabidiol (CBD; GWP42003-P) in Infants with Infantile Spasms Following an Initial Open-label Pilot Study.
Clinical Trial Type	Phase 3.
Indication	Infantile spasms (IS).
Primary Objective	**Pilot Phase:** • To determine the maximum safe, tolerable dose and dosing regimen of GWP42003-P in infants with IS, to be utilized in the pivotal phase and open-label extension (OLE). • To assess the number and proportion of patients considered treatment responders, defined as those free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period. *Note: Resolution of hypsarrhythmia requires reduction of the electroencephalography (EEG) background below 300 µV AND elimination of any electrodecrements or epochs of discontinuity. Persistence of some background slowing and interictal epileptiform discharges may be seen and still be consistent with resolution of hypsarrhythmia.* **Pivotal Phase:** • To assess the number and proportion of patients considered treatment responders, defined as those free of spasms and have resolution of hypsarrhythmia, at the end of the 2-week blinded treatment period versus placebo. **OLE:** • To assess the long term safety of GWP42003-P in infants with IS.
Secondary Objective(s)	**All Phases:** • **Key:** To assess the number and proportion of patients who are free of clinical spasms, as observed on video-electroencephalography (video-EEG) at the end of the treatment period. • **Key:** To assess the number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period. • To assess changes in spasms and seizure subtypes by caregiver observation during the treatment period. • To determine time to cessation of spasms during the treatment

Secondary Objective(s) (continued)	period, as determined by caregiver diaries. • To explore the effect of GWP42003-P on quality of life. **Pivotal Phase Only:** • To assess the safety and tolerability of GWP42003-P. • To determine the population pharmacokinetics (POPPK) of CBD and its metabolites (6-hydroxy-cannabidiol [6-OH-CBD], 7-carboxy-cannabidiol [7-COOH-CBD] and 7-hydroxy-cannabidiol [7-OH-CBD]). **OLE Only:** • To assess the number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, after 3, 6, 9 and 12 months of treatment. • To assess the number and proportion of responders who relapse and the time to relapse. • To explore the effect of GWP42003-P on growth, adaptive behavior and development. • To determine the population POPPK of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD).
Trial Design	This is a multisite trial to evaluate the efficacy and safety of GWP42003-P in patients with IS who have failed to become spasm-free following treatment with 1 or more approved IS therapies (i.e., any therapy for the treatment of IS approved in Europe or the United States (US) [e.g., steroids and/or vigabatrin (VGB)]). All approved therapies must be discussed with the patient's parent(s)/legal representative before the patient is considered for the trial (discussions regarding treatment options must be documented). The trial will comprise of a pilot safety phase, followed by a pivotal phase, with a 1 year open-label extension available to all patients who complete either phase. The pilot phase will be open-label with 2 sequential cohorts of 5 patients (aged between 6 and 24 months in the first cohort and between 1 and 24 months in the second cohort), who will receive GWP42003-P for 2 weeks. The pivotal phase will comprise 192 patients, aged 1–24 months, who will undergo a 2-week, randomized, placebo-controlled, double-blind treatment period. An independent data safety monitoring committee (DSMC) will be used throughout the study; they will consider safety of the patients and will confirm doses and dose regimens to be investigated in the pivotal phase, as well as the plans for dose titration. Patients will enter the pilot and pivotal phase at the respective screening visits (Visit 1, Day −7 to Day −1) for assessment of eligibility, which includes a prolonged video-EEG. Patients who

Trial Design (continued)	satisfy all eligibility criteria will then be administered GWP42003-P (pilot phase) or randomized to GWP42003-P (1 of 2 dose levels) or placebo at a 1:1:1 ratio (pivotal phase) (Visit 2, Day 1 [+3 days]). The High Dose Level will be as recommended by the DSMC; the Low Dose Level will be defined as 50% of the High Dose Level. Patients in the placebo group will be split into 2 equivalent cohorts: half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes. Following baseline assessments, patients will titrate the investigational medicinal product (IMP) in 10 mg/kg/day increments to the target dose level (or equivalent volume of placebo in the pivotal phase) and will continue at this dose, or the highest tolerated dose up to a maximum of 40 mg/kg/day, for the remainder of the 2-week treatment phase. Patients in the pilot phase will remain in the clinic as inpatients during the 4-day titration period. If deemed safe by the DSMC, then it is planned for those in the pivotal phase to titrate in an outpatient setting. Further clinic-based assessments will take place after 3 days' dosing (Visit 3, Day 4 [+1 day]). All patients in the pilot and pivotal phases will return to the clinic after 2 weeks of dosing (Visit 4, Day 15 [+3 days]) or earlier if they withdraw prematurely. All patients who complete treatment will then have the opportunity to receive GWP42003-P during the subsequent OLE phase. The OLE phase will last for a maximum of 1 year. Patients who enter the OLE phase will remain on the same dose (pilot phase) or will transition to their target dose of GWP42003-P over 4 days in a blinded manner (pivotal phase). Patients may continue at this dose, or the highest tolerated dose up to a maximum of 40 mg/kg/day, for the remainder of the OLE phase. GWP42003-P may be discontinued at the discretion of the investigator. During the OLE phase, clinic visits will take place on Day 19 (Visit 5 [+1 day]), Day 29 (Visit 6 [±3 days]), Day 43 (Visit 7 [±3 days]), Day 71 (Visit 8 [±3 days]), Day 127 (Visit 9 [±7 days]), Day 211 (Visit 10 [±7 days]), and on Day 295 (Visit 11 [±7 days]). Patients will return to the site for an end of OLE treatment visit on Day 379 (Visit 12 [±7 days]) or earlier if they withdraw prematurely from the OLE phase. Following end of treatment, withdrawal, or discontinuation of IMP, all patients will taper the IMP over 10 days followed by safety follow-up. Patient diaries will be completed each day by the caregiver during the trial.
Primary Endpoint	**Pilot Phase:** • To assess the safety as determined by adverse events (AEs), clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs and physical examinations during the treatment period. • The number and proportion of patients who are free of spasms

Primary Endpoint (continued)	and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG. **Pivotal Phase:** • The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG. **OLE:** • To assess the long term safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period.
Secondary Endpoint(s)	**All Phases:** The following endpoints will be analyzed separately for each phase: • **Key:** The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period. • **Key:** The number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period. • Changes in spasms and seizure subtypes by caregiver observation during the treatment period. • Time to cessation of spasms during the treatment period, as determined by caregiver diaries. • Caregiver Global Impression of Change (CGIC). • Physician Global Impression of Change (PGIC). **Pivotal Phase Only:** • Safety and tolerability as determined by AEs, clinical laboratory tests, ECG, physical examinations and vital signs. • Measurement, where possible, of plasma concentrations of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model. **OLE Only:** • The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, as determined by video-EEG after 3, 6, 9 and 12 months of treatment. • Number and proportion of responders with relapse of spasms, and the time to relapse, as determined by caregiver diaries. • Changes from baseline in length (height), body weight, and head circumference. • Change from baseline in Vineland Adaptive Behavior Scales,

Secondary Endpoint(s) (Continued)	Second Edition (Vineland-II) score. • Measurement, where possible, of plasma concentrations of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model.
Sample Size	The pilot phase is not powered and comprises 10 patients. The pivotal phase will comprise 192 patients. Patients will be randomized to receive 1 of 2 dose levels of GWP42003-P (High Dose Level or Low Dose Level), or matching placebo, on a 1:1:1 basis (64 per treatment group). Patients in the placebo group will be further split into 2 cohorts (32 patients receiving High Dose Level volumes and 32 patients receiving Low Dose Level volumes), but it is assumed that these 2 cohorts can be pooled for the analyses of efficacy. Assuming a 20% screen failure rate, it is expected that approximately 245 patients will need to be screened to achieve this target. [redacted] This is based on a 2-sided 5% significance level, based on a Fisher's exact test.
Summary of Patient Eligibility Criteria	**Inclusion Criteria** For inclusion in the trial, patients must fulfil ALL of the following criteria: • **Pilot phase:** Patient is male or female aged 6–24 months (inclusive) in the first cohort or aged 1-24 months (inclusive) in the second cohort, at the time of consent. **OR** **Pivotal phase:** Patient is male or female aged 1–24 months (inclusive) at the time of consent. • Patient's parent(s)/legal representative is willing and able to give informed consent for the patient's participation in the trial. • Patient and their caregiver are willing and able (in the investigator's opinion) to comply with all trial requirements. • Patient is diagnosed with IS (i.e., spasms and hypsarrhythmia are still evident on video-EEG at screening). *Note: To be considered hypsarrhythmia, as defined for use in the study, the EEG background must be slowed and have multifocal spikes. In addition, it must be EITHER high voltage (above 300 µV) OR have electrodecrement/discontinuity.*

Summary of Patient Eligibility Criteria (continued)	• Patient has failed to respond adequately (i.e., spasms and/or hypsarrhythmia are observed on video-EEG at screening) following treatment with 1 or more approved IS therapies (i.e., any therapy for the treatment of IS approved in Europe or the US [e.g., steroids and/or VGB]. • Patient's parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law. • Patient's parent(s)/legal representative is willing to allow the patient's primary care practitioner (if they have one) and consultant (if they have one) to be notified of participation in the trial, if the primary care practitioner/consultant is different to the investigator. • All non-pharmacological interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for 2 weeks prior to screening. **Exclusion Criteria** The patient may not enter the trial if ANY of the following apply: • Patient is currently taking or has taken clobazam or any oral mammalian target of rapamycin (mTOR) inhibitor within the 2 weeks prior to the screening visit. • Patient has a QT interval, corrected for heart rate with Bazett's formula (QTcB), of > 460 msec on ECG. *Note: If the QTcB is above > 460 msec, the investigator should repeat the ECG 3 times and contact the GW medical monitor, prior to screen failure or entry into the pilot/pivotal phase.* • Patient's caregiver is currently giving or has given recreational or medicinal cannabis, or synthetic cannabinoid-based medications, to the patient within the 1 month prior to the screening visit, as determined by investigator interview with patient's caregiver. • Patient's caregiver is unwilling to abstain from giving the patient (including the patient's mother abstaining themselves, if breastfeeding) recreational or medicinal cannabis, or synthetic cannabinoid-based medications (other than the study IMP), during the trial, as determined by investigator interview with patient's caregiver. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP(s), such as sesame oil. • Patient has significantly impaired hepatic function at the screening visit, defined as **any** of the following: – Serum alanine aminotransferase (ALT) or aspartate

Summary of Patient Eligibility Criteria (continued)	aminotransferase (AST) > 5 × upper limit of normal (ULN). – Serum ALT or AST > 3 × ULN **and** (total bilirubin [TBL] > 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; patients must not be allocated any IMP prior to this. Note: If transaminases are elevated, the investigator may choose to confirm the transaminase elevations by repeat testing during the screening period; results should be discussed with the GW medical monitor prior to screen failure or entry into the pilot or pivotal phase.* • Patient has received an IMP as part of a clinical trial within a minimum of 5 half-lives 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 trial, may influence the result of the trial, or may affect the patient's ability to take part in the trial. • Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient or confound assessment of efficacy if they took part in the trial. • Patient has been previously included in the pilot or pivotal phase of this trial. • 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.
Criteria for Withdrawal	The patient must be withdrawn from the trial if ANY of the following apply: • Any issue with eligibility criteria that is considered to potentially compromise the safety of the patient. • Administrative decision by the investigator, GW, or regulatory authority. • Protocol deviation that is considered to potentially compromise the safety of the patient. • Withdrawal of the patient's parent(s)/legal representative consent. • QTcB of 500 msec or greater on ECG, or a shift from baseline QTcB of 60 msec or greater. *Note: Prior to withdrawal for the QTcB shifts noted above, the*

Criteria for Withdrawal (continued)	*investigator should repeat the ECG 3 times and contact the GW medical monitor.* ***If the above QTcB criteria are confirmed, the patient must be withdrawn from the trial.*** • Lost to follow-up. • ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • ALT or AST > 8 × ULN. • ALT or AST > 5 × ULN for more than 2 weeks. • ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5). *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 trial for ANY of the following: • Any other issue with eligibility criteria (non-safety related). • Any requirement to increase the dose of concomitant AED(s) or to add in new AED(s) during the pilot or pivotal phase. • If a patient is not showing evidence of benefit during the OLE phase (the option of withdrawing from the trial will be discussed with the caregiver at each visit). • Patient/caregiver 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 trial.
Investigational Medicinal Product: Formulation, Mode of Administration, Dose and Regimen	*GWP42003-P:* Clear, colorless to yellow solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose [0.5 mg/mL]) and strawberry flavoring (0.2 mg/mL). *Placebo to match GWP42003-P:* Clear, colorless to yellow solution containing the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose [0.5 mg/mL]) and strawberry flavoring (0.2 mg/mL). *Mode of administration:* Oral. Dosing via a gastric/nasogastric tube (as required) may be considered following approval by the GW medical monitor. *Dose (pilot phase):* All patients will titrate up to a target dose of 40 mg/kg/day over 4 days (10 mg/kg/day) and will continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the

Investigational Medicinal Product: Formulation, Mode of Administration, Dose and Regimen (continued)	remainder of the 2-week treatment phase. *Dose (pivotal phase):* Patients will titrate the IMP to the target dose level over 4 days and will continue at this dose, or the highest tolerated dose up to the target dose level, for the remainder of the blinded treatment phase. *Dose (OLE phase):* Patients will remain on the same dose (pilot phase) or will transition to the target dose of GWP42003-P, or the highest tolerated dose up to 40 mg/kg/day, over 4 days (10 mg/kg/day), in a blinded manner (pivotal phase). Patients may continue at this dose for the remainder of the OLE phase. GWP42003-P may be discontinued at any time during the OLE phase, at the discretion of the investigator, but patients who have become spasm-free and have resolution of hypsarrhythmia will be encouraged to continue to attend all subsequent clinic visits. *Dosage:* IMP is taken twice daily (morning and evening), maintaining consistency with regard to feeds/meals and other concomitant medications, and can be taken with other concomitant medications as directed by the investigator. In the event that the IMP is poorly tolerated, dosing may be changed to 3 times daily (while keeping the equivalent total daily dose), following approval by the GW medical monitor. The recommended dosing intervals are: • 12-hourly (8-hourly minimum) for twice daily dosing. • 6-hourly (minimum) for 3 times daily dosing.
Control Group	The control group in the pivotal phase will receive equivalent dosing volumes of matching placebo.
Procedures	**Pilot and Pivotal Phase** *Visit 1 (Day −7 to Day −1): Screening* The following will be collected/assessed: • Informed consent. • Eligibility criteria. • Patient demographics. • Full medical history. • Concomitant medication review. • Physical examination (including length [height], body weight, and head circumference). • Vital signs (including supine blood pressure). • ECG. • Video-EEG (8–24 hours in duration). • Clinical laboratory samples (blood and urine [if possible]) for: – Serum biochemistry. – Hematology.

Procedures (continued)	– Urinalysis. *To minimize the volume of blood required, serum biochemistry and hematology results from samples analyzed up to 3 days prior to Visit 1 may be used.* • AEs. • Caregiver paper diary issue and training. The caregiver will be required to record all AEs, concomitant antiepileptic drugs (AEDs) and rescue medications, seizures, and spasms from the time of consent. Patients can be re-screened only once, in exceptional cases, at the discretion of the investigator and GW medical monitor. *Visit 2 (Day 1 [+3 Days])* The following will be collected/assessed for patients who satisfy all eligibility criteria during the screening period: • Concomitant medication review. • Physical examination (including length [height], body weight, and head circumference). • Vital signs (including supine blood pressure). • CGIC memory aid. • PGIC memory aid. • Vineland-II. • Caregiver diary review for: – Spasm/seizure information. – Changes in concomitant AEDs. – Usage of rescue medication. – AEs. • AEs. • IMP dispensing. The first dose of IMP will be taken in the clinic in the morning of Day 1 with an ECG assessment between 3 and 5 hours postdose. Pivotal phase only: A pharmacokinetic (PK) blood sample will be taken any time between 1 and 12 hours postdose, provided the risk/benefit outcome is favorable in the investigator's opinion. The PK blood sampling time and time of last dose must be recorded. Pilot phase only: Following Visit 2, all patients will remain in the clinic as inpatients during the 4-day titration period. *Daily Safety Checks (Day 2 to Day 7 [Inclusive])* Caregivers will be asked for information on the following (can be conducted by telephone):

Procedures (continued)	• Spasm/seizure information. • Changes in concomitant AEDs. • Usage of rescue medication. • AEs. *Visit 3 (Day 4 [+1 Day])* The following will be collected/assessed: • Concomitant medication review. • Vital signs (including supine blood pressure). • ECG (prior to the day's first dose of IMP). • Clinical laboratory samples (blood and urine [if possible]) for: – Serum biochemistry. – Hematology. – Urinalysis. • Caregiver diary review for: – Spasm/seizure information. – IMP usage. – Changes in concomitant AEDs. – Usage of rescue medication. – AEs. • AEs. All patients will take their IMP in the clinic with an additional ECG assessment between 3 and 5 hours postdose. Patients in the pilot phase will then be discharged from the clinic. *Visit 4 (Day 15 [+3 Days]): End of Pilot or Pivotal Phase/Withdrawal* The following will be collected/assessed: • Concomitant medication review. • Physical examination (including length [height], body weight, and head circumference). • Vital signs (including supine blood pressure). • ECG (prior to the day's first dose of IMP). • Video-EEG (8–24 hours in duration). • Clinical laboratory samples (blood and urine [if possible]) for: – Serum biochemistry. – Hematology. – Urinalysis. • Pivotal phase only: PK blood sampling (prior to the day's first dose of IMP, provided the risk/benefit outcome is favorable in the investigator's opinion).

Procedures (continued)	• CGIC. • PGIC. • Caregiver diary review for: – Spasm/seizure information. – IMP usage. – Changes in concomitant AEDs. – Usage of rescue medication. – AEs. • AEs. • IMP compliance. • IMP dispensing for transition to the OLE phase, if necessary. All patients will take their IMP in the clinic with an additional ECG assessment between 3 and 5 hours postdose. Pivotal phase only: A further PK blood sample will be taken around 2 hours postdose, provided the risk/benefit outcome is favorable in the investigator's opinion. **OLE Phase** Following Visit 4, daily safety checks will be made during the first week of GWP42003-P dosing. *Daily Safety Checks (Day 16 to Day 22 [Inclusive])* Caregivers will be asked for information on the following (can be conducted by telephone): • Spasm/seizure information. • Changes in concomitant AEDs. • Usage of rescue medication. • AEs. *Visit 5 (Day 19 [+1 Day])* The following will be collected/assessed: • Concomitant medication review. • Vital signs (including supine blood pressure). • ECG. • Clinical laboratory samples (blood and urine [if possible]) for: – Serum biochemistry. – Hematology. – Urinalysis. • Caregiver diary review for: – Spasm/seizure information. – IMP usage.

Procedures (continued)	– Changes in concomitant AEDs. – Usage of rescue medication. – AEs. • AEs. All patients will take their IMP in the clinic. <u>Pivotal phase only:</u> Patients transitioning from the pivotal phase to the OLE only: A PK blood sample will be taken any time between 4 and 12 hours postdose, provided the risk/benefit outcome is favorable in the investigator's opinion. <u>*Visit 6 (Day 29 [±3 Days])*</u> The following will be collected/assessed: • Concomitant medication review. • Physical examination (including length [height], body weight, and head circumference). • Vital signs (including supine blood pressure). • ECG. • Video-EEG (8–24 hours in duration). • Clinical laboratory samples (blood and urine [if possible]) for: – Serum biochemistry. – Hematology. – Urinalysis. • CGIC. • PGIC. • Caregiver diary review for: – Spasm/seizure information. – IMP usage. – Changes in concomitant AEDs. – Usage of rescue medication. – AEs. • AEs. • IMP compliance. • IMP dispensing. <u>*Visit 7 (Day 43 [±3 Days]); Visit 8 (Day 71 [±3 Days]); Visit 9 (Day 127 [±7 Days]); Visit 10 (Day 211 [±7 Days]); Visit 11 (Day 295 [±7 Days]); Visit 12 (Day 379 [±7 Days]): End of OLE Treatment/Withdrawal*</u> The following will be collected/assessed at each of the above visits: • Concomitant medication review.

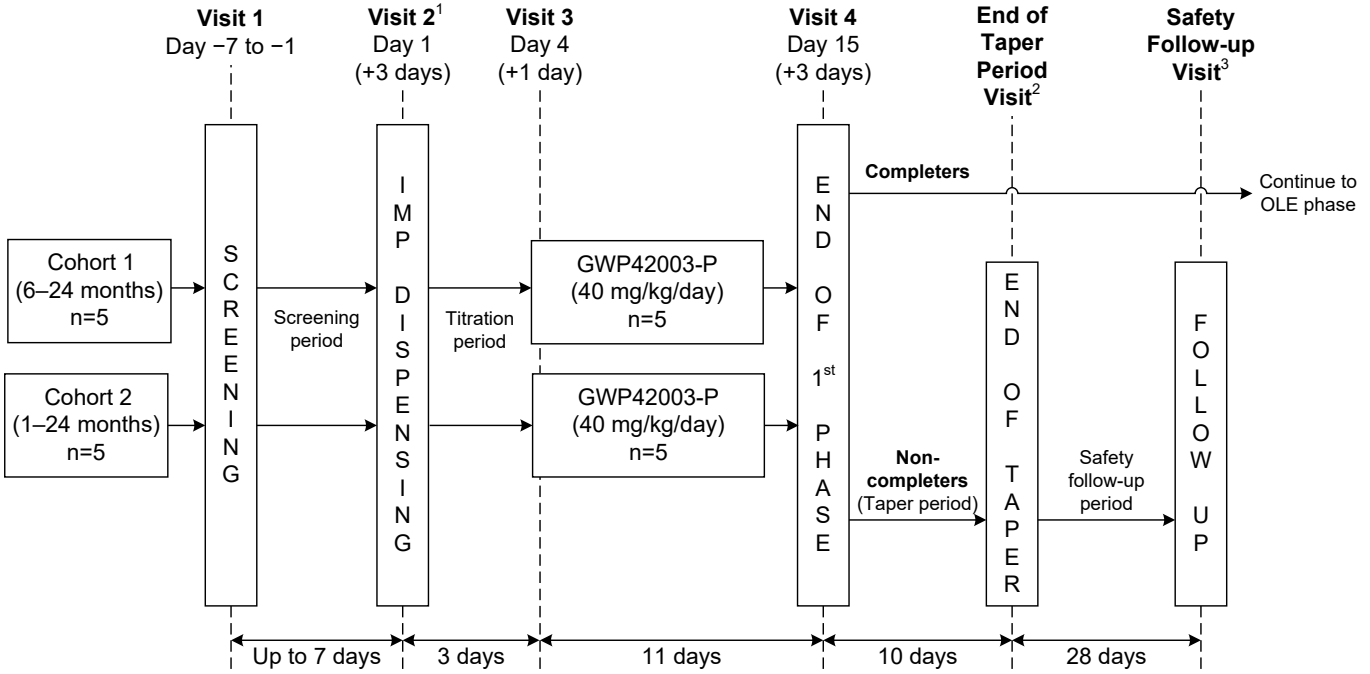
Procedures (continued)	• Physical examination (including length [height], body weight, and head circumference). • Vital signs (including supine blood pressure). • ECG. • Clinical laboratory samples (blood and urine [if possible]) for: – Serum biochemistry. – Hematology. – Urinalysis. • CGIC. • PGIC. • Caregiver diary review for: – Spasm/seizure information. – IMP usage. – Changes in concomitant AEDs. – Usage of rescue medication. – AEs. • AEs. • IMP compliance. • IMP dispensing (only if necessary at Visit 12). The following will also be collected/assessed in addition to the above: • Video-EEG (8–24 hours in duration) (Visits 7 and 9–12, or on withdrawal). • Vineland-II (Visits 10 and 12, or on withdrawal). **Taper Period (10 Days)** Following end of treatment, discontinuation of IMP, or withdrawal, all patients will taper IMP (unless continued dosing is not possible due to an AE). *End of Taper Period Visit (+3 Days)* The following will be collected/assessed: • Concomitant medication review. • Physical examination (including length [height], body weight, and head circumference). • Vital signs (including supine blood pressure). • ECG. • Clinical laboratory samples (blood and urine [if possible]) for: – Serum biochemistry. – Hematology. – Urinalysis.

Procedures (continued)	• Caregiver diary review for: – Spasm/seizure information. – IMP usage. – Changes in concomitant AEDs. – Usage of rescue medication. – AEs. • AEs. • IMP compliance. **Safety Follow-up Period (4 Weeks)** Following end of dosing (including taper period), all patients will commence a 4-week safety follow-up period, which includes weekly safety telephone calls followed by a safety follow-up visit. *Weekly Safety Telephone Calls (±3 Days)* Caregivers will be asked for information on the following: • Spasm/seizure information. • Changes in concomitant AEDs. • Usage of rescue medication. • AEs. *Safety Follow-up Visit (+3 Days)* The following will be collected (can be via telephone): • Spasm/seizure information. • Changes in concomitant AEDs. • Usage of rescue medication. • AEs. The caregiver should return the completed caregiver diary following the safety follow-up visit.
Statistical Considerations	The following endpoints will be assessed using appropriate statistical tests: Primary **Pilot Phase:** • Safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period. • The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG. **Pivotal Phase:** • The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the initial

Statistical Considerations (continued)	2-week treatment phase, as determined by video-EEG. **OLE:** • To assess the long term safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period. <u>Secondary</u> **Pilot Phase Only:** • The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period. • The number and proportion of patients who have resolution of hypsarrhythmia as, observed on video-EEG at the end of the treatment period. • Changes in spasms and seizure subtypes by caregiver observation during the treatment period. • Time to cessation of spasms during the treatment period, as determined by caregiver diaries. • CGIC. • PGIC. **Pivotal Phase Only:** • The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period. • The number and proportion of patients with resolution of hypsarrhythmia, at the end of the initial 2-week treatment phase. • Changes in spasms and seizure subtypes during the initial 2-week treatment phase. • Time to cessation of spasms during the treatment period, as determined by caregiver diaries. • CGIC. • PGIC. • Safety and tolerability as determined by AEs, clinical laboratory tests, ECG, physical examinations and vital signs. • Measurement, where possible, of plasma concentrations of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model. **OLE Only:** • The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period.

Statistical Considerations (continued)	• The number and proportion of patients who have resolution of hypsarrhythmia as, observed on video-EEG at the end of the treatment period. • Changes in spasms and seizure subtypes by caregiver observation during the treatment period. • Time to cessation of spasms during the treatment period, as determined by caregiver diaries. • The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, as determined by video-EEG after 3, 6, 9 and 12 months of treatment. • The number and proportion of responders with relapse of spasms, and the time to relapse, as determined by caregiver diaries. • Changes from baseline in length (height), body weight, and head circumference. • CGIC. • PGIC. • Change from baseline in Vineland-II score. • Measurement, where possible, of plasma concentrations of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model. To control the type I error, a step-up Hochberg's procedure will be used for the primary endpoint of the pivotal phase. If both of the observed p-values from the Low Dose Level and High Dose Level 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. All safety data will be summarized using appropriate statistical methods.
Sponsor	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom

Figure 1-1 Trial Design and Treatment Schematic: Pilot Phase (two sequential cohorts; Cohort 1 & Cohort 2)

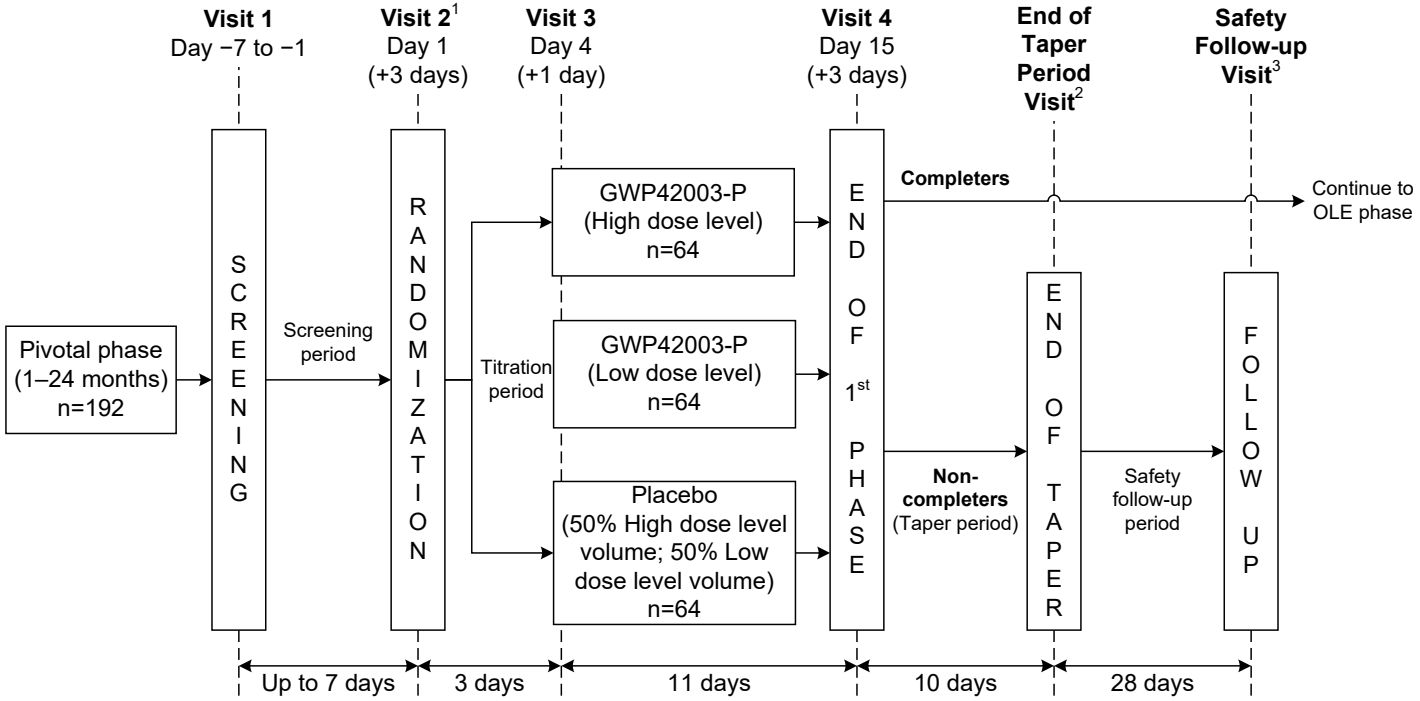


[1]All patients will titrate GWP42003-P in an inpatient setting. Daily safety checks will be made during the first week (Day 2-7) of IMP dosing (can be conducted by telephone).

[2]IMP is to be tapered over 10 days following the decision not to enter the OLE phase or withdrawal from the trial (unless continued dosing is not possible due to an AE).

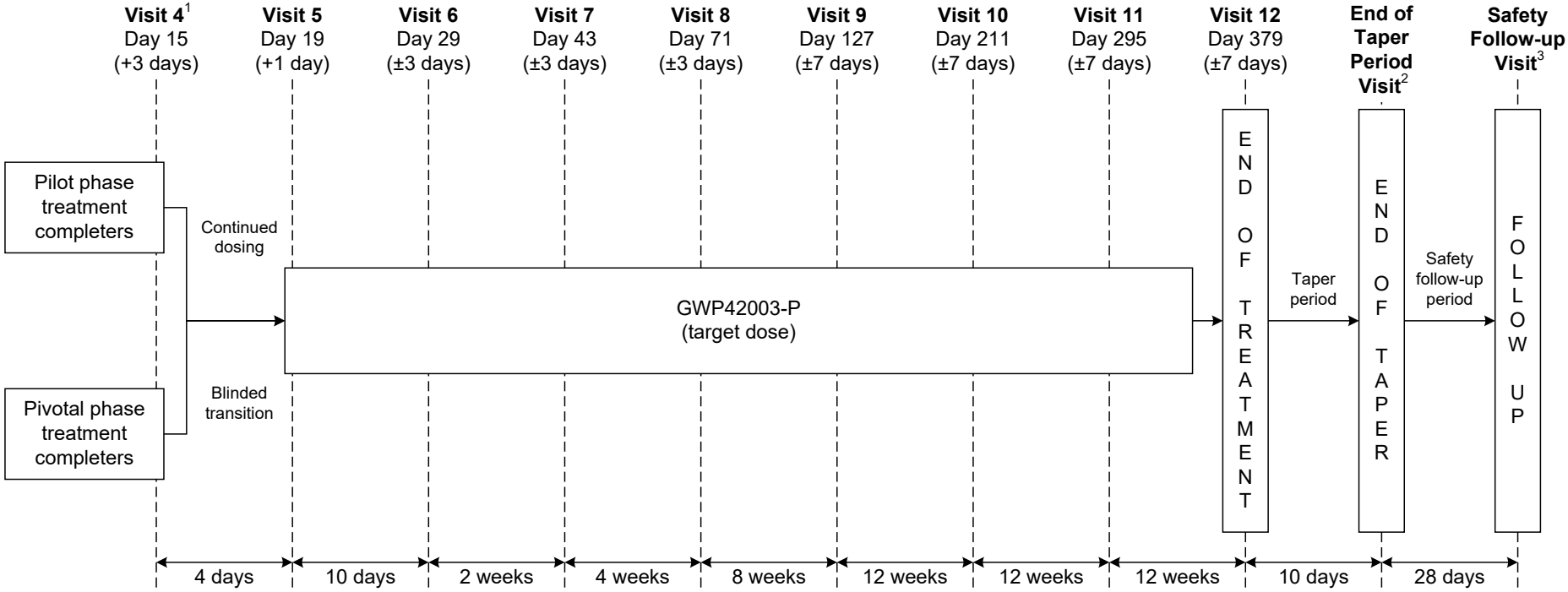
[3]For patients who withdraw, the safety follow-up visit is to occur 28 (+3) days after date of final dose (including tapered dose); weekly (±3 days) telephone calls must be made during the safety follow-up period.

Figure 1-2 Trial Design and Treatment Schematic: Pivotal Phase



[1]Following Visit 2, daily safety checks will be made during the first week (Day 2-7) of blinded IMP dosing (can be conducted by telephone).
[2]IMP is to be tapered over 10 days following the decision not to enter the OLE phase or withdrawal from the trial (unless continued dosing is not possible due to an AE).
[3]For patients who withdraw, the safety follow-up visit is to occur 28 (+3) days after date of final dose (including tapered dose); weekly (±3 days) telephone calls must be made during the safety follow-up period.

Figure 1-3 Trial Design and Treatment Schematic: Open-label Extension Phase



[1]Following Visit 4, daily safety checks will be made during the first week (Day 16-22) of OLE IMP dosing (can be conducted by telephone).
[2]IMP is to be tapered over 10 days following discontinuation of IMP, end of treatment, or withdrawal from the trial (unless continued dosing is not possible due to an AE).
[3]The safety follow-up visit is to occur 28 (+3) days after date of final dose (including tapered dose); weekly (±3 days) telephone calls must be made during the safety follow-up period.

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List of Abbreviations

6-OH-CBD	6-hydroxy-cannabidiol
7-COOH-CBD	7-carboxy-cannabidiol
7-OH-CBD	7-hydroxy-cannabidiol
ACTH	Adrenocorticotrophic hormone (corticotropin)
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine amino transaminase or alanine aminotransferase
AST	Aspartate amino transaminase or aspartate aminotransferase
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data safety monitoring committee
EAP	Expanded access program
EEG	Electroencephalography/electroencephalogram
ECG	12-lead electrocardiogram
EU	European Union
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GCP	Good clinical practice
GW	GW Research Ltd
IB	Investigator brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IS	Infantile spasms

ITT	Intention to treat
IU	International units
IVRS	Interactive voice response system
IWRS	Interactive web response system
LGS	Lennox–Gastaut syndrome
mTOR	Mammalian target of rapamycin
µV	Microvolt
OLE	Open-label extension
PGIC	Physician Global Impression of Change
PI	Principal investigator
PK	Pharmacokinetic
POPPK	Population pharmacokinetics
PRN	Packaging reference number
PVD	Pharmacovigilance department
QTcB	QT interval corrected for heart rate with Bazett's formula
RCT	Randomized controlled trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
TSC	Tuberous sclerosis complex
ULN	Upper limit of normal
US	United States
VFD	Visual field defects
VGB	Vigabatrin

Definition of Terms

Term	Definition
Day 1	The day a patient first receives investigational medicinal product in this trial.
End of trial	Last patient last visit or last contact, whichever occurs later.
Enrolled patient	Any patient whose parent(s)/legal representative has provided written informed consent to take part in the trial.
Hypsarrhythmia - eligibility	To be considered hypsarrhythmia, as defined for use in the study, the electroencephalography (EEG) background must be slowed and have multifocal spikes. In addition, it must be EITHER high voltage (above 300 µV) OR have electrodecrement/discontinuity.
Hypsarrhythmia - resolution	Resolution of hypsarrhythmia requires reduction of the EEG background below 300 µV AND elimination of any electrodecrements or epochs of discontinuity. Persistence of some background slowing and interictal epileptiform discharges may be seen and still be consistent with resolution of hypsarrhythmia.
International normalized ratio	A calculation made to standardize prothrombin time.
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.
Status epilepticus	Any seizure lasting 30 minutes or longer.

2 OBJECTIVES

2.1 Primary

2.1.1 Pilot Phase

To determine the maximum safe, tolerable dose and dosing regimen of GWP42003-P in infants with Infantile Spasms (IS), to be utilized in the pivotal phase and open-label extension (OLE).

To assess the number and proportion of patients considered treatment responders, defined as those free of spasms and resolution of hypsarrhythmia, at the end of the 2-week treatment period.

Note: Resolution of hypsarrhythmia requires reduction of the electroencephalography (EEG) background below 300 µV AND elimination of any electrodecrements or epochs of discontinuity. Persistence of some background slowing and interictal epileptiform discharges may be seen and still be consistent with resolution of hypsarrhythmia.

2.1.2 Pivotal Phase

To assess the number and proportion of patients considered treatment responders, defined as those free of spasms and resolution of hypsarrhythmia, at the end of the 2-week blinded treatment period versus placebo.

2.1.3 Open-label Extension

To assess the long term safety of GWP42003-P in infants with IS.

2.2 Secondary

2.2.1 All Phases

Key: To assess the number and proportion of patients who are free of clinical spasms, as observed on video-electroencephalography (video-EEG) at the end of the treatment period.

Key: To assess the number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period.

To assess changes in spasms and seizure subtypes by caregiver observation during the treatment period.

To determine time to cessation of spasms during the treatment period, as determined by caregiver diaries.

To explore the effect of GWP42003 P on quality of life.

2.2.2 Pivotal Phase Only

To determine assess the safety and tolerability of GWP42003-P.

To determine the population pharmacokinetics (POPPK) of CBD and its metabolites (6-hydroxy-cannabidiol [6-OH-CBD], 7-carboxy-cannabidiol [7-COOH-CBD] and 7-hydroxy-cannabidiol [7-OH-CBD]).

2.2.3 Open-label Extension Only

To assess the number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, after 3, 6, 9 and 12 months of treatment.

To assess the number and proportion of responders who relapse and the time to relapse.

To explore the effect of GWP42003-P on growth, adaptive behavior and development.

To determine the population pharmacokinetics (POPPK) of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD).

3 BACKGROUND AND RATIONALE

3.1 Disease

IS constitutes a distinct form of epilepsy of early infancy characterized by epileptic spasms with or without an interictal EEG pattern of hypsarrhythmia[1]. The epileptic spasms characteristic of IS usually consist of sudden, generally bilateral and symmetrical contractions of the muscles of the neck, trunk, and extremities which can be accompanied by a brief loss of consciousness. The spasms can be divided into 3 types depending on which muscle groups are predominantly affected (flexor, extensor, or mixed flexor–extensor). The most common are mixed flexor–extensor spasms and flexor spasms, which account for 50% and 42% of seizures, respectively[2]. Individual spasms are often brief and normally comprise an initial phasic component lasting 1–2 seconds followed by a less intense but more sustained tonic contraction[3]. They frequently occur in clusters, which can consist of as few as 2 or > 100 spasms, with 3–30 seconds between each individual spasm[3,4]. Less common spasms include extensor spasms of the legs and spine, simple head nodding, and (rarely) asymmetrical spasms[1,5]. The most characteristic EEG pattern of IS is hypsarrhythmia, which classically consists of random, high-voltage (> 200 μV), nonsynchronous spikes and slow-wave activity in all cortical areas that varies from moment to moment in duration and location[3]. However, in some cases of IS, hypsarrhythmia may be modified/atypical or even absent[1,6]. Where present, the hypsarrhythmic EEG pattern most frequently occurs during non-rapid eye movement sleep, and is greatly reduced or absent during clinical attacks of epileptic spasms (ictal electrodecrement) and during rapid eye movement sleep[1,3]. The association of clustered epileptic spasms and hypsarrhythmia, with or without atypical features, constitute a subset of IS known as West syndrome[1]. Other subsets of IS include IS without hypsarrhythmia, in which clustered epileptic spasms occur with no interictal hypsarrhythmic EEG pattern, and IS single-spasm variant (with or without hypsarrhythmia), in which no clustering of epileptic spasms occurs[1]. The incidence of IS ranges from 0.16 to 0.42 per 1,000 live births with a prevalence of 1.4–2.0 per 10,000 children aged 10 years or younger[7,8]. Boys are affected slightly more often than girls (60:40 ratio)[3].

Although epileptic spasms can arise *de novo* throughout childhood, the onset of IS almost always occurs within the first 2 years of life (90% of patients presenting within the first year), with peak onset between 3 and 7 months of age[1,3]. In some patients, onset of IS may be preceded by diagnosis of early infantile epileptic encephalopathy,

also known as Ohtahara syndrome, which presents within the first 3 months of life (often within the first 2 weeks) and is associated with a suppression-burst EEG pattern[9]. Approximately 75% of patients with Ohtahara syndrome progress to develop West syndrome within the first 6 months of age[10]. However, Ohtahara syndrome is very rare and precedes West syndrome in only 2.6% of cases[11]. The spasms characteristic of IS are refractory to treatment with most conventional antiepileptic drugs (AEDs) and although they almost always resolve with time (usually by 2 years of age), the long-term prognosis is poor[4]. More than half of children with IS develop other forms of severe epilepsy such as Lennox–Gastaut syndrome (LGS; an epileptic encephalopathy characterized by multiple seizure types and a slow spike-and-wave EEG pattern[12]), and the majority (80–90%) manifest some degree of mental retardation, often accompanied by motor- and behavioral problems[2].

IS is associated with a wide range of underlying etiologies and there is growing evidence that IS results from disturbances in key genetic pathways of brain development[13]. One of the most common specific underlying disorders is tuberous sclerosis complex (TSC), diagnosed in approximately 5–7% of children with IS[14]. TSC is characterized by the formation of nonmalignant tumors (tubers) in multiple organ systems that results from inadequate suppression of mammalian target of rapamycin (mTOR) signaling due to inactivating mutations in either of 2 tumor suppressor genes (*TSC1* and *TSC2*)[15]. Around 40% patients diagnosed with TSC present with IS[16] and it has been suggested that IS may occur when the mTOR pathway is perturbed in a specific neuronal population at a key neurodevelopmental stage[13]. Other brain malformations, such as lissencephaly, can also underlie IS. The 2 genes most commonly associated with classic lissencephaly (*PAFAH1B1* and *DCX*) are strongly associated with IS, which is prevalent in up to 80% of children with *PAFAH1B1* mutations or deletions[13]. Both *PAFAH1B1* and *DCX* are expressed in inhibitory interneurons; thus, lissencephaly-associated IS may be due to deficits in this neuronal population rather than the cortical malformation *per se*[13]. Collectively, congenital brain malformations (including TSC) are the underlying etiology in around 15% of IS cases[14]. Congenital chromosomal abnormalities (genomic imbalances) can also predispose to IS, the most common being Down syndrome (trisomy 21) which is the underlying etiology in approximately 5% of children with IS[14]. Inversely, only around 3% of Down syndrome patients present with IS[17]. With the exception of *PAFAH1B1* deletion in Miller–Dieker syndrome[18], the biological mechanism(s) of IS in syndromes of genomic imbalance are not known. As well as underlying congenital

disorders, IS is associated with a range of extrinsic etiologies. Pre-, peri- and postnatal brain injuries, including hypoxic–ischemic encephalopathy, stroke, periventricular leukomalacia/hemorrhage, and infection, cumulatively account for around one-quarter of cases of IS[14]. Other etiologies have been identified, such as specific endocrine or metabolic disorders, but these are individually uncommon. In approximately one-third of IS cases no evidence of a neurologic disorder is found[14]. Importantly, the underlying etiology is the most important factor affecting developmental outcome[19].

Adrenocorticotrophic hormone (ACTH), also known as corticotropin, is a long-established therapy for IS and was approved by the United States (US) Food and Drug Administration (FDA) in 2010 (as H.P. Acthar® Gel) as monotherapy in infants and children under 2 years of age. Cosyntropin (known outside the US as tetracosactide) is a synthetic alternative and consists of the first 24 amino acids occurring in ACTH. Currently, synthetic ACTH is not approved by the FDA for the treatment of IS, although orphan drug designation was granted for tetracosactide (as Synacthen® Depot) in 2012. An early randomized controlled trial (RCT) compared ACTH (20–30 international units [IU]/day) with the oral corticosteroid prednisone (2 mg/kg/day) in 24 patients with IS[20]. In the initial phase of the trial (prior to crossover), 5 of the 12 patients (42%) treated with ACTH were both spasm- and hypsarrhythmia-free after 2–6 weeks' treatment compared with 4 of the 12 patients (33%) treated with prednisone. Furthermore, of the 8 non-responders who received prednisone, 4 (50%) responded after crossover to ACTH. A later RCT compared a larger dose of ACTH (150 IU/m^2/day; n = 15) with prednisone (2 mg/kg/day; n = 14) and demonstrated that 87% of patients taking ACTH were both spasm- and hypsarrhythmia-free after 2 weeks' treatment compared with 29% of patients taking prednisone[21]. Of the 10 non-responders who received prednisone, 9 received ACTH and 8 (88%) responded. Tetracosactide (0.50–0.75 mg [40–60 IU] every 2 days; n = 25) was compared with prednisolone (the active form of prednisone; 40–60 mg/day; n = 30) for the treatment of IS in a later RCT which excluded patients with a diagnosis or high risk of TSC[22]. After 2 weeks' treatment, 76% of patients who received tetracosactide were spasm-free compared with 70% of patients who received prednisolone. In those for whom it was measured, resolution of hypsarrhythmia occurred in 89% of the responders to tetracosactide compared with 71% of the responders to prednisolone. A recent RCT comparing ACTH (40–60 IU every 2 days; n = 44) with prednisolone (40–60 mg/day; n = 48) for the treatment of hypsarrhythmia in West syndrome not due to TSC demonstrated a significantly greater improvement with prednisolone compared with ACTH after 2 weeks' treatment[23]. However, it was

recently concluded that the evidence is insufficient to recommend the use of prednisolone or other forms of corticosteroids as being as effective as ACTH for the short-term treatment of IS[24].

Several trials have compared low-dose ACTH with high-dose ACTH in the treatment of IS[25,26,27]. One RCT demonstrated that cessation of spasms and disappearance of hypsarrhythmia occurred in 14 of 24 patients (58%) treated with low-dose ACTH (20–30 IU/day for 2–6 weeks, followed by a 1-week taper period) compared with 13 of 26 patients (50%) treated with high-dose ACTH (150 IU/m^2/day for 3 weeks, followed by a 9-week taper period)[25]. Similarly, in a separate RCT in 30 children with West syndrome, a good initial response was observed in 60% of patients treated with low-dose ACTH (0.4 IU/kg/day for 2 weeks, increased to 1.0 IU/kg/day if no response was seen, followed by a 2-week taper period) compared with 53% of patients treated with high-dose ACTH (50 IU/day for 2 weeks, followed by a 2-week taper period)[26]. In a RCT comparing low-dose tetracosactide (0.005 mg/kg/day, equivalent to 8 IU/kg/day natural ACTH; n = 13) with high-dose tetracosactide (0.2 mg/kg/day, equivalent to 40 IU/kg/day natural ACTH; n = 13), 75% of low-dosed patients were both spasm- and hypsarrhythmia-free after 2 weeks' treatment compared with 85% of high-dosed patients[27]. Due to the similar efficacy between doses, it was recently recommended that low-dose ACTH should be considered as an alternative to high-dose ACTH for the treatment of IS[24]. Although ACTH is the preferred treatment for short-term control of IS[24,28], side effects are common and long-term exposure is associated with serious adverse events (SAEs), including fulminant infections secondary to immunosuppression, hypertension, glucosuria and metabolic abnormalities[3,29]. Furthermore, there is evidence that ACTH may contribute to the enlargement of cardiac rhabdomyoma in TSC patients[30,31]. 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%[5].

Vigabatrin (VGB) is a newer AED and was approved by the FDA in 2009 (as Sabril®) to treat IS in children aged 1 month to 2 years[3]. VGB is a structural analog of γ-aminobutyric acid (GABA; the major inhibitory neurotransmitter in the brain) that irreversibly inhibits GABA-transaminase and thereby increases brain levels of GABA[32]. The initial, prospective RCT compared VGB (100–150 mg/kg/day) with ACTH (10 IU/day) in 42 patients with IS[33]. After 20 days' treatment, 11 of 23 patients (48%) treated with VGB were spasm-free compared with 14 of 19 patients

(74%) treated with ACTH. Resolution of hypsarrhythmia occurred in 36% of the responders to VGB, compared with 78% of the responders to ACTH. Of note, VGB was more effective than ACTH as treatment for cerebral malformations and TSC. In a separate RCT, which compared VGB (150 mg/kg/day; n = 11) with the oral steroid hydrocortisone (15 mg/kg/day; n = 11) for the treatment of IS specifically due to TSC, 100% of patients taking VGB were spasm-free after 1 month's treatment compared with 45% taking hydrocortisone[34]. Furthermore, of the non-responders who received hydrocortisone, all became spasm-free on switching to VGB therapy. In contrast, a later placebo-controlled trial of VGB as first-line treatment of IS did not include any patients with TSC[35]. After 5 days' treatment, 7 of 20 patients (35%) who received VGB (50–150 mg/kg/day) were spasm-free compared with 2 of 20 patients (10%) who received placebo. Resolution of hypsarrhythmia occurred in 71% of the responders to VGB compared with 50% of the responders to placebo. Following a subsequent open-label phase, 15 patients (42% of those who entered the phase) were spasm-free with VGB monotherapy after 6 months' treatment, 14 of whom demonstrated resolution of hypsarrhythmia. Patients with a diagnosis or high risk of TSC were also excluded in a larger RCT comparing VGB (100–150 mg/kg/day; n = 52) with tetracosactide (0.50–0.75 mg [40–60 IU] every 2 days; n = 25) or high-dose prednisolone (40–60 mg/day; n = 30) for the treatment of IS[22]. After 2 weeks' treatment, 54% of patients who received VGB were spasm-free compared with 73% of patients who received either tetracosactide or prednisolone. In those for whom it was measured, resolution of hypsarrhythmia occurred in 71% of the responders to VGB compared with 81% of the responders to hormonal treatment.

A separate RCT of VGB (18–148 mg/kg/day; n = 142) included 25 patients diagnosed with TSC[36]. Of these patients, 52% were both spasm- and hypsarrhythmia-free after 2 weeks' treatment compared with 16% of patients with other etiologies. Furthermore, after 71 days' treatment, 92% of patients with TSC who began VGB therapy were spasm-free compared with 56% of patients with other etiologies, although whether these patients received additional treatments during this time is unclear. Following recruitment of more patients into the trial and use of intent-to-treat analysis, however, only 21% of patients with TSC could be classed as primary responders after 2 weeks' treatment compared with 9% of patients with other etiologies[37]. Although VGB is generally well tolerated, long-term treatment with VGB is associated with irreversible peripheral visual field defects (VFD), the risk of which increases with increasing dose and cumulative exposure[32]. The prevalence of VGB-associated VFD in children with refractory complex partial seizures is approximately 15%; however, a recent study found that 34% of patients who received

VGB treatment for IS subsequently developed VFD with TSC patients at higher risk (60% developing VFD)[38]. Furthermore, relapse rates of up to 63% have been reported in the 6 months following effective VGB treatment[39]. One RCT followed up patients at 4 years of age and demonstrated that for those with no identified etiology, psychomotor development scores were significantly lower in those allocated VGB compared with those allocated hormonal treatment[40]. In light of these clinical data, recent guidelines have concluded that VGB is possibly effective in the short-term control of IS, especially in the case of TSC, although treatment with ACTH/oral steroids may result in a better long-term neurodevelopmental outcome than treatment with VGB in children with IS due to unknown etiologies[24,28]. Other agents used in the treatment of IS include valproic acid, pyridoxine (vitamin B6), nitrazepam, zonisamide, topiramate, sulthiame, levetiracetam, lamotrigine, intravenous immunoglobulin, thyrotropin-releasing hormone, and ketogenic diet[5,24,41]. However, there is currently insufficient evidence to determine whether these therapies are effective.

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) Δ^9-tetrahydrocannabinol (THC). 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 comprises 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[42] and the orphan receptor GPR55[43]. Importantly, CBD lacks the psychoactivity associated with THC. Further to this, CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity[44]. Data concerning adverse events (AEs) of CBD in humans are limited; 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[44]. A recent abstract at the American Epilepsy Society 2015 Annual Meeting described the safety profile of GWP42003-P (up to 25 mg/kg/day) in 313 adults and children in a compassionate use program in the US[45]. The most common AEs (i.e., reported in ≥ 10% of patients) were somnolence (23%), diarrhea (23%), fatigue (17%), decreased appetite (17%), convulsions (17%), and vomiting (10%). Dropouts due to AEs were 4%.

3.3 Rationale

The approved pharmacological therapies currently available for IS often produce serious adverse effects, and a significant proportion of patients develop medically-intractable epilepsy[46]. Consequently, there is a clear need for new, safe and efficacious pharmaceutical treatments for infantile spasms. Given the limitations of current AEDs, it has been suggested that CBD should be tested for anticonvulsive efficacy in RCTs, especially in infantile epileptic syndromes[44]. Although there are no completed RCTs to date investigating the efficacy of CBD for the treatment of IS, a recent parent survey has reported that 92% of children with IS and/or LGS experienced a reduction in seizures while taking CBD-enriched cannabis, with 13% becoming seizure-free[47]. The CBD-enriched cannabis was well-tolerated and children often experienced improved sleep, increased alertness, and better mood. Moreover, in a recent open-label expanded access program (EAP) of GWP42003-P (up to 50 mg/kg/day) in 9 patients with a diagnosis of infantile or epileptic spasms (aged 2-16 years), 67% of patients had achieved a > 50% reduction in seizures after 2 weeks' treatment, with 33% becoming seizure-free[48]. Improvements in alertness, verbal capacity/communications, and cognitive availabilities were also reported. Side effects were reported in 90% of patients, yet were alleviated by AED dose adjustments without loss of seizure control. In the recently completed GWEP1332 trial in Dravet syndrome, the primary efficacy endpoint was a comparison between GWP42003-P and placebo measuring the median percentage change in the monthly frequency of convulsive seizures during the 14-week treatment period compared with the 4-week baseline observation period. In this study, preliminary data showed patients taking GWP42003-P achieved a median reduction in monthly convulsive seizures of 39% compared with a reduction on placebo of 13%, which was statistically significant (p=0.01). The trial randomized 120 patients into 2 arms, GWP42003-P 20 mg/kg/day (n=61) and placebo (n=59). GWP42003-P or placebo was added to current AED treatment regimens. On average, patients were taking approximately 3 AEDs, having previously tried and failed an average of more than 4

other AEDs. The average age of trial participants was 10 years and 30% of patients were less than 6 years of age.

3.3.1 Selection of Study Dose

Standard treatment regimens with currently approved IS therapies involve achieving high maintenance dose levels rapidly[49]. For example, VGB is initially given at a dose of 50 mg/kg/day and can be titrated by 25–50 mg/kg/day increments every 3 days to a maximum dose of 150 mg/kg/day[50]; both of these doses are approximately 3 times the recommended initial and maximal dose of VGB in adults. Moreover, treatment with ACTH, which is injected intramuscularly, begins at the maintenance dose immediately (150 IU/m^2/day recommended)[51]. Consequently, due to the urgency required in achieving efficacious doses to treat this population, rapid titration to a maximal safe and tolerable maintenance dose is proposed in this trial in infants with IS. The titration regimen proposed for use on this trial was discussed, and agreed, with consultants. Due to the rapid titration of the IMP, all patients in the pilot phase will be inpatient during the 4-day titration period. Following independent data safety monitoring committee (DSMC) review, adjustment of doses and dose regimens may occur during the trial, as well as plans for the dose titration during the pivotal phase.

The DSMCs of the GW studies in Dravet syndrome patients (GWEP1332, GWEP1424) and LGS patients (GWEP1414, GWEP1423) recommended a target of 20 mg/kg/day as a safe and tolerable dose during a 14-week treatment period. The lower age limit in these studies is 2 years of age. Three of the 4 studies are now complete; preliminary data from the GWEP1332 trial show GWP42003-P was generally well tolerated. The most common AEs (occurring in greater than 10% of GWP42003-P-treated patients [n=61]) were: somnolence, diarrhea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection and convulsion. Of those patients on GWP42003-P for whom an AE was reported, 84% of these AEs were mild or moderate.

Data on the safety of GWP42003-P is also emerging from the physician-initiated EAP being conducted in the US as well as other compassionate use worldwide. This program has been running since January 2014 and, at the time of writing, has now exposed 693 patients to CBD oral solution. The last data cut (September 2015) shows that the mean maximum exposure achieved in this patient population of refractory epilepsies was a daily dose of approximately 25 mg/kg CBD with a maximum dose of 51 mg/kg in 1 patient. Among the 350 patients in the safety data set, 47% were taking > 20 and ≤ 30 mg/kg/day CBD and 18% taking > 30 and ≤ 50 mg/kg/day CBD. In healthy adults administered doses of up to 1500 mg GWP42003-P twice daily for

6 consecutive days with a single morning dose on Day 7, treatment emergent adverse events (TEAEs) reported in 95.8% of all subjects were of mild or moderate severity. The twice daily dose of 1500 mg equates to 40 mg/kg/day in a 75 kg adult. In addition, 75.0% of subjects administered single doses of up to 6000 mg CBD (equivalent to 80 mg/kg in a 75 kg adult) reported TEAEs, all of mild or moderate severity. When 1500 mg GWP42003-P was administered to subjects alongside a high fat breakfast, a 4.85-fold increase in the maximum measured plasma concentration and a 4.20-fold increase in exposure (measured as area under the concentration-time curve calculated to the last observable concentration at time t) for CBD were observed. The extent of the food effect was also reflected in CBD metabolite exposure. The exposure increase coincided with a higher incidence, but no increased severity, of TEAEs in the fed compared to the fasted group[52].

In view of the higher metabolic rate of children aged up to 2 years, it has been recommended by consultants that dosing should be approximately 30–40% higher than that used for patients 2 years and older. To reflect this, and in light of the emerging RCT and EAP data detailed above, a target dose of 40 mg/kg/day is proposed in this trial in infants with IS.

3.4 Clinical Hypothesis

The primary clinical hypothesis is that there will be a difference between GWP42003-P and placebo during the pivotal phase in their effect on IS, as measured by elimination of clinical spasms and hypsarrhythmia.

This trial will also evaluate the effect of GWP42003-P compared with placebo on time to cessation of clinical spasms and changes in other seizure types. The safety and tolerability of GWP42003-P will also be assessed during the pilot phase, pivotal phase (compared with placebo) and OLE phase of the trial.

4 EXPERIMENTAL PLAN

4.1 Trial Design

This is a multisite trial to evaluate the efficacy and safety of GWP42003-P in patients with IS who have failed to become spasm- and hypsarrhythmia-free following treatment with 1 or more approved IS therapies (e.g., steroids and/or VGB). All approved therapies must be discussed with the patient's parent(s)/legal representative before the patient is considered for the trial (discussions regarding treatment options must be documented). The trial will comprise of a pilot safety phase, followed by a pivotal phase, with a 1 year open-label extension available to all patients who complete either phase. The pilot phase will be open-label with 2 sequential cohorts of 5 patients, the first cohort aged between 6 and 24 months and the second cohort aged between 1 and 24 months, who will receive GWP42003-P for 2 weeks. The pivotal phase will comprise 192 patients, aged 1–24 months, who will undergo a 2-week, randomized, placebo-controlled, double-blind treatment period.

An independent DSMC will be used throughout the study; they will consider safety of the patients, and will confirm doses and dose regimens to be investigated in the pivotal phase, as well as the plans for dose titration. If required, following DSMC review, adjustment of doses and dose regimens will also take place following the first cohort of 5 patients in the pilot phase.

Patients will enter the pilot and pivotal phases at the respective screening visits (Visit 1, Day −7 to −1) for assessment of eligibility, which includes a prolonged video-EEG. Patients who satisfy all eligibility criteria will then be administered GWP42003-P (pilot phase) or randomized to GWP42003-P (1 of 2 dose levels) or placebo at a 1:1:1 ratio (pivotal phase) (Visit 2, Day 1 [+3 days]). The High Dose Level will be as recommended by the DSMC; the Low Dose Level will be defined as 50% of the High Dose Level. Patients in the placebo group will be split into 2 equivalent cohorts: half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes. Following baseline assessments, patients will titrate the IMP in 10 mg/kg/day increments to the target dose level (or equivalent volume of placebo in the pivotal phase) and will continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the 2-week treatment phase. Patients in the pilot phase will remain in the clinic as inpatients during the 4-day dose titration period. If deemed safe by the DSMC then it is planned for those in the pivotal phase to titrate in an outpatient setting. Further clinic-based assessments will take place after 3 days' dosing (Visit 3, Day 4 [+1 day]). All patients in the pilot and pivotal phases will return to the clinic after 2 weeks' dosing (Visit 4, Day 15 [+3 days]) or earlier if they withdraw prematurely. All patients who complete

treatment will then have the opportunity to receive GWP42003-P during the subsequent OLE phase. The OLE phase will last for a maximum of 1 year.

Patients who enter the OLE phase will remain on the same dose (pilot phase) or will transition to their target dose of GWP42003-P over 4 days in a blinded manner (pivotal phase). Patients may continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the OLE phase. GWP42003-P may be discontinued at the discretion of the investigator (Section 9.1.2). During the OLE phase, clinic visits will take place on Day 19 (Visit 5 [+1 day]), Day 29 (Visit 6 [±3 days]), Day 43 (Visit 7 [±3 days]), Day 71 (Visit 8 [±3 days]), Day 127 (Visit 9 [±7 days]), Day 211 (Visit 10 [±7 days]), and on Day 295 (Visit 11 [±7 days]). Patients will return to the site for an end of OLE treatment visit on Day 379 (Visit 12 [±7 days]) or earlier if they withdraw prematurely from the OLE phase. Following end of treatment, withdrawal, or discontinuation of IMP, all patients will taper the IMP over 10 days followed by safety follow-up. Patient diaries will be completed each day by the caregiver during the trial.

A series of schematic diagrams (Figure 1-1, Figure 1-2, and Figure 1-3), presented at the end of Section 1, depict the overall trial design. More detailed information on treatment and trial procedures is provided in Section 8 and Section 9, respectively.

4.1.1 Primary Endpoint

4.1.1.1 Pilot Phase

To assess the safety as determined by AEs, clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs and physical examinations during the treatment period.

The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG.

4.1.1.2 Pivotal Phase

The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, at the end of the 2-week blinded treatment period, as determined by video-EEG.

4.1.1.3 Open-label Extension

To assess the long term safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period.

4.1.2 Secondary Endpoint(s)

4.1.2.1 All Phases

The following endpoints will be analyzed separately for each phase:

Key: The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period.

Key: The number and proportion of patients who have resolution of hypsarrhythmia as, observed on video-EEG at the end of the treatment period.

Changes in spasms and seizure subtypes by caregiver observation during the treatment period.

Time to cessation of spasms during the treatment period, as determined by caregiver diaries.

Caregiver Global Impression of Change (CGIC).

Physician Global Impression of Change (PGIC).

4.1.2.2 Pivotal Phase Only

Safety and tolerability as determined by AEs, clinical laboratory tests, ECG, physical examinations and vital signs.

Measurement, where possible, of plasma concentrations of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model.

4.1.2.3 Open-label Extension Only

The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, as determined by video-EEG after 3, 6, 9 and 12 months of treatment.

The number and proportion of responders with relapse of spasms, and the time to relapse, as determined by caregiver diaries.

Changes from baseline in length (height), body weight, and head circumference.

Change from baseline in Vineland Adaptive Behavior Scales, Second Edition (Vineland II) score.

Measurement, where possible, of plasma concentrations of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD and 7-OH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model.

4.2 Number of Sites

Approximately 50 sites are expected to participate in this trial.

Additional sites may be used in order to supplement recruitment.

4.3 Number of Patients

The pilot phase is not powered and comprises 10 patients.

The pivotal phase will comprise 192 patients. Patients will be randomized to receive 1 of 2 dose levels of GWP42003-P (High Dose Level or Low Dose Level), or matching placebo on a 1:1:1 basis (64 per treatment group). Patients in the placebo group will be further split into 2 cohorts (32 patients receiving High Dose Level dosing volumes and 32 patients receiving Low Dose Level dosing volumes), but it is assumed that these 2 cohorts can be pooled for the analyses of efficacy. Assuming a 20% screen failure rate, it is expected that approximately 245 patients will need to be screened to achieve this target. Recruitment will be competitive between participating sites.

The sample size calculation is explained fully in Section 13.1.

5 INVESTIGATIONAL MEDICINAL PRODUCT

Please refer to the separate pharmacy manual for more detailed information on the IMP.

5.1 GWP42003-P Oral Solution

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

Table 5.1-1 Formulation of GWP42003-P Oral Solution

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

5.2 Placebo Oral Solution

Placebo to match GWP42003-P oral solution is presented as a clear, colorless to yellow solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring (Table 5.2-1).

Table 5.2-1 Formulation of Placebo Oral Solution

Material	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Refined 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 in accordance with good manufacturing practice guidelines. The IMP will be presented in 100 mL amber glass bottles with child-resistant, tamper-evident screw caps, and packed in cartons. Sufficient IMP will be dispensed at Visits 2, 4, 6–11, and for the taper period, if necessary, considering the weight of the patient and the length of time until the next visit. 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 interactive voice response system (IVRS)/interactive web response system (IWRS). Label text will include the following information, as a minimum:

- Sponsor's name and address.
- Product identification (e.g., "GWP42003-P or Placebo").
- Concentration/potency.
- Study code.
- Batch number.
- Expiry date.
- Storage conditions.
- Instruction: "For clinical trial use only".
- Instruction: "Keep out of the sight and reach of children".
- Any other information required by local regulatory authorities.

Directions for use will be provided separately to the patient's caregiver.

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 trial dispensing period at each site. These records must contain at least the minimum and maximum daily temperatures and must be made available to the appropriate GW personnel for review throughout the trial. Temperature during transit of IMP to the site must be checked on receipt and compliance/non-compliance to the minimum and maximum recorded.

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

Caregivers will be provided with instructions regarding home storage requirements for the IMP.

5.3.3 Supply and Return of Investigational Medicinal Product

IMP will be transported by G-Pharm or delegated contractors to approved country depots and clinical sites in compliance with good distribution practice guidelines. All IMP will be shipped with a product release certificate that includes a physical description of the product for confirmation of identity on receipt.

Once a site has been activated via the IVRS/IWRS at trial initiation, IMP will be shipped to the identified responsible person, such as the pharmacist, at the investigator's site, who will check the amount received (against the IVRS/IWRS Shipment Request) and condition of the drug (i.e., integrity, physical appearance, temperature during transit). Details of the IMP received will be recorded in the IMP accountability record (see Section 5.3.4). The site will acknowledge the IMP receipt via the IVRS/IWRS 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/IWRS. 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 must 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 2, 4, 6–11, and for the taper period, if necessary. Patients will be asked to return all IMP (used and unused) at each relevant visit (Visits 4, 6–12, and the end of taper period visit, if applicable). The site will check the returned IMP against the usage recorded in the paper diary. Any discrepancies

will be discussed with the patient's 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 the relevant drug distribution depot. At the end of the trial, 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.

5.3.5 Post-trial Provision

All patients who complete the pilot and pivotal phase of the trial will have the opportunity to receive GWP42003-P during the subsequent OLE phase. The OLE phase will last for a maximum of 1 year.

A summary of the results of this trial will be made available on http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu/ (as applicable), as required by US and European Union (EU) Law.

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.

6.1 Inclusion Criteria

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

6.1.1 **Pilot phase:** Patient is male or female aged 6–24 months (inclusive) in the first cohort or aged 1-24 months (inclusive) in the second cohort, at the time of consent.

OR

Pivotal phase: Patient is male or female aged 1–24 months (inclusive) at the time of consent.

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

6.1.3 Patient and their caregiver are willing and able (in the investigator's opinion) to comply with all trial requirements.

6.1.4 Patient is diagnosed with IS (i.e., clinical spasms and hypsarrhythmia are observed on video-EEG at screening).

Note: To be considered hypsarrhythmia, as defined for use in the study, the EEG background must be slowed and have multifocal spikes. In addition, it must be EITHER high voltage (above 300 µV) OR have electrodecrement/discontinuity.

6.1.5 Patient has failed to respond adequately (i.e., clinical spasms and/or hypsarrhythmia are still evident on video-EEG at screening) following treatment with 1 or more approved IS therapies (i.e., therapy for the treatment of IS approved in Europe or the US [e.g., steroids and/or VGB]) for the treatment of IS.

6.1.6 Patient's parent(s)/legal representative is willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law.

6.1.7 Patient's parent(s)/legal representative is willing to allow the patient's primary care practitioner (if they have one) and consultant (if they have

one) to be notified of participation in the trial, if the primary care practitioner/consultant is different to the investigator.

6.1.8 All non-pharmacological interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for 2 weeks prior to screening.

6.2 Exclusion Criteria

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

6.2.1 Patient is currently taking or has taken clobazam or any oral mTOR inhibitor within the 2 weeks prior to the screening visit.

6.2.2 Patient has a QT interval, corrected for heart rate with Bazett's formula (QTcB), of > 460 msec on ECG.

Note: If the QTcB is above > 460 msec, the investigator should repeat the ECG 3 times and contact the GW medical monitor, prior to screen failure or entry into the pilot/pivotal phase.

6.2.3 Patient's caregiver is currently giving or has given recreational or medicinal cannabis, or synthetic cannabinoid-based medications, within the 1 month prior to the screening visit, as determined by investigator interview with patient's caregiver.

6.2.4 Patient's caregiver is unwilling to abstain from giving the patient (including the patient's mother abstaining themselves, if breastfeeding) recreational or medicinal cannabis, or synthetic cannabinoid-based medications (other than the study IMP) during the trial, as determined by investigator interview with patient's caregiver.

6.2.5 Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP(s), such as sesame oil.

6.2.6 Patient has significantly impaired hepatic function at the screening visit, defined as any of the following:

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

ii) Serum ALT or AST > 3 × ULN **and** (total bilirubin [TBL] > 2 × ULN **or** international normalized ratio [INR] > 1.5).

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; patients must not be allocated any IMP prior to this. ***Note:*** *If transaminases are elevated, the Investigator may choose to confirm the transaminase elevations by repeat testing during the screening period; results should be discussed with the GW medical monitor prior to screen failure or entry into the pilot or pivotal phase.*

6.2.7 Patient has received an IMP as part of a clinical trial within a minimum of 5 half-lives prior to the screening visit.

6.2.8 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 trial, may influence the result of the trial, or may affect the patient's ability to take part in the trial.

6.2.9 Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient or confound assessment of efficacy if they took part in the trial.

6.2.10 Patient has been previously included in the pilot or pivotal phase of this trial.

6.2.11 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.

7 PATIENT ENROLLMENT

Before patients may be entered into the trial, GW requires a copy of the relevant site's institutional review board (IRB) or independent ethics committee (IEC) written approval of the protocol, informed consent form (ICF), and other patient information material. Patients will be considered enrolled in the trial from the time written informed consent is provided. The patient's parent(s)/legal representative must personally sign and date the ICF prior to any procedures being performed (refer to Section 9.2.1 and Section 15.2).

7.1 Treatment Assignment

At the start of Visit 1, patients will be allocated a unique patient number using an IVRS/IWRS. After confirmation of eligibility at Visit 2, patients will be assigned GWP42003-P (pilot phase) or randomly allocated to GWP42003-P or matching placebo (pivotal phase) using the IVRS/IWRS. G-Pharm or delegated contractors will provide all IMP in a packed and labeled state and the IVRS/IWRS 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

For the pivotal phase, 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 by GW or delegated contractor and not divulged to any other person involved in the trial until the database has been locked and unblinding authorized by the relevant GW personnel. For access to blinded treatment assignment, see Section 8.5.

8 TREATMENT PROCEDURES

8.1 Investigational Medicinal Product Dosage, Administration, and Schedule

The use of placebo in the current trial is deemed necessary to determine the efficacy and safety of the current intervention, since one or more approved interventions have already been tried and have failed to alleviate the patient's symptoms. For details regarding IMP formulations, see Section 5.

8.1.1 Dose Administration

The IMP will be administered orally by the patient's caregiver twice each day (morning and evening), maintaining consistency with regard to feeds/meals and other concomitant medications, using the syringe(s) provided. Dosing via a gastric/nasogastric tube (as required) may be considered following approval by the GW medical monitor; details of dose administration via the gastric/nasogastric tube will be provided in a separate pharmacy manual. The IMP may be taken with other concomitant medications, as directed by the investigator. In the event that the IMP is poorly tolerated, dosing may be changed to 3 times daily (while keeping the equivalent total daily dose) following approval by the GW medical monitor. The recommended dosing intervals are:

- 12-hourly (8-hourly minimum) for twice daily dosing.
- 6-hourly (minimum) for 3 times daily dosing.

8.1.2 Dose Escalation and Dose Adjustments

All patients will be weighed during each clinic visit where IMP is dispensed (i.e., no physical exam performed at Visit 3 [Day 4] or Visit 5 [Day 19]). The volumes of IMP solution to be taken each day during the titration periods, and for the remainder of each phase of the trial, will be calculated and provided to the patient's caregiver. If an unacceptable AE develops at any time during the titration periods, dosing should initially be amended or suspended, at the investigator's discretion, until the event has resolved or is well tolerated. During the maintenance periods, patients should continue on a stable dosing regimen at the target dose. However, if the patient is not able to tolerate the target dose, the investigator may consider temporarily or permanently reducing the dose or dosage for the remainder of the maintenance period.

Eligible patients will be assigned GWP42003-P (pilot phase) or randomly allocated to GWP42003-P or matching placebo (pivotal phase) and will titrate the IMP over 4 days according to the titration regimen, an example titration regimen up to

40 mg/kg/day over 4 days is shown in Table 8.1.2-1. Patients in the pilot phase will remain in the clinic as inpatients during the 4-day titration period. If the DSMC confirms it is safe then patients in the pivotal phase will titrate the IMP as outpatients. For the pivotal phase there will be 2 dose levels; the High Dose Level will be as recommended by the DSMC, the Low Dose Level will be defined as 50% of the High Dose Level. Patients in the placebo group will be split into 2 equivalent cohorts: half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes. In both phases, daily safety checks will be made during the first week of IMP dosing.

Table 8.1.2-1 Example Titration Regimen: Pilot and Pivotal Phase

Day	IMP Dosage[1]	Total Daily IMP Dose[2]
1	5 mg/kg (am/pm)	10 mg/kg
2	10 mg/kg (am/pm)	20 mg/kg
3	15 mg/kg (am/pm)	30 mg/kg
4 onwards	20 mg/kg (am/pm)	40 mg/kg

[1]Volumes of IMP to be taken each day will be calculated using the patient's weight and the required dose.
[2]Patients may taper to and remain on a lower dose if unable to tolerate the target dose.

Patients from the pivotal phase who enter the OLE will taper their blinded IMP while simultaneously titrating their OLE IMP (GWP42003-P) over 4 days according to the titration regimen, an example titration regimen up to 40 mg/kg/day over 4 days is shown in Table 8.1.2-2. No further titration will be required for patients in the pilot phase; they will remain on the same GWP42003-P dose going into the OLE phase. Daily safety checks will be made during the first week of OLE IMP dosing. GWP42003-P may be discontinued at any time during the OLE phase, at the discretion of the investigator (see Section 9.1.2).

Table 8.1.2-2 Example Titration Regimen: Transition to the OLE Phase (Pivotal Phase Only)

Day	Blinded IMP Dosage[1]	OLE IMP Dosage[1]	Total Daily IMP Dose (Patients Randomized to Placebo)[2]	Total Daily IMP Dose (Patients Randomized to GWP42003-P)[2]
15	20 mg/kg (am/pm)	0	0	40 mg/kg
16	15 mg/kg (am/pm)	5 mg/kg (am/pm)	10 mg/kg	40 mg/kg
17	10 mg/kg (am/pm)	10 mg/kg (am/pm)	20 mg/kg	40 mg/kg
18	5 mg/kg (am/pm)	15 mg/kg (am/pm)	30 mg/kg	40 mg/kg
19 onwards	0	20 mg/kg (am/pm)	40 mg/kg	40 mg/kg

[1]Volumes of IMP to be taken each day will be calculated using the patient's weight and the required dose.
[2]Patients may taper to and remain on a lower dose if unable to tolerate the target dose.

Following the end of treatment, all patients will commence a taper period (tapering 10% per day for 10 days). Patients who withdraw early should also begin the taper period following the withdrawal visit (unless continued dosing is not possible due to an AE). Patients who discontinue IMP during the OLE phase should also begin the taper period following the investigator's decision to discontinue. The IVRS/IWRS will generate the patient's daily IMP dosing volumes for the 10-day taper period.

8.2 Concomitant Therapy

All non-pharmacological interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for at least 2 weeks prior to screening and must remain stable throughout the pilot and pivotal phases of the trial. During the screening period, patients should continue to take their current IS therapy at a stable dose. After starting treatment, and during the pilot and pivotal phase, every effort should be made to keep the patient's current IS therapy stable; current therapy may be tapered or stopped, in response to AEs, at the discretion of the investigator. Increases in the dose of existing concomitant AEDs or commencement of new AEDs are not allowed during the pilot or pivotal phases, and should the investigator deem that an increase in concomitant AED or new AED be needed, the subject may need to be withdrawn from the trial (see Section 10). During the OLE, in response to AEs or if there are symptoms of toxicity due to a suspected drug-drug interaction, the investigator may decrease the dose of GWP42003-P or other concomitant AEDs following discussion with the GW medical monitor. Any request for an increase in concomitant AED dose, or addition of a new AED in the OLE must be discussed with the GW medical monitor prior to implementing, and will be based on confirmation of benefit over risk of continued treatment with or discontinuation of GWP42003-P. It should be noted that there is the potential for drug-drug interactions with strong inhibitors/inducers of CYP3A4 or CYP2C19; if alternatives cannot be found these should be co-administered with caution and monitoring as clinically indicated. Monitoring of concomitant AEDs may be requested by the investigator as clinically indicated. Any AED monitoring should be documented in the CRF. Further information on drug interactions can be found in the Investigator Brochure (IB)[53].

As the risk of hepatotoxicity with valproate is high in the trial population, investigators should pay particular attention to liver enzyme levels in patients who are taking valproate concomitantly.

The use of rescue medication is allowed if clinically indicated. Any medication, other than the IMP, taken during the trial must be recorded on the case report form (CRF).

8.3 Prohibited Therapy During Trial Period

The following medications are prohibited both prior to and during the trial, as stated below. However, any patients taking these medications after starting treatment on the trial should not be withdrawn from the trial unless there are safety concerns. If applicable, the possible effects of these medications on the trial endpoints will be considered during the assessment of the evaluable period (see Section 13.6.1).

- Any new non-pharmacological interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) or changes in regimen during the pilot and pivotal phases of the trial (and within the 2 weeks prior to the screening visit).
- Clobazam and oral mTOR inhibitors during the pilot and pivotal phase of the trial (and within the 2 weeks prior to the screening visit).
- Recreational or medicinal cannabis, or synthetic cannabinoid-based medications (and within the 1 month prior to the screening visit).
- Any other IMP taken as part of a clinical trial (and within a minimum of 5 half-lives prior to the screening visit).

Furthermore, any increases to existing AEDs or commencement of new AEDs during the pilot or pivotal phase may result in the patient being withdrawn from the trial.

8.4 Compliance in Investigational Medicinal Product Administration

The patient's caregiver will record IMP intake on each treatment day in the paper diary. Caregivers should return all IMP (used and unused) at each of Visits 4, 6–12, and the end of taper period visit, if applicable. The diary-reported dosing information will be checked and any discrepancies discussed with the patient's 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 (Pivotal Phase Only)

The identity of IMP assigned to patients in the pivotal phase will be held by the IVRS/IWRS. The principal investigator (PI) at each site, or his/her designee, is responsible for ensuring that information on how to access the IVRS/IWRS 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 trial 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 1 working day of the event and must document the time, date and reason(s) for unblinding in the patient's medical notes and on the CRF.

9 TRIAL PROCEDURES

A list of the required trial procedures is provided in the subsections that follow; refer also to the schedule of assessments (APPENDIX 1). Assessments or tests that are not done and examinations that are not conducted must be reported as such on the CRF.

The location of the source data for the following procedures will be documented, per site, in a signed source data verification plan; for further details see Section 16.2.

9.1 Trial Procedures by Visit

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

9.1.1 Pilot and Pivotal Phase

9.1.1.1 Visit 1 (Day −7 to −1): Screening

Following collection of parent(s)/legal representative informed consent (Section 9.2.1), patients will be assigned a unique patient number using an IVRS/IWRS (Section 9.2.2). The following will then be collected/assessed within a screening period which must be no more than 7 days in duration, during which time patients must continue to take their current IS therapy at a stable dose:

- Eligibility criteria (Section 6).
- Patient demographics (Section 9.2.3).
- Full medical history (Section 9.2.4).
- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.

  - Urinalysis.

    To minimize the volume of blood required, serum biochemistry and hematology results from samples analyzed up to 3 days prior to Visit 1 may be used.

- AEs (Section 12).
- Caregiver paper diary issue and training (Section 9.2.13). The caregiver will be required to record all AEs, concomitant AEDs and rescue medications, seizures, and spasms from the time of consent.

Patients can be re-screened only once, in exceptional cases, at the discretion of the investigator and GW medical monitor.

9.1.1.2 Visit 2 (Day 1 [+3 Days])

This visit will occur up to 7 (+3) days after Visit 1 (screening). Patients who satisfy all eligibility criteria (Section 6) during the screening period will be assigned GWP42003-P (pilot phase) or randomly allocated to GWP42003-P or matching placebo (pivotal phase) using the IVRS/IWRS (Section 9.2.2). Eligible patients must begin treatment within 7 days of their video-EEG screening assessment. The following will be collected/assessed prior to the patient receiving IMP:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- CGIC memory aid (Section 9.2.12.1).
- PGIC memory aid (Section 9.2.12.2).
- Vineland-II (Section 9.2.12.3).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

Patients will receive sufficient IMP for 2 weeks of dosing. Patients in the pilot phase will remain in the clinic as inpatients during the 4-day titration period. For all patients, the first dose of IMP will be taken in the clinic on the morning of Day 1 with

an ECG assessment between 3 and 5 hours postdose (Section 9.2.8). For patients involved in the pivotal phase of the trial, a PK blood sample will be taken, provided the risk/benefit outcome is favorable in the investigator's opinion (Section 9.2.11). If a PK blood sample is collected, the investigator must note the sampling time and the dosing times of IMP and of any concomitant AEDs taken that day and the previous day. Patients will titrate to their target dose of GWP42003-P (or equivalent volume of placebo in the pivotal phase; Section 8.1.2) and will continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the 2-week treatment phase. During this time, the patient's current IS therapy may be continued or tapered, at the discretion of the investigator. All non-pharmacological interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must remain stable during the pilot and pivotal phases of the trial. Following Visit 2, daily safety checks will be made during the first week of IMP dosing.

9.1.1.3 Daily Safety Checks (Day 2 to Day 7 [Inclusive])

Safety checks will be made daily (including weekends, where possible) from Day 2 to Day 7 (inclusive). Safety checks can be conducted by telephone (where applicable they will be incorporated into scheduled visits, e.g., Visit 3 [Day 4]). During each safety check, caregivers will be asked about the following, along with confirmation that the relevant details have been recorded in the caregiver diary:

- Spasm/seizure information.
- Changes in concomitant AEDs.
- Usage of rescue medication.
- AEs.

Confirmation that the safety check has taken place will be recorded in the CRF.

9.1.1.4 Visit 3 (Day 4 [+1 Day])

This visit will occur 3 (+1) days after Visit 2. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Vital signs (Section 9.2.7).
- ECG (prior to the day's first dose of IMP; Section 9.2.8).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.

  - Hematology.
  - Urinalysis.
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All patients will take their IMP in the clinic with an additional ECG assessment between 3 and 5 hours postdose (Section 9.2.8). Patients in the pilot phase will then be discharged from the clinic.

9.1.1.5 Visit 4 (Day 15 [+3 Days]): End of Pilot or Pivotal Phase/Withdrawal

This visit will occur 14 (+3) days after Visit 2 or earlier if the patient withdraws from the pilot or pivotal phase of the trial. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (prior to the day's first dose of IMP; Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- **Pivotal phase only**: PK blood sampling (prior to the day's first dose of IMP, provided the risk/benefit outcome is favorable in the investigator's opinion; Section 9.2.11).
- CGIC (Section 9.2.12.1).

- PGIC (Section 9.2.12.2).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

Patients will take their IMP in the clinic with an additional ECG assessment between 3 and 5 hours postdose (Section 9.2.8). For patients involved in the pivotal phase of the trial, a further PK blood sample will be taken, provided the risk/benefit outcome is favorable in the investigator's opinion (Section 9.2.11). If PK blood samples are collected, the investigator must note the sampling times and the dosing times of the IMP and of any concomitant AEDs taken that day and the previous day. All IMP will be collected and compliance reviewed.

Patients who have successfully completed the pilot or pivotal phase will have the opportunity to receive GWP42003-P during the subsequent OLE phase at Visit 4. Patients from the pilot phase who enter the OLE phase will remain at the target dose which was reached during the pilot phase. Patients from the pivotal phase who enter the OLE phase will receive sufficient blinded IMP for tapering along with sufficient OLE IMP (GWP42003-P) for simultaneous titration and subsequent dosing for 2 weeks. All patients in the pivotal phase who enter the OLE phase will transition to the target dose of GWP42003-P (in a blinded manner; Section 8.1.2) and may continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the OLE phase. Following Visit 4, daily safety checks will be made during the first week of GWP42003-P dosing.

For patients who withdraw early, the IVRS/IWRS will be contacted to confirm withdrawal from the trial. Patients who opt not to enter the OLE phase or who withdraw from the pilot or pivotal phase early should begin the taper period, if possible (Section 9.1.3), and sufficient IMP will be dispensed.

9.1.2 Open-label Extension Phase

The OLE phase will last for a maximum of 1 year.

During the OLE phase, GWP42003-P may be discontinued by the investigator if:

- The patient has become spasm-free, as determined by clinical assessment by the investigator.

  OR

- The patient is not perceived to be receiving any benefit from GWP42003-P, as determined by clinical assessment by the investigator.

For any patients who have their IMP discontinued by the investigator, the IVRS/IWRS will be contacted to confirm IMP discontinuation. All patients should commence the taper period, if possible (Section 9.1.3), and sufficient IMP will be dispensed if required.

If the investigator decides to discontinue GWP42003-P following resolution of spasms, the parent(s)/legal representative will be encouraged to allow the patient to remain in the trial to complete the remaining assessments. The investigator must contact the GW medical monitor to discuss the discontinuation process, including the subsequent assessments to be conducted.

If the investigator decides to discontinue GWP42003-P because the patient is not perceived to be receiving any benefit from GWP42003-P, the patient will **not** be asked to complete the remaining trial assessments and will be withdrawn from the trial as per Section 10 (withdrawal to be registered in the IVRS/IWRS).

Patients who have **not** demonstrated complete resolution of spasms but are perceived to be receiving some benefit from GWP42003-P may remain in the OLE and receive other concomitant medications during the OLE phase. The option of withdrawal from the trial will be discussed with the caregiver at each visit.

In cases of relapse, patients may restart IMP only if ALL of the following criteria are fulfilled:

- The patient had their IMP discontinued by the investigator due to resolution of spasms.
- The patient has remained in the trial to complete the remaining assessments.
- The decision to restart IMP is discussed with the GW medical monitor.

The IVRS/IWRS will then be contacted to confirm restart of IMP. Patients restarting IMP will re-titrate to their target dose of GWP42003-P and may continue at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the OLE phase. The next scheduled clinic visit will then be performed according to the Schedule of Assessments (APPENDIX 1).

9.1.2.1 Daily Safety Checks (Day 16 to Day 22 [Inclusive])

Safety checks will be made daily (including weekends, where possible) from Day 16 to Day 22 (inclusive). Safety checks can be conducted by telephone (where applicable they will be incorporated into scheduled visits, e.g.. Visit 5 [Day 19]). During each safety check, caregivers will be asked about the following, along with confirmation that the relevant details have been recorded in the caregiver diary:

- Spasm/seizure information.
- Changes in concomitant AEDs.
- Usage of rescue medication.
- AEs.

Confirmation that the safety check has taken place will be recorded in the CRF.

9.1.2.2 Visit 5 (Day 19 [+1 Day])

This visit will occur 18 (+1) days after Visit 2. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All patients will take their IMP in the clinic. For patients transitioning from the pivotal phase to the OLE a PK blood sample will be taken, provided the risk/benefit outcome is favorable in the investigator's opinion (Section 9.2.11). If a PK blood sample is collected, the investigator must note the sampling time and the dosing times of IMP and of any concomitant AEDs taken that day.

9.1.2.3 Visit 6 (Day 29 [±3 Days])

This visit will occur 28 (±3) days after Visit 2. Collection of Visit 6 assessments earlier than Day 29 (i.e., on Day 26, 27, or 28) must only occur if there have been no witnessed spasms over the preceding 48 hours (minimum). The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- CGIC (Section 9.2.12.1).
- PGIC (Section 9.2.12.2).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All IMP will be collected and compliance reviewed. Patients will then receive sufficient IMP for 2 weeks' dosing.

9.1.2.4 Visit 7 (Day 43 [±3 Days])

This visit will occur 42 (±3) days after Visit 2. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- CGIC (Section 9.2.12.1).
- PGIC (Section 9.2.12.2).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All IMP will be collected and compliance reviewed. Patients will then receive sufficient IMP for 4 weeks' dosing.

9.1.2.5 Visit 8 (Day 71 [±3 Days])

This visit will occur 70 (±3) days after Visit 2. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).

- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- CGIC (Section 9.2.12.1).
- PGIC (Section 9.2.12.2).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All IMP will be collected and compliance reviewed. Patients will then receive sufficient IMP for 8 weeks of dosing.

9.1.2.6 Visit 9 (Day 127 [±7 Days])

This visit will occur 126 (±7) days after Visit 2. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.

  - Urinalysis.
- CGIC (Section 9.2.12.1).
- PGIC (Section 9.2.12.2).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All IMP will be collected and compliance reviewed. Patients will then receive sufficient IMP for 12 weeks of dosing.

9.1.2.7 Visit 10 (Day 211 [±7 Days])

This visit will occur 210 (±7) days after Visit 2. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- CGIC (Section 9.2.12.1).
- PGIC (Section 9.2.12.2).
- Vineland-II (Section 9.2.12.3).
- Caregiver diary review (Section 9.2.13) for:

  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All IMP will be collected and compliance reviewed. Patients will then receive sufficient IMP for 12 weeks of dosing.

9.1.2.8 Visit 11 (Day 295 [±7 Days])

This visit will occur 294 (±7) days after Visit 2. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- CGIC (Section 9.2.12.1).
- PGIC (Section 9.2.12.2).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.

- AEs (Section 12).

All IMP will be collected and compliance reviewed. Patients will then receive sufficient IMP for 12 weeks of dosing.

9.1.2.9 Visit 12 (Day 379 [±7 Days]): End of OLE Treatment/Withdrawal

This visit will occur 378 (±7) days after Visit 2 or earlier if the patient withdraws from the OLE phase of the trial. The following will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Video-EEG (Section 9.2.9).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- CGIC (Section 9.2.12.1).
- PGIC (Section 9.2.12.2).
- Vineland-II (Section 9.2.12.3).
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All IMP will be collected and compliance reviewed. For patients who withdraw early, the IVRS/IWRS will be contacted to confirm withdrawal from the trial. All

patients should commence the taper period, if possible (Section 9.1.3), and sufficient IMP will be dispensed.

9.1.3 Taper Period (10 Days)

Following end of treatment, all patients will taper the IMP 10% per day over 10 days. Patients who withdraw early should also begin the taper period following the appropriate withdrawal visit (unless continued dosing is not possible due to an AE). Patients who discontinue IMP during the OLE phase should also begin the taper period following the investigator's decision to discontinue. The IVRS/IWRS will generate the patient's daily IMP dosing volumes for the 10-day taper period, during which time paper diary information will continue to be recorded.

9.1.3.1 End of Taper Period Visit (+3 Days)

This visit will occur 10 (+3) days after the end of treatment/withdrawal visit (if IMP is tapered). 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 will be collected/assessed:

- Concomitant medication review (Section 9.2.5).
- Physical examination (Section 9.2.6).
- Vital signs (Section 9.2.7).
- ECG (Section 9.2.8).
- Clinical laboratory samples (blood and urine [if possible]; Section 9.2.10) for:
  - Serum biochemistry.
  - Hematology.
  - Urinalysis.
- Caregiver diary review (Section 9.2.13) for:
  - Spasm/seizure information.
  - IMP usage.
  - Changes in concomitant AEDs.
  - Usage of rescue medication.
  - AEs.
- AEs (Section 12).

All IMP will be collected and compliance reviewed.

9.1.4 Safety Follow-up Period (4 Weeks)

Following end of dosing (including taper period), all patients will commence a 4-week safety follow-up period to ascertain the status of AEs continuing after cessation of IMP or any new AEs commencing after discontinuation. Patients who discontinue IMP during the OLE phase should begin the safety follow-up period following the end of the taper period. During the safety follow-up period, paper diary information will continue to be recorded.

9.1.4.1 Weekly Safety Telephone Calls (±3 Days)

Safety telephone calls will be made weekly (±3 days) from the date of final dosing until the safety follow-up visit, or until the next scheduled clinic visit for patients remaining in the trial following discontinuation of IMP by the investigator. During each safety telephone call, caregivers will be asked for information on the following:

- Spasm/seizure information.
- Changes in concomitant AEDs.
- Usage of rescue medication.
- AEs.

9.1.4.2 Safety Follow-up Visit (+3 Days)

This visit will occur 28 (+3) days after the end of taper period visit or date of final dosing, and can be conducted over the telephone. The following will be collected:

- Spasm/seizure information.
- Changes in concomitant AEDs.
- Usage of rescue medication.
- AEs.

The caregiver should return the completed caregiver diary following the safety follow-up visit.

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

9.2 Trial Procedure Listing

9.2.1 Informed Consent

The parent(s)/legal representative of the patient must personally sign and date the IRB/IEC-approved ICF before any trial-specific procedures are performed or any patient-related data is recorded for the trial. GW requires a physician to be present for consent and to sign the consent form also. The original signed ICF should be retained and a copy provided to the patient's parent(s)/legal representative. The patient's 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 Interactive Voice Response System/Interactive Web Response System

The IVRS/IWRS will be used to assign patients to treatment groups, manage IMP supply, and to provide treatment allocation information in the event of patient unblinding (pivotal phase only).

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

- Obtain a patient number (Visit 1).
- Assign GWP42003-P (pilot phase) or randomize a patient (pivotal phase) (Visit 2).
- Obtain dispensing information (Visits 2, 4, 6–11, and for the taper period, if necessary).
- Provide IMP discontinuation/IMP restart/completion/taper/premature termination information.

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

9.2.3 Demographics

The following information will be obtained for each patient (as allowed per local regulations):

- Date of birth.
- Sex.
- Race.
- Date of onset of IS.

- Gestational age at birth.
- Birthweight.

9.2.4 Medical History

The following medical history will be obtained for each patient:

- Prior and current seizures/spasms.
- Prior AEDs/steroids.
- Prior IS treatment details (all approved therapies must be discussed with the patient's parent(s)/legal representative before the patient is considered for the trial; discussions regarding treatment options must be documented).
- Presence of abnormal EEG patterns that are consistent with IS, including hypsarrhythmia.
- Neuroimaging history.
- Unequivocally normal development at onset of IS.
- Etiologic classification of IS:
  - idiopathic (genetic).
  - symptomatic (structural / metabolic).
  - cryptogenic (unknown).

In addition, any relevant, significant medical history will be obtained, and is defined as any condition or disease that:

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

9.2.5 Concomitant Medication

Details of all current and prior medication, including AEDs/steroids, will be obtained. Any changes in concomitant medication during the trial must be recorded on the CRF at trial visits. Refer to Section 8.2 and Section 8.3 for further information.

9.2.6 Physical Examination

Physical examinations will include length (height), body weight, and head circumference measurements.

9.2.7 Vital Signs

Vital signs measurements (systolic and diastolic blood pressure, pulse rate, body temperature and respiratory rate), taken in a supine position at rest for 5 minutes, will be completed alongside the physical examination. The methods/procedures employed for vital signs measurements must be consistent throughout the trial, where possible. Any deviation in methods used must be reported to the study monitor.

9.2.8 12-lead Electrocardiogram

ECG recordings will be performed after 5 minutes in a supine position. A physician must review the ECG immediately (annotated, signed and dated) and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately on the CRF. Additional ECG measurements can be taken at any time during the trial, if clinically indicated.

9.2.9 Video-electroencephalography

Prolonged video-EEG monitoring (minimum 8 hours in duration, extendable to 24 hours) will be performed to document clinical spasms and EEG patterns consistent with IS. At least 1 full sleep-wake cycle must be observed during each video-EEG assessment. The investigator must review the video-EEG during screening to confirm eligibility, during which time patients must continue to take their current IS therapy at a stable dose. If no clinical spasms and hypsarrhythmia are observed during the initial 8-hour recording at screening, every effort should be taken to extend monitoring up to a maximum of 24 hours to confirm eligibility, if the site has the capability. Eligible patients must begin treatment within 7 days of their video-EEG screening assessment. In addition to being read at the trial site, all video-EEG recordings will be centrally read retrospectively (see APPENDIX 2 for further details regarding the central reader). The assessment by the central reader for the video-EEG assessment screening will be considered final. Any video-EEG findings considered to represent an AE must be documented on the CRF.

9.2.10 Clinical Laboratory Sampling

Due to the nature of the disease being studied, and the need for prompt treatment of patients, it will be necessary to use local laboratories for the clinical laboratory aspects of the trial.

Urine samples (provided urine can be obtained) will be analyzed at the trial site by use of a dipstick with any relevant findings being sent for further urinalysis at a local laboratory (urinalysis, microscopy, culture and sensitivity, as applicable).

Clinical laboratory sample parameters required from the local laboratories are detailed in Table 9.2.10-1.

Table 9.2.10-1 Biochemistry, Hematology, Urinalysis

Biochemistry (Serum)[1]	Hematology (Whole Blood)[1]	Urinalysis (Urine)[1]
Essential Parameters[2]		
Alanine aminotransferase	Hematocrit	Glucose
Alkaline phosphatase	Hemoglobin	Nitrites
Aspartate aminotransferase	Mean corpuscular hemoglobin	pH
Creatinine	Platelets	Protein
Gamma-glutamyl transferase	Red blood cell count	White blood cells
Potassium	White blood cell count with automated differential	
Sodium		
Triglycerides		
Total bilirubin		
Urea (blood urea nitrogen)		
Additional Parameters[3]		
Albumin	Mean cell volume	
Calcium		
Creatinine clearance		
Prothrombin time (plasma)		
Total protein		

[1]Refer to the laboratory manual.
[2]Analyzed as a priority.
[3]Analyzed in addition to the essential parameters, wherever possible.

To minimize the volume of blood required, serum biochemistry and hematology results from samples analyzed up to 3 days prior to Visit 1 may be used for screening purposes. The samples must be analyzed at the same local laboratory that is being used for the clinical laboratory aspects of the trial.

All laboratory results will be reviewed and the reports signed and dated by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. All laboratory results must be documented on the CRF. For reporting and follow-up of potential cases of drug-induced liver injury, see Section 12.7.

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. The maximum amount of blood taken in any 24-hour period, including PK blood samples, will be 3 mL/kg of body weight and will not exceed a

total of 50 mL within any 8-week period[54]. A separate laboratory manual will provide guidance on the priority of blood samples to be taken in relation to the maximum permitted blood volumes. The caregiver must be advised that it may not be safe for the patient to undertake further blood tests within 1 month of any trial-related blood draws and to inform the investigator if the patient suffered any blood loss during the 1 month period leading up to a planned blood draw.

9.2.11 Pharmacokinetic Blood Sampling

Blood samples may be taken from patients involved in the pivotal phase, and progressing to the OLE from the pivotal phase, for the determination of CBD and its metabolites (6-OH-CBD, 7-COOH-CBD, and 7-OH-CBD) to provide an understanding of the PK of CBD. In addition, an exploration of the relationship between plasma levels of CBD with safety and efficacy may be performed. In this trial, a sparse sampling approach will be employed to minimize the impact on patients in terms of potential discomfort and to keep the blood volume taken as low as practicable. Suggested sampling times are as follows:

- Day 1: between 1 and 12 hours after the day's first dose of IMP.
- Day 15: prior to the day's first dose of IMP and around 2 hours postdose.
- Day 19: between 4 and 12 hours after the day's first dose of IMP (only for patients in the pivotal phase who transition to the OLE).

These sampling times should be considered optimal; however, since the data will be fitted to a population PK model developed from other clinical trials, the investigator should use their discretion regarding sampling time to minimize distress/discomfort to the patient. IMP dosing time and blood sampling time should be recorded accurately. The dosing time of any concomitant AEDs and timing of feeds/meals should also be recorded.

Analysis of all PK samples will be conducted at a central bioanalytical laboratory. Blood sample volume requirements and processing procedures will also be detailed in a separate laboratory manual; the maximum amount of blood taken in a single draw for PK analyses will be approximately 1 mL. The maximum number of PK blood draws will be determined by the criteria stated in Section 9.2.10. The caregiver must be advised that it may not be safe for the patient to undertake further blood tests within 1 month of any trial-related blood draws and to inform the investigator if the patient suffered any blood loss during the 1-month period leading up to a planned blood draw.

9.2.12 Questionnaires Completed at Scheduled Visits

With the exception of the PGIC, all questionnaires should be completed by the main caregiver. In situations where this is not possible, this information must be captured over the telephone, ideally on the day of the visit or otherwise within 3 days. The same person should complete the questionnaires in order to maintain consistency. Copies of questionnaires can be found in APPENDIX 3.

9.2.12.1 Caregiver Global Impression of Change

The CGIC comprises a single question to be rated on a 7-point scale:

> *"Since the patient started treatment, please assess the status of the patient's overall condition (comparing their condition now to their condition before treatment) using the scale below."*

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

The caregiver will be asked to record the status of the patient's overall condition at Visit 2 (Day 1, i.e., prior to commencement of IMP) as a memory aid for subsequent visits.

9.2.12.2 Physician Global Impression of Change

The PGIC comprises the same, single question as the CGIC (Section 9.2.12.1) to be rated on the same, 7-point scale by the investigator. The investigator will be asked to record the status of the patient's overall condition at Visit 2 (Day 1, i.e., prior to commencement of IMP) as a memory aid for subsequent visits.

9.2.12.3 Vineland Adaptive Behavior Scales, Second Edition

The Vineland-II[55] is an individually administered instrument for assessing adaptive behaviors and is widely used in pediatric clinical trials due to its applicability to children of all ages and developmental levels. The Vineland-II will be completed by the caregiver using a rating scale. Due to the possibility of cognitive/developmental delay, caregivers should start the assessment at the lowest age, irrespective of the patient's actual age.

9.2.13 Caregiver Diary

Caregivers will be instructed how to complete a paper diary and will be asked to record the following patient information daily throughout the trial. Caregivers must bring the paper diary to each clinic visit for review by the investigator.

9.2.13.1 Spasm/Seizure Information

The caregiver must record whether the patient had any episodes of spasms and/or other subtypes of epileptic seizure on a daily basis.

9.2.13.2 Usage of Investigational Medicinal Product

Information on IMP intake on each treatment day must be recorded by the caregiver. IMP administration compliance checks will be conducted according to Section 8.4.

9.2.13.3 Changes in Concomitant Medication

Any changes in the patient's concomitant medication (including AEDs/steroids) or IS therapies must be recorded by the caregiver. Any changes in concomitant medication during the trial must be recorded on the CRF at trial visits.

9.2.13.4 Usage of Rescue Medication

Details of each administration of rescue medication must be recorded by the caregiver (drug name and dose level). The use of any rescue medication during the trial must be recorded on the CRF at trial visits.

9.2.13.5 Adverse Events

Details of any AEs must be recorded by the caregiver. Refer to Section 12 for definitions, procedures and further information on AE reporting.

10 WITHDRAWAL

In accordance with the Declaration of Helsinki[56], the International Conference on Harmonisation (ICH) Tripartite Guideline for GCP Topic E6(R1)[57], the FDA regulations relating to GCP and clinical trials[58,59,60], the EU Clinical Trials Directive[61], the EU GCP Directive[62] and/or other applicable regulations, a patient has the right to withdraw from the trial at any time and for any reason, with no obligation to provide a reason, and without prejudice to his or her future medical care by the physician or at the institution.

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

- Any issue with eligibility criteria that is considered to potentially compromise the safety of the patient.
- Administrative decision by the investigator, GW, or a regulatory authority.
- Protocol deviation that is considered to compromise potentially the safety of the patient.
- Withdrawal of the patient's parent(s)/legal representative consent.
- QTcB of 500 msec or greater on ECG, or a shift from baseline QTcB of 60 msec or greater.

  Note: Prior to withdrawal for the QTcB shifts noted above, the investigator should repeat the ECG three times and contact the GW medical monitor. ***If the above QTcB criteria are confirmed, the patient must be withdrawn from the trial.***
- Lost to follow-up.
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).

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 trial for any of the following:

- Any other issue with eligibility criteria (non-safety related).
- Any requirement to increase the dose of concomitant AED(s) or to add in new AED(s) during the pilot or pivotal phase.
- If a patient is not showing evidence of benefit during the OLE phase (the option of withdrawing from the trial will be discussed with the caregiver at each visit).
- Patient/caregiver 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 trial.

Should a patient's parent(s)/legal representative request or decide to withdraw the patient from the trial, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients who are withdrawn should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator's clinical judgment. All assessments required at Visit 4 (end of pilot or pivotal phase/withdrawal) or Visit 12 (end of OLE treatment/withdrawal), as appropriate, should be conducted if possible. If the tapered dose is administered, caregivers should continue to complete the paper diary and return for the end of taper period visit, if possible. For patients who begin to taper IMP but are subsequently withdrawn, the end of taper period visit assessments (including ECG and clinical laboratory sampling) should be conducted, if possible; this visit should occur on the final day of dosing or as soon as possible after this date. Patients who are withdrawn due to an AE should be followed up according to Section 12.6. All information should be reported on the applicable CRF pages (refer to Section 9.2). Wherever possible, a safety follow-up visit should take place 28 days after the last dose of IMP (refer to Section 9.1.4.2). If the parent(s)/legal representative of withdrawing patients decline to give a reason for withdrawal of consent, the investigator must respect these 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 IRB/IEC within 3 days.

12 ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event

For the purposes of this trial 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, which may or may not be considered to be related to the IMP. Any event that is the result of a trial 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-trial 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 trial 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 medicine is developed (e.g., change in dose, population, monitoring need, consent forms). This is particularly true for events that threaten life or function. Such SAEs will be reported promptly to regulatory authorities, applicable IRBs/IECs 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 trial 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 Pharmacovigilance Department (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 site files and faxed to the GW PVD (see APPENDIX 2). 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.

Any other problem discovered after the safety follow-up visit which is deemed to be an unexpected safety issue and is likely to have an impact on patients who have taken part in the trial must be treated as an SAE and reported to the GW PVD. Such post-trial SAEs do not need to be recorded on the patient's CRF if editing rights to the CRF have been removed due to final trial data lock. GW PVD may request safety

follow-up information after the final trial visit in order to investigate a potential safety issue.

Contact details for the GW PVD are provided at the front of the site files for all trial sites, and upon the GW SAE report form.

12.4 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.

12.5 Reporting Procedures for All Adverse Events

All AEs (including SAEs) occurring during the trial 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-treatment follow-up visit, 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., fever and malaise due to a respiratory tract infection.

B) Adverse Event Start Date and Stop Date

The start and stop dates of the event must be provided. All AEs require these fields to be completed in full. Partial dates or missing dates are not normally acceptable and significant effort must be undertaken to obtain any unknown information. If a precise date is not known an estimated date should be provided instead. When a complete date cannot be given, 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 12.4 above.

F) Action Taken with Trial 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.
- Trial medication interrupted.
- Trial medication stopped.

12.6 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 after the safety follow-up visit (i.e., after the trial).

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's parent(s)/legal representative may also voluntarily withdraw the patient 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 patient, GW may contact the investigator for additional follow-up information.

12.7 Potential Cases of Drug-Induced Liver Injury

All investigational sites are required to submit to the GW PVD the laboratory results for any patient after starting treatment that meets 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 2 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 fax number for SAE reporting (see APPENDIX 2) 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 to 48 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, alkaline phosphatase and gamma-glutamyl transferase levels, detailed history and physical examination. Patients should be followed 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.

12.8 Notification of Safety Information to Investigators, Regulatory Authorities, and IRBs/IECs

In accordance with the EU Clinical Trials Directive[61], relevant parts of the FDA Code of Federal Regulations[63], and any national regulations, GW will inform investigators, regulatory authorities and relevant IRBs/IECs of all relevant safety information. This

will include the reporting of relevant SAEs and all suspected unexpected serious adverse reactions (SUSARs).

This information will be provided through 3 sources:

1. IB[53]: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the trial. The IB is updated annually.
2. Development core safety information: this document forms the safety section of the IB[53], or is updated as an addendum to the IB[53]. 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 IRBs/IECs which have approved the trial and investigators. As required, the investigator should notify their regional IRBs/IECs of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

In the US, investigators are normally required to report promptly to their IRBs all unanticipated problems involving risks to patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance[58] the following clarification is provided in determining what constitutes an unanticipated problem:

In general, an AE observed during the conduct of a trial 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 trial (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the trial cannot be understood.

The FDA guidance[63] states that, accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, any investigators participating in a multisite trial 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 IRBs/IECs 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 trial 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

13.1 Sample Size, Power, and Significance Levels

The pilot phase is not powered and comprises 10 patients. Both cohorts in the pilot phase will comprise 5 patients, the first cohort aged between 6 and 24 months and the second cohort aged between 1 and 24 months, who will all receive GWP42003-P.

The pivotal phase will comprise 192 patients, aged 1–24 months, who will be randomized to receive 1 of 2 dose levels of GWP42003-P (High Dose Level or Low Dose Level) or matching placebo on a 1:1:1 basis (64 per treatment group). Patients in the placebo group will be further split into 2 cohorts (32 patients receiving Low Dose Level dosing volumes and 32 patients receiving High Dose Level dosing volumes), but it is assumed that these 2 cohorts can be pooled for the analyses of efficacy.

Assuming a 20% screen failure rate, it is expected that approximately 245 patients will need to be screened to achieve this target (202 patients included in the pilot and pivotal phases in total).

[redacted]

This is based on a 2-sided 5% significance level, based on a Fisher's exact test.

13.2 Interim Analysis

No formal interim analysis will be conducted. A review of safety and efficacy data will be conducted after the end of the pilot phase, and blinded data review(s) may be conducted to support IMP clinical development. However, for the pivotal phase, it is anticipated that the database will be locked and treatment unblinded, prior to the completion of the OLE phase.

13.3 Analysis Sets

Statistical analysis will be performed according to a statistical analysis plan (SAP) . Details of any deviations from the SAP will be documented in the clinical study report.

There will be 3 analysis sets for this trial:

Pilot or Pivotal Phase Safety

All patients exposed to at least 1 dose of IMP during the pilot or pivotal phase will be used for summaries of the safety endpoints during both phases.

OLE Phase Safety

All patients exposed to at least 1 dose of IMP during the OLE phase will be used for summaries of the safety endpoints during the OLE phase.

Intention to Treat (ITT)

All patients in the pivotal phase who are randomized and receive IMP will be included and analyzed according to their randomized treatment group. The ITT analysis set is the primary analysis set for all efficacy endpoints.

13.3.1 Protocol Deviations

Protocol deviations will be listed and reasons for exclusion from the analysis sets 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. Categorical variables will be summarized showing the number and percentage of patients falling into each category.

13.5 Accountability and Background Characteristics

13.5.1 Enrollment and Disposition

All patients (screened, treated, entering the OLE, prematurely terminating IMP) will be accounted for in the enrollment and disposition summary tables.

13.5.2 Baseline and Demographic Characteristics

Baseline characteristics, including demographics, medical history, and concomitant medications will be summarized by treatment group and overall as appropriate.

13.6 Endpoints and Statistical Methods

For the pivotal phase, only data from this phase will be used for analysis of the primary and secondary endpoints; data from the pilot phase may be used in subsequent sensitivity analyses. Data from all phases will be used for a number of

descriptive summaries for certain endpoints. All safety endpoints for the phases of the trial will be summarized as detailed in Section 13.6.5 below.

For the pivotal phase of the trial, statistical hypothesis testing will be performed on the secondary endpoints as appropriate.

Since there is a single primary analysis endpoint for the pivotal phase, 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 3 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. To control the type I error, a step-up Hochberg's procedure will be used for the primary endpoint of the pivotal phase. If both of the observed p-values from the Low Dose Level and High Dose Level 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.

13.6.1 Evaluable Period

The start of the evaluable period (Day 1) is defined as the first day the patient took IMP in the trial or the day of randomization/initial assignment of IMP if this date is unknown. The end of the evaluable period for the pilot or pivotal phase is defined as the last day on which the study IMP was taken during the pilot or pivotal phase. The end of the evaluable period for the OLE phase is defined as the last day on which a study-related assessment was undertaken during the OLE phase as opposed to the last day on which the study IMP was taken. This is to allow data collected after discontinuation of the study IMP due to resolution of spasms to form part of the evaluable period.

13.6.2 Primary Endpoint(s)

13.6.2.1 Pilot Phase

The following endpoints will be analyzed descriptively only:

- Safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period (see Section 13.6.5)

- The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG.

13.6.2.2 Pivotal Phase

The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the initial 2-week treatment phase, will be analyzed by treatment group using a chi-square test. However, if the number of patients in either of the treatment groups is less than 5 then a Fisher's exact test will be performed instead.

Patients who withdraw from the trial or patients who do not have a video EEG performed at the end of the 2-week treatment period will be included in the primary, and key secondary analyses as not being free of spasms and not having resolution of hypsarrhythmia.

Details of sensitivity analyses due to missing data and handling of patients potentially receiving rescue medication will be fully detailed in the SAP prior to unblinding.

13.6.2.3 Open-label Extension

To assess the long term safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period (see Section 13.6.5).

13.6.3 Secondary Endpoint(s)

13.6.3.1 Pilot Phase

For the pilot phase, the following secondary endpoints will be analyzed descriptively only:

- The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period.
- The number and proportion of patients who have resolution of hypsarrhythmia, as observed on video-EEG at the end of the treatment period.
- Changes in spasms and seizure subtypes by caregiver observation during the treatment period.
- Time to cessation of spasms during the treatment period, as determined by caregiver diaries.
- CGIC.
- PGIC.

Safety data is detailed in Section 13.6.5 below.

13.6.3.2 Pivotal Phase

For the pivotal phase, the number and proportion of patients who are free of clinical spasms, and the proportion of patients with resolution of hypsarrhythmia at the end of the initial 2-week treatment phase, will be analyzed by treatment group using a chi-square test. However, if the number of patients in either of the treatment groups is less than 5 then a Fisher's exact test will be performed instead.

Changes in spasms and seizure subtypes during the initial 2-week treatment phase will be analyzed descriptively only.

The time to cessation of spasms during the initial 2-week treatment phase will be calculated as the number of days from first dose of IMP to the first day in which no spasms were recorded in the patient diary. Patients who do not have cessation of spasms by Visit 4 will be censored on the day of Visit 4. The time to cessation of spasms will be analyzed descriptively as well as with a log-rank test.

The CGIC and PGIC will be analyzed by treatment group using ordinal logistic regression, including treatment group as a factor and sex as a covariate in the model.

Safety and tolerability as determined by AEs, clinical laboratory tests, 12-lead electrocardiogram (ECG), physical examinations and vital signs.

Measurement where possible of plasma concentrations of CBD and its major metabolites (7-OH-CBD, 6-OH-CBD, and 7-COOH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model.

13.6.3.3 Open-label Extension

For the OLE phase, the following secondary endpoints will be analyzed descriptively only:

- The number and proportion of patients who are free of clinical spasms, as observed on video-EEG at the end of the treatment period.
- The number and proportion of patients who have resolution of hypsarrhythmia as, observed on video-EEG at the end of the treatment period.
- Changes in spasms and seizure subtypes by caregiver observation during the treatment period.
- Time to cessation of spasms during the treatment period, as determined by caregiver diaries.

- The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, as determined by video-EEG after 3, 6, 9 and 12 months of treatment.
- The number and proportion of responders with relapse of spasms, and the time to relapse, as determined by caregiver diaries.
- Changes from baseline in length (height), body weight, and head circumference.
- CGIC.
- PGIC.
- Change from baseline in Vineland-II score.

Safety data is detailed in Section 13.6.5 below.

Measurement, where possible, of plasma concentrations of CBD and its major metabolites (7-OH-CBD, 6-OH-CBD, and 7-COOH-CBD) will be investigated using a sparse sampling approach, with the aim to define a POPPK model.

13.6.4 Pharmacokinetics

Where possible, POPPK analyses for CBD and its metabolites (6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD) will be conducted using results from analysis of sparse samples collected during the pivotal phase of the trial.

13.6.5 Safety

13.6.5.1 Treatment Compliance and Extent of Treatment Exposure

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

13.6.5.2 Adverse Events

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

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

Descriptive presentations of TEAEs will be given by preferred term and system organ class for the safety analysis set for each phase of the trial separately. The number of patients reporting at least 1 TEAE will be provided.

The following summaries will be produced:

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

13.6.5.3 Clinical Laboratory Data

For each phase of the trial, 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.

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

For each phase of the trial, vital signs, ECG, and physical examination data will be summarized at screening, baseline, and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs from baseline to end of treatment will also be summarized.

14 DATA SAFETY MONITORING COMMITTEE

An independent DSMC will be used in this trial.

The DSMC will comprise a minimum of 4 members and will include an independent pediatric epileptologist and an independent pediatrician.

The DSMC will review safety data from the initial 2-week treatment phase of patients in the pilot phase, (once patients in cohort 1 and cohort 2 have completed Day 15). Following these reviews the DSMC will recommend whether it is safe to continue, modify, or stop the trial.

The DSMC will also review blinded safety data from the initial 2-week treatment phase of patients in the pivotal phase and will recommend whether to continue, modify, or stop the trial.

Ad hoc meetings may also take place based on new and/or unexpected safety signals, to enable DSMC members to discuss and provide recommendations.

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

15 REGULATORY AND ETHICAL OBLIGATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this trial 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(R1)[57], the EU Clinical Trials Directive[61], the EU GCP Directive[62] and the clinical trial regulations adopting European Commission Directives into national legislation[64,65,66,67,68].

15.2 Informed Consent

An initial generic ICF will be prepared by GW and provided to the investigator, who will tailor this for their site by adding the site's contact details and by using headed paper. The GW clinical manager will communicate updates to the template by letter. The written informed consent document 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 from the patient's parent(s)/legal representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial and before any trial-specific procedures are performed or any patient-related data are recorded for the trial. All approved IS therapies must be discussed with the patient's parent(s)/legal representative. It will be clearly explained to the patient's parent(s)/legal representative that initiation with the next recognized IS therapy may be delayed by participating in this trial. The patient's parent(s)/legal representative must have ample time to consider the information provided before giving written consent. More specific definitions of 'ample time' may be in force if required by IRBs/IECs or local regulations.

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

15.3 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, master ICF, other parent(s)/legal representative information material, any proposed advertising material, and any further documentation requested must be submitted to the IRB/IEC for written approval. GW

must receive a copy of the written approval of the appropriate version of the protocol and ICF before recruitment of patients into the trial and shipment of IMP.

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

The investigator will be responsible for obtaining ongoing IRB/IEC approval/renewal throughout the duration of the trial. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to GW.

15.4 Pre-trial Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any parent(s)/legal representative of patients to consent for entry into the trial:

- Signed and dated protocol signature page.
- Copy of IRB/IEC-approved ICF (including version number and date) and other patient information material.
- Copy of the IRB/IEC approval of the protocol, ICF (including version number and date) and other patient information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/IEC composition and/or written statement of the IRB/IEC in compliance with the FDA regulations relating to GCP and clinical trials[58,59,60,69], the EU Clinical Trials Directive[61], the EU GCP Directive[62], or the ICH Tripartite Guidelines for GCP Topic E6(R1)[57] where the EU Clinical Trials and GCP Directives do not apply.
- Signed and dated laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed and dated clinical trial agreement (including patient/investigator indemnity insurance and financial agreement).
- Form FDA 1572, if required.
- Drug Enforcement Administration license, if required.

- Completed financial disclosure statements for the PI and all sub-investigators, if relevant.

GW will ensure that the site is informed of when screening of patients can commence.

15.5 Patient Confidentiality

The investigator must ensure that the patient's anonymity is maintained. In the CRFs or other documents submitted to GW, patients should be identified by their initials and race (if allowed per local regulations) and their trial patient number only. Documents that are not for submission to GW, e.g., signed ICFs, should be kept in strict confidence by the investigator. Video recordings will be taken of patients as part of the video-EEG assessments; the information will be kept confidential and secure, and will be used only for the purpose for which it was collected (informed consent will be taken in relation to this).

In compliance with the FDA regulations relating to GCP and clinical trials[58,59,60,69], and the EU Clinical Trials Directive[61]/ICH Tripartite Guidelines for GCP Topic E6(R1)[57], it is required that the investigator and institution permit authorized representatives of the company, the regulatory authorities and the IRB/IEC have direct access to review the patient's original medical records for verification of trial-related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the trial. The investigator is obligated to inform the patient that his/her trial-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 trial 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 Trial 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 document. The IRB/IEC 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 IRB/IEC for information only. The investigator must send a copy of the approval letter from the IRB/IEC to GW.

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

16.2 Trial Documentation and Storage

The investigator must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries in and/or corrections to CRFs will be included on the GW Delegation of Authority and Signature form.

Source documents are original documents, data and records containing all protocol-specified information 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, microfiches, radiographs and correspondence. A source data verification plan, identifying the source for each data point at each site, will be agreed with each site prior to patient recruitment. In the rare situations of data being recorded directly into the CRF in error, then the source data from the CRF should be transcribed into the patient's notes with appropriate signature and date to provide a full audit trail.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all trial-related, essential documentation (as outlined in the ICH Tripartite Guidelines for GCP Topic R6(R1)[57], 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.

- Trial files containing the protocol with all amendments, IB, copies of pre-trial documentation (see Section 15.4) and all correspondence to and from the IRB/IEC and GW.
- Enrollment log of all patients whose parent(s)/legal representative gave consent to take part in the trial.
- Screening and recruitment log of all patients screened and whether or not they were recruited into the trial (i.e., randomized/assigned GWP42003-P and/or dosed with IMP).
- 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 and diary data must be maintained and be readily available.

Following completion or termination of a clinical trial, GW will initiate proper archive of clinical trial-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 must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements[62] or if needed by GW.

GW will inform the investigators for each site in writing of the need for record retention. No trial document may be destroyed without prior written agreement between GW and the investigator. Should the investigator wish to assign the trial 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 Trial 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 trial, 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 diary data at regular intervals throughout the trial 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 must have access to patient medical records and other trial-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate 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 sites, 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[58,59,60,69], ICH Tripartite Guidelines for GCP Topic E6(R1)[57] and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and then returned to GW or the CRO, as applicable.

16.4 Quality Assurance

In accordance with the FDA regulations[58,59,60,69], EU Clinical Trials Directive[61]/ICH Tripartite Guidelines for GCP Topic E6(R1)[57] and the sponsor's audit plans, representatives from GW's Clinical Quality Assurance Department may select this trial for audit. Inspection of site facilities, e.g., pharmacy, drug storage areas, laboratories, and review of trial-related records will occur to evaluate the trial conduct and compliance with the protocol, the EU Clinical Trials Directive[61]/ICH Tripartite Guidelines for GCP Topic E6(R1)[57] and applicable regulatory requirements.

16.5 Compensation

GW will indemnify the investigator and the trial site in the event of any claim in respect of personal injury arising due to a patient's involvement in the trial, providing that the trial 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 trial patient would not otherwise have been exposed, providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

16.6 Publication Policy

GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical trial are appropriately published and disseminated. They will coordinate this dissemination and may solicit input and assistance from the chief/principal investigators. A summary of the results of this trial will be made available on http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu/ (as applicable), as required by US and EU Law.

The raw data from this trial may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analyses and are permitted to present such information along with methods and results of the clinical trial at symposia, national or regional professional meetings and to publish it in theses or dissertations. If video-EEG data are presented, the identity of the patient must be obscured.

All publications, e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this trial, 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 6 months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

16.7 Intellectual Property Rights

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

16.8 Confidential Information

GW and the PI must ensure that only personnel directly concerned with the trial are party to confidential information and that any information coming to either party about the other during the course of the trial must be kept strictly confidential and

must not be disclosed to any third party or made use of without the prior written consent of the other.

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67 UK Statutory Instrument 2008 No. 941: The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008. May 2008.

68 UK Statutory Instrument 2012 No. 1916: The Human Medicines Regulations 2012. August 2012.

69 US Food and Drug Administration Code of Federal Regulations Title 21 (Food and Drugs) Part 11—Electronic Records; Electronic Signatures (Subpart B—Electronic Records). http://www.ecfr.gov/cgi-bin/text-idx?SID=d8c9d937237add821240e27ce3b941e6&mc=true&node=pt21.1.11&rgn=div5, Accessed 07 Sept 2016.

APPENDIX 1 SCHEDULE OF ASSESSMENTS

	Pilot or Pivotal phase				**Open-Label Extension Phase**									
Visit Number Day (Visit Window)	**Visit 1** Day −7 to −1	**Visit 2**[1] Day 1 (+3 days)	**Visit 3** Day 4 (+1 day)	**Visit 4**[2] Day 15 (+3 days)	**Visit 5** Day 19 (+1 day)	**Visit 6** Day 29 (±3 days)	**Visit 7** Day 43 (±3 days)	**Visit 8** Day 71 (±3 days)	**Visit 9** Day 127 (±7 days)	**Visit 10** Day 211 (±7 days)	**Visit 11** Day 295 (±7 days)	**Visit 12** Day 379 (±7 days)	**End of Taper Period Visit**[3] (+3 days)	**Safety Follow-up Visit**[4] (+3 days)
Informed consent	X													
Patient number	X													
Eligibility criteria	X	X[5]												
Start of IMP dosing		X												
Inpatient stay (pilot phase only)		X	X											
Demographics	X													
Medical history	X													
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X		X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X	X[6]	X[7]	X[7]	X	X	X	X	X	X	X	X	X	
Video-EEG (8–24 hours)	X			X		X	X		X	X	X	X		

	Pilot or Pivotal phase				Open-Label Extension Phase									
Visit Number Day (Visit Window)	**Visit 1** Day −7 to −1	**Visit 2**[1] Day 1 (+3 days)	**Visit 3** Day 4 (+1 day)	**Visit 4**[2] Day 15 (+3 days)	**Visit 5** Day 19 (+1 day)	**Visit 6** Day 29 (±3 days)	**Visit 7** Day 43 (±3 days)	**Visit 8** Day 71 (±3 days)	**Visit 9** Day 127 (±7 days)	**Visit 10** Day 211 (±7 days)	**Visit 11** Day 295 (±7 days)	**Visit 12** Day 379 (±7 days)	**End of Taper Period Visit**[3] (+3 days)	**Safety Follow-up Visit**[4] (+3 days)
Clinical laboratory sampling (blood/urine)	X		X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling[8]		X		X	X									
Caregiver paper diary issue/training	X													
CGIC		X[9]		X		X	X	X	X	X	X	X		
PGIC		X[9]		X		X	X	X	X	X	X	X		
Vineland-II		X								X		X		
IMP dispensing[10]		X		X		X	X	X	X	X	X			
IMP compliance review				X		X	X	X	X	X	X	X	X	
Caregiver diary review		X	X	X	X	X	X	X	X	X	X	X	X	X
Spasm/seizure information		X	X	X	X	X	X	X	X	X	X	X	X	X
IMP usage[11]			X	X	X	X	X	X	X	X	X	X	X	

	Pilot or Pivotal phase				Open-Label Extension Phase									
Visit Number Day (Visit Window)	**Visit 1** Day −7 to −1	**Visit 2**[1] Day 1 (+3 days)	**Visit 3** Day 4 (+1 day)	**Visit 4**[2] Day 15 (+3 days)	**Visit 5** Day 19 (+1 day)	**Visit 6** Day 29 (±3 days)	**Visit 7** Day 43 (±3 days)	**Visit 8** Day 71 (±3 days)	**Visit 9** Day 127 (±7 days)	**Visit 10** Day 211 (±7 days)	**Visit 11** Day 295 (±7 days)	**Visit 12** Day 379 (±7 days)	**End of Taper Period Visit**[3] (+3 days)	**Safety Follow-up Visit**[4] (+3 days)
Changes in concomitant AEDs		X	X	X	X	X	X	X	X	X	X	X	X	X
Usage of rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X

[1]All patients in the pilot phase will titrate GWP42003-P in an inpatient setting. In both phases (pilot and pivotal), daily safety checks will be made during the first week of IMP dosing (can be conducted by telephone). Each safety check will conduct the same assessments as listed for safety follow-up visit.

[2]Daily safety checks will be made during the first week of OLE IMP dosing (can be conducted by telephone). Each safety check will conduct the same assessments as listed for safety follow-up visit.

[3]IMP is to be tapered over 10 days following discontinuation of IMP, end of treatment, or withdrawal (unless continued dosing is not possible due to an AE).

[4]Safety follow-up visit is to occur 28 (+3) days after date of final dose (including tapered dose); weekly (±3 days) telephone calls must be made during the follow-up period. Each safety telephone call will conduct the same assessments as listed for safety follow-up visit.

[5]Based on assessment of clinical laboratory and video-EEG results.

[6]ECG to be performed between 3 and 5 hours after the day's first dose of IMP only.

[7]ECG to be performed both prior to the day's first dose of IMP and between 3 and 5 hours after this dose.

[8]Only for patients involved in the pivotal phase, and progressing to the OLE from the pivotal phase. To be conducted only if the risk/benefit outcome is favorable, in the investigator's opinion.

[9]Memory aid only (worksheet completed).

[10]If necessary, IMP will also be dispensed for taper period.

[11]IMP usage to be recorded on a dosing schedule which will form part of the paper diary

APPENDIX 2 TRIAL PERSONNEL

Appendix 2.1 Investigator Details

At the time of protocol production, the participating investigators had not been confirmed. A list of all investigators will be maintained within the GW master files (electronically and added to the trial master file at the end of the trial).

Appendix 2.2 Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting:	**Fax:** [redacted] **US Toll-free Fax:** [redacted] Tel: [redacted]
Sponsor:	GW Research Ltd Sovereign House Vision Park Chivers Way Histon Cambridge CB24 9BZ United Kingdom Tel: +44 (0) 1223 266 800 Fax: +44 (0) 1223 235 667
Medical Advisor & Clinical Project Manager:	Please refer to the Sponsor and Related Contact Details form in the trial site file.
Clinical Trial Supplies:	G-Pharm Ltd Tel: Fax: [redacted]

Appendix 2.3 Contract Research Organizations

Details of the contract research organizations, clinical and bioanalytical laboratories, and central EEG reader for the trial are provided below. A corresponding list will be maintained within the GW master files (electronically and added to the trial master file at the end of the trial).

Video-EEG vendor	Lifelines Neurodiagnostic Systems Inc. 411 Edwardsville Road Troy, IL 62294 US
Central Video-EEG reader	[redacted] Chief of the Division of Pediatric Neurology

	[redacted] of the Neurosciences Institute Children's Hospital Los Angeles 4650 Sunset Boulevard Los Angeles, CA 90027 US
Contract Data Management	Cytel Inc ICC, Bat, C, 2nd Floor Route de Pré Bois 20 C.P. 1839 1215 Geneva 15 Switzerland
Central Laboratory(Central AED & CBD PK)	*Managed from:* Covance Clinical Laboratory Services 7 Rue Moïse-Marcinhes 1217 Geneva Switzerland *Sample analysis will be carried out at:* Covance Laboratories Ltd Otley Road Harrogate North Yorkshire HG3 1PY UK
Contract IVRS Provider	PAREXEL Informatics Castle Wharf 4 Canal Street Nottingham NG1 7EH UK

APPENDIX 3 QUESTIONNAIRES

Appendix 3.1 Caregiver Global Impression of Change

An example of the CGIC questionnaire, to be completed by the caregiver, is given below.

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

- Very much improved ☐
- Much improved ☐
- Slightly improved ☐
- No change ☐
- Slightly worse ☐
- Much worse ☐
- Very much worse ☐

Not done ☐

Appendix 3.2 Physician Global Impression of Change

An example of the PGIC questionnaire, to be completed by the investigator, is given below.

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

- Very much improved ☐
- Much improved ☐
- Slightly improved ☐
- No change ☐
- Slightly worse ☐
- Much worse ☐
- Very much worse ☐

Not done ☐

Appendix 3.3 Vineland Adaptive Behavior Scales, Second Edition

A sample of the Vineland-II questionnaire is given below:

About the Individual:

Name: _____ Telephone: _____

Current or Highest Grade Completed (if applicable): _____

School or Other Facility (if applicable): _____

Language Spoken at Home: _____

Does the individual have any disabling conditions? _____

Sex (circle one): F M

	Year	Month	Day
Test Date:	_____	_____	_____
Birth Date:	_____	_____	_____
Chronological Age:	_____	_____	_____

Vineland™-II

Record Booklet

Vineland Adaptive Behavior Scales, Second Edition

Parent/Caregiver Rating Form

Sara S. Sparrow, Domenic V. Cicchetti, and David A. Balla

A revision of the Vineland Social Maturity Scale by Edgar A. Doll

About the Respondent:

Name: _____ Sex: _____

Relationship to Individual: _____ Telephone: _____

11 12 A B C D E

Product Number 31013

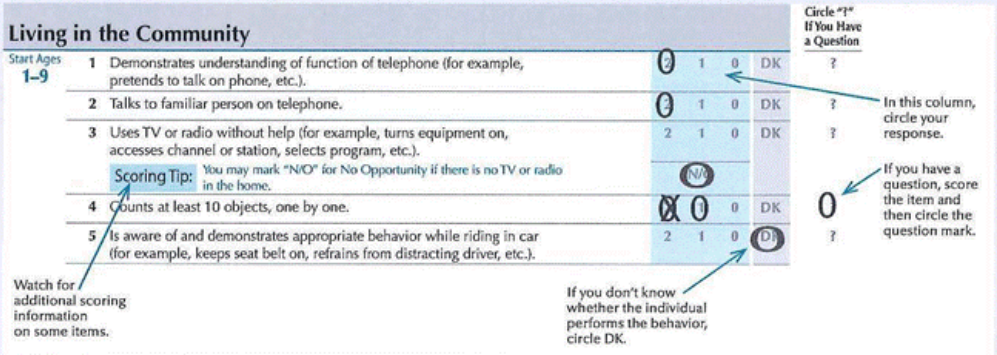
Directions:

This booklet contains phrases that describe many different behaviors that people show at home, school, work, or other settings. The behaviors range from those appropriate for infants to those appropriate for adults. Some may be too hard for younger children, and some may be too easy for older children or for adults. Thus, the child, adolescent, or adult you are rating may not show all the behaviors described in the items.

In each section, find the starting point (Start Ages 0–5) for the individual's age. Read each phrase, and mark the response that best describes the individual's behavior. The response that you choose should reflect how often the individual performs the behavior without help, when the behavior is needed. Mark your scores in this booklet by circling one response option for each item.

- Circle "2" if the individual usually performs the behavior without help or reminders.
- Circle "1" if the individual sometimes performs the behavior without help or reminders or partially performs the behavior without help or reminders.
- Circle "0" if the individual never performs the behavior or never performs it without help or reminders.
- If you have never seen the individual perform a behavior and don't know whether he or she performs it, circle "DK" for Don't Know.
- If an item has a Scoring Tip, use the tip to help you decide which response option to circle.
- If an item has a Scoring Tip that says you may circle "N/O" for No Opportunity, you may circle that option, if appropriate, instead of a "2," "1," "0," or "DK."
- Some sections do not apply to children younger than 3 years of age. If the child you are rating is younger than the age of the first start point, do not mark any items in that section.

Here is an example:



Continued on next page

2

Directions continued

If you want to change a response, mark an X through it, and circle your new choice.

If you have a question about any item, first mark the response that best describes the individual's behavior, and then circle the question mark (?) to the right of the response options.

Use the following table to help you choose the response that best describes the behavior of the individual you are rating.

RATING	THE INDIVIDUAL:
2 Usually	Usually performs the behavior without help or reminders when it is needed; or Performed the behavior at a younger age but now has outgrown it
1 Sometimes or Partially	Sometimes performs the behavior without help or reminders when it is needed; or Sometimes does it without help but sometimes needs help; or Sometimes does it without help but needs reminders; or Performs part of the behavior without help or reminders
0 Never	Never performs the behavior without help or reminders; or Never performs the behavior, because he or she is unable; or Never performs the behavior, because he or she is too young; or Never performs the behavior, because he or she is not allowed to; or Never performs the behavior, because he or she has a physical disability that prevents the behavior

Remember to respond in each section to every item after the start point for the individual's age.

Communication

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Listening and Understanding

							Circle "?" If You Have a Question
Start Ages 0–4	1	Turns eyes and head toward sound.	2	1	0	DK	?
	2	Looks toward parent or caregiver when hearing parent's or caregiver's voice.	2	1	0	DK	?
	3	Responds to his or her name spoken (for example, turns toward speaker, smiles, etc.).	2	1	0	DK	?
	4	Demonstrates understanding of the meaning of no, or word or gesture with the same meaning (for example, stops current activity briefly).	2	1	0	DK	?
	5	Demonstrates understanding of the meaning of yes, or word or gesture with the same meaning (for example, continues activity, smiles, etc.).	2	1	0	DK	?
	6	Listens to story for at least 5 minutes (that is, remains relatively still and directs attention to the storyteller or reader).	2	1	0	DK	?
	7	Points to at least three major body parts when asked (for example, nose, mouth, hands, feet, etc.).	2	1	0	DK	?
Start Ages 5+	8	Points to common objects in a book or magazine as they are named (for example, dog, car, cup, key, etc.).	2	1	0	DK	?
	9	Listens to instructions.	2	1	0	DK	?
	10	Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door"; etc.).	2	1	0	DK	?
	11	Points to at least five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).	2	1	0	DK	?
	12	Follows instructions with two actions or an action and two objects (for example, "Bring me the crayons and the paper"; "Sit down and eat your lunch"; etc.).	2	1	0	DK	?
	13	Follows instructions in "if-then" form (for example, "If you want to play outside, then put your things away"; etc.).	2	1	0	DK	?
	14	Listens to a story for at least 15 minutes.	2	1	0	DK	?
	15	Listens to a story for at least 30 minutes.	2	1	0	DK	?
	16	Follows three-part instructions (for example, "Brush your teeth, get dressed, and make your bed"; etc.).	2	1	0	DK	?
	17	Follows instructions or directions heard 5 minutes before.	2	1	0	DK	?
	18	Understands sayings that are not meant to be taken word for word (for example, "Button your lip"; "Hit the road"; etc.).	2	1	0	DK	?
	19	Listens to an informational talk for at least 15 minutes.	2	1	0	DK	?
	20	Listens to an informational talk for at least 30 minutes.	2	1	0	DK	?

Talking

							Circle "?" If You Have a Question
Start Ages 0–4	1	Cries or fusses when hungry or wet.	2	1	0	DK	?
	2	Smiles when you smile at him or her.	2	1	0	DK	?
	3	Makes sounds of pleasure (for example, coos, laughs, etc.).	2	1	0	DK	?
	4	Makes nonword baby sounds (that is, babbles).	2	1	0	DK	?
	5	Makes sounds or gestures (for example, waves arms) to get parent's or caregiver's attention.	2	1	0	DK	?
	6	Makes sounds or gestures (for example, shakes head) if he or she wants an activity to stop or keep going.	2	1	0	DK	?

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Communication, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Talking, *continued*						Circle "?" If You Have a Question
	7	Waves good-bye when another person waves or parent or caregiver tells him or her to wave.	2	1	0	DK	?
	8	Says "Da-da," "Ma-ma," or another name for parent or caregiver (including parent's or caregiver's first name or nickname).	2	1	0	DK	?
	9	Points to object he or she wants that is out of reach.	2	1	0	DK	?
	10	Points or gestures to indicate preference when offered a choice (for example, "Do you want this one or that one?"; etc.).	2	1	0	DK	?
	11	Repeats or tries to repeat common words immediately upon hearing them (for example, ball, car, go, etc.).	2	1	0	DK	?
	12	Names at least three objects (for example, bottle, dog, favorite toy, etc.).	2	1	0	DK	?
	13	Says one-word requests (for example, up, more, out, etc.).	2	1	0	DK	?
	14	Uses first names or nicknames of brothers, sisters, or friends, or says their names when asked.	2	1	0	DK	?
	15	Answers or tries to answer with words when asked a question.	2	1	0	DK	?
	16	Names at least 10 objects.	2	1	0	DK	?
	17	States own first name or nickname (for example, Latesha, Little Sister, etc.) when asked.	2	1	0	DK	?
	18	Uses phrases with a noun and a verb (for example, "Katie stay"; "Go home"; etc.).	2	1	0	DK	?
	19	Asks questions by changing inflection of words or simple phrases ("Mine?"; "Me go?"; etc.); grammar is not important.	2	1	0	DK	?
	20	Says at least 50 recognizable words.	2	1	0	DK	?
	21	Uses simple words to describe things (for example, dirty, pretty, big, loud, etc.).	2	1	0	DK	?
	22	Asks questions beginning with what or where (for example, "What's that?"; "Where doggie go?"; etc.).	2	1	0	DK	?
	23	Uses negatives in sentences (for example, "Me no go"; "I won't drink it"; etc.); grammar is not important.	2	1	0	DK	?
	24	Tells about experiences in simple sentences (for example, "Ginger and I play"; "Dan read me a book"; etc.).	2	1	0	DK	?
Start Ages 5–13	25	Says correct age when asked.	2	1	0	DK	?
	26	Says at least 100 recognizable words.	2	1	0	DK	?
	27	Uses in, on, or under in phrases or sentences (for example, "Ball go under chair"; "Put it on the table"; etc.).	2	1	0	DK	?
	28	Uses and in phrases or sentences (for example, "Mom and Dad"; "I want ice cream and cake"; etc.).	2	1	0	DK	?
	29	Says first and last name when asked.	2	1	0	DK	?
	30	Identifies and names most common colors (that is, red, blue, green, yellow, orange, purple, brown, and black). **Scoring Tip:** Mark a "2" if the individual names 6 to 8 colors; mark a "1" if the individual names 2 to 5 colors; mark a "0" if the individual names 0 or 1 color.	2	1	0	DK	?
	31	Asks questions beginning with who or why (for example, "Who's that?"; "Why do I have to go?"; etc.).	2	1	0	DK	?
	32	Uses present tense verbs ending in ing (for example, "Is singing"; "Is playing"; etc.).	2	1	0	DK	?

6

Communication, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

		Talking, *continued*					Circle "?" If You Have a Question
	33	Uses possessives in phrases or sentences (for example, "That's her book"; "This is Carlos's ball"; etc.).	2	1	0	DK	?
	34	Uses pronouns in phrases or sentences; must use correct gender and form of the pronoun, but sentences need not be grammatically correct (for example, "He done it"; "They went"; etc.).	2	1	0	DK	?
	35	Asks questions beginning with when (for example, "When is dinner?"; "When can we go home?"; etc.).	2	1	0	DK	?
	36	Uses regular past tense verbs (for example, walked, baked, etc.); may use irregular past tense verbs ungrammatically (for example, "I runned away"; etc.).	2	1	0	DK	?
	37	Uses behind or in front of in phrases or sentences (for example, "I walked in front of her"; "Terrell is behind you"; etc.).	2	1	0	DK	?
	38	Pronounces words clearly without sound substitutions (for example, does not say "wabbit" for "rabbit," "Thally" for "Sally," etc.).	2	1	0	DK	?
	39	Tells basic parts of a story, fairy tale, or television show plot; does not need to include great detail or recount in perfect order.	2	1	0	DK	?
Start Ages 14+	40	Says month and day of birthday when asked.	2	1	0	DK	?
	41	Modulates tone of voice, volume, and rhythm appropriately (for example, does not consistently speak too loudly, too softly, or in a monotone, etc.).	2	1	0	DK	?
	42	Tells about experiences in detail (for example, tells who was involved, where activity took place, etc.).	2	1	0	DK	?
	43	Gives simple directions (for example, on how to play a game or how to make something). Scoring Tip: Mark a "2" if the directions are clear enough to follow; mark a "1" if the individual articulates directions but they are not clear enough to follow; mark a "0" if the individual never attempts to articulate directions.	2	1	0	DK	?
	44	Uses between in phrases or sentences (for example, "The ball went between the cars; etc.).	2	1	0	DK	?
	45	Says own telephone number when asked.	2	1	0	DK	?
	46	Easily moves from one topic to another in conversation.	2	1	0	DK	?
	47	Stays on topic in conversations; does not go off on tangents.	2	1	0	DK	?
	48	Explains ideas in more than one way (for example, "This was a good book. It was exciting and fun to read"; etc.).	2	1	0	DK	?
	49	Has conversations that last 10 minutes (for example, relates experiences, contributes ideas, shares feelings, etc.).	2	1	0	DK	?
	50	Uses irregular plurals correctly (for example, children, geese, mice, women, etc.).	2	1	0	DK	?
	51	Says complete home address (that is, street or rural route, apartment number, city, and state), with or without zip code, when asked.	2	1	0	DK	?
	52	Describes a short-term goal and what he or she needs to do to reach it (for example, says, "I want to get an A on my test, so I'm going to study hard"; etc.).	2	1	0	DK	?
	53	Gives complex directions to others (for example, to a distant location, for recipe with many ingredients or steps, etc.). Scoring Tip: Mark a "2" if the directions are clear enough to follow; mark a "1" if the individual articulates directions but they are not clear enough to follow; mark a "0" if the individual never attempts to articulate directions.	2	1	0	DK	?
	54	Describes a realistic long-range goal that can be done in 6 months or more (for example, says, "I want to buy a bike, so I'll babysit and run errands to earn enough money to buy it"; etc.).	2	1	0	DK	?

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Communication, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

		Reading and Writing					Circle "?" If You Have a Question
Start Ages 3–13	1	Identifies one or more alphabet letters as letters and distinguishes them from numbers.	2	1	0	DK	?
	2	Recognizes own name in printed form.	2	1	0	DK	?
	3	Identifies at least 10 printed letters of the alphabet.	2	1	0	DK	?
	4	Prints or writes using correct orientation (for example, in English from left to right; in some languages from right to left or top to bottom).	2	1	0	DK	?
	5	Copies own first name.	2	1	0	DK	?
	6	Identifies all printed letters of the alphabet, upper- and lowercase.	2	1	0	DK	?
	7	Prints at least three simple words from example (for example, cat, see, bee, etc.).	2	1	0	DK	?
	8	Prints or writes own first and last name from memory.	2	1	0	DK	?
	9	Reads at least 10 words aloud.	2	1	0	DK	?
	10	Prints at least 10 simple words from memory (for example, hat, ball, the, etc.).	2	1	0	DK	?
	11	Reads simple stories aloud (that is, stories with sentences of three to five words).	2	1	0	DK	?
	12	Prints simple sentences of three or four words; may make small errors in spelling or sentence structure.	2	1	0	DK	?
	13	Prints more than 20 words from memory; may make small spelling errors.	2	1	0	DK	?
Start Ages 14+	14	Reads and understands material of at least second-grade level.	2	1	0	DK	?
	15	Puts lists of words in alphabetical order.	2	1	0	DK	?
	16	Writes simple correspondence at least three sentences long (for example, postcards, thank-you notes, e-mail, etc.).	2	1	0	DK	?
	17	Reads and understands material of at least fourth-grade level.	2	1	0	DK	?
	18	Writes reports, papers, or essays at least one page long; may use computer.	2	1	0	DK	?
	19	Writes complete mailing and return addresses on letters or packages.	2	1	0	DK	?
	20	Reads and understands material of at least sixth-grade level.	2	1	0	DK	?
	21	Edits or corrects own written work before handing it in (for example, checks punctuation, spelling, grammar, etc.).	2	1	0	DK	?
	22	Writes advanced correspondence at least 10 sentences long; may use computer.	2	1	0	DK	?
	23	Reads and understands material of at least ninth-grade level.	2	1	0	DK	?
	24	Reads at least two newspaper articles weekly (print or electronic version).	2	1	0	DK	?
	25	Writes business letters (for example, requests information, makes complaint, places order, etc.); may use computer.	2	1	0	DK	?

8

Daily Living

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Caring for Self

							Circle "?" If You Have a Question
Start Ages 0–8	1	Opens mouth when food is offered.	2	1	0	DK	?
	2	Eats solid foods (for example, cooked vegetables, chopped meats, etc.).	2	1	0	DK	?
	3	Sucks or chews on finger foods (for example, crackers, cookies, toast, etc.).	2	1	0	DK	?
	4	Drinks from a cup or glass; may spill.	2	1	0	DK	?
	5	Lets someone know when he or she has wet or soiled diaper or pants (for example, points, vocalizes, pulls at diaper, etc.).	2	1	0	DK	?
	6	Feeds self with spoon; may spill.	2	1	0	DK	?
	7	Sucks from straw.	2	1	0	DK	?
	8	Takes off clothing that opens in the front (for example, a coat or sweater); does not have to unbutton or unzip the clothing.	2	1	0	DK	?
	9	Pulls up clothing with elastic waistbands (for example, underwear or sweatpants).	2	1	0	DK	?
	10	Feeds self with fork; may spill.	2	1	0	DK	?
	11	Drinks from a cup or glass without spilling.	2	1	0	DK	?
	12	Feeds self with spoon without spilling.	2	1	0	DK	?
	13	Urinates in toilet or potty chair.	2	1	0	DK	?
	14	Puts on clothing that opens in the front (for example, a coat or sweater); does not have to zip or button the clothing.	2	1	0	DK	?
	15	Asks to use toilet.	2	1	0	DK	?
	16	Defecates in toilet or potty chair.	2	1	0	DK	?
	17	Is toilet-trained during the day. Scoring Tip: Mark "2" if the individual uses the toilet without help and without accidents; mark "1" if the individual needs help, such as with wiping, or has some accidents; mark "0" if the individual always needs help or has frequent accidents.	2	1	0	DK	?
	18	Zips zippers that are fastened at the bottom (for example, in pants, on backpacks, etc.).	2	1	0	DK	?
	19	Wipes or blows nose using tissue or handkerchief.	2	1	0	DK	?
	20	Is toilet-trained during the night.	2	1	0	DK	?
	21	Puts shoes on correct feet; does not need to tie laces.	2	1	0	DK	?
	22	Fastens snaps.	2	1	0	DK	?
Start Ages 9+	23	Holds spoon, fork, and knife correctly.	2	1	0	DK	?
	24	Washes and dries face using soap and water.	2	1	0	DK	?
	25	Brushes teeth. Scoring Tip: Mark a "2" if the individual brushes teeth without help, including putting toothpaste on the brush, and without being told to brush; mark "1" if the individual needs help brushing or putting toothpaste on the brush or needs frequent reminders; mark "0" if the individual never brushes without help or without being reminded.	2	1	0	DK	?
	26	Buttons large buttons in front, in correct buttonholes.	2	1	0	DK	?
	27	Covers mouth and nose when coughing and sneezing.	2	1	0	DK	?

9

Daily Living, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Caring for Self, *continued*

						Circle "?" If You Have a Question
28	Buttons small buttons in front, in correct buttonholes.	2	1	0	DK	?
29	Connects and zips zippers that are not fastened at the bottom (for example, in jackets, sweatshirts, etc.).	2	1	0	DK	?
30	Turns faucets on and adjusts temperature by adding hot or cold water.	2	1	0	DK	?
31	Wears appropriate clothing during wet or cold weather (for example, raincoat, boots, sweater, etc.).	2	1	0	DK	?
32	Bathes or showers and dries self.	2	1	0	DK	?
	Scoring Tip: Mark a "2" if the individual bathes or showers without help, including turning the water on and off; mark a "1" if the individual needs help with any part of bathing or drying or with turning the water on and off; mark "0" if the individual never bathes or showers without help or without reminders.					
33	Finds and uses appropriate public restroom for his or her gender.	2	1	0	DK	?
34	Washes and dries hair (with towel or hair dryer).	2	1	0	DK	?
35	Cares for minor cuts (for example, cleans wound, puts on bandage, etc.).	2	1	0	DK	?
36	Takes medicine as directed (that is, follows directions on label).	2	1	0	DK	?
37	Uses thermometer to take own or another's temperature.	2	1	0	DK	?
38	Seeks medical help in an emergency (for example, recognizes symptoms of serious illness or injury, such as shortness of breath, chest pain, uncontrolled bleeding, etc.).	2	1	0	DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if the individual has not been in a medical emergency.		N/O			
39	Follows directions for health care procedures, special diet, or medical treatments.	2	1	0	DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a health concern that requires special procedures, diet, or treatments.		N/O			
40	Keeps track of medications (nonprescription and prescription) and refills them as needed.	2	1	0	DK	?
41	Makes appointments for regular medical and dental checkups.	2	1	0	DK	?

Caring for Home

						Circle "?" If You Have a Question
Start Ages 1–13	1 Is careful around hot objects (for example, the stove or oven, an open fire, etc.).	2	1	0	DK	?
	2 Helps with simple household chores (for example, dusts, picks up clothes or toys, feeds pet, etc.).	2	1	0	DK	?
	3 Clears unbreakable items from own place at table.	2	1	0	DK	?
	4 Cleans up play or work area at end of an activity (for example, finger painting, model building, etc.).	2	1	0	DK	?
	5 Puts away personal possessions (for example, toys, books, magazines, etc.).	2	1	0	DK	?
	6 Is careful when using sharp objects (for example, scissors, knives, etc.).	2	1	0	DK	?
Start Ages 14+	7 Clears breakable items from own place at table.	2	1	0	DK	?
	8 Helps prepare foods that require mixing and cooking (for example, cake or cookie mixes, macaroni and cheese, etc.).	2	1	0	DK	?
	9 Uses simple appliances (for example, a toaster, can opener, bottle opener, etc.).	2	1	0	DK	?

10

Daily Living, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Caring for Home, *continued*

						Circle "?" If You Have a Question
10	Uses microwave oven for heating, baking, or cooking (that is, sets time and power setting, etc.).	2	1	0	DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if there is no microwave in the home.		N/O			
11	Puts clean clothes away in proper place (for example, in drawers or closet, on hooks, etc.).	2	1	0	DK	?
12	Uses tools (for example, a hammer to drive nails, a screwdriver to screw and unscrew screws, etc.).	2	1	0	DK	?
13	Washes dishes by hand, or loads and uses dishwasher.	2	1	0	DK	?
14	Sweeps, mops, or vacuums floors thoroughly.	2	1	0	DK	?
	Scoring Tip: Mark "2" if the individual mops, sweeps, or vacuums so well that the task does not have to redone; mark a "1" if the individual doesn't consistently complete the task well; mark a "0" if the individual never mops, sweeps, or vacuums, or does the task so poorly that it always needs to be redone.					
15	Clears table completely (for example, scrapes and stacks dishes, throws away disposable items, etc.).	2	1	0	DK	?
16	Uses household products correctly (for example, laundry detergent, furniture polish, glass cleaner, etc.).	2	1	0	DK	?
17	Prepares basic foods that do not need mixing but require cooking (for example, rice, soup, vegetables, etc.).	2	1	0	DK	?
18	Cleans one or more rooms other than own bedroom.	2	1	0	DK	?
19	Uses sharp knife to prepare food.	2	1	0	DK	?
20	Uses stove or oven for heating, baking, or cooking (that is, turns burners on and off, sets oven temperature, etc.).	2	1	0	DK	?
21	Prepares food from ingredients that require measuring, mixing, and cooking.	2	1	0	DK	?
22	Washes clothing as needed.	2	1	0	DK	?
23	Performs maintenance tasks as needed (for example, replaces light bulbs, changes vacuum cleaner bag, etc.).	2	1	0	DK	?
24	Plans and prepares main meal of the day.	2	1	0	DK	?

Living in the Community

						Circle "?" If You Have a Question
Start Ages 1–9	1 Demonstrates understanding of function of telephone (for example, pretends to talk on phone, etc.).	2	1	0	DK	?
	2 Talks to familiar person on telephone.	2	1	0	DK	?
	3 Uses TV or radio without help (for example, turns equipment on, accesses channel or station, selects program, etc.).	2	1	0	DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if there is no TV or radio in the home.		N/O			
	4 Counts at least 10 objects, one by one.	2	1	0	DK	?
	5 Is aware of and demonstrates appropriate behavior while riding in car (for example, keeps seat belt on, refrains from distracting driver, etc.).	2	1	0	DK	?
	6 Demonstrates understanding of the function of money (for example, says, "Money is what you need to buy things at the store"; etc.).	2	1	0	DK	?
	7 Uses sidewalk (where available) or shoulder of road when walking or using wheeled equipment (skates, scooter, tricycle, etc.).	2	1	0	DK	?

11

Daily Living, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Living in the Community, *continued*

							Circle "?" If You Have a Question
	8	Demonstrates understanding of function of clock (for example, says, "Clocks tell time"; "What time can we go?"; etc.).	2	1	0	DK	?
	9	Follows household rules (for example, no running in the house, no jumping on the furniture, etc.).	2	1	0	DK	?
	10	Demonstrates computer skills necessary to play games or start programs with computer turned on; does not need to turn computer on by self. Scoring Tip: You may mark "N/O" for No Opportunity if there is no computer in the home.	2	1	0	DK N/O	?
	11	Summons to the telephone the person receiving a call or indicates that the person is not available.	2	1	0	DK	?
Start Ages 10–15	12	Identifies penny, nickel, dime, and quarter by name when asked; does not need to know the value of coins.	2	1	0	DK	?
	13	Looks both ways when crossing streets or roads.	2	1	0	DK	?
	14	Says current day of the week when asked.	2	1	0	DK	?
	15	Demonstrates understanding of right to personal privacy for self and others (for example, while using restroom or changing clothes, etc.).	2	1	0	DK	?
	16	Demonstrates knowledge of what phone number to call in an emergency when asked.	2	1	0	DK	?
	17	Tells time using a digital clock or watch.	2	1	0	DK	?
	18	States value of penny (1 cent), nickel (5 cents), dime (10 cents), and quarter (25 cents).	2	1	0	DK	?
	19	Discriminates between bills of different denominations (for example, refers to $1 bills, $5 bills, etc., in conversation; etc.).	2	1	0	DK	?
	20	Obeys traffic lights and Walk and Don't Walk signs.	2	1	0	DK	?
	21	Points to current or other date on calendar when asked.	2	1	0	DK	?
	22	Demonstrates understanding that some items cost more than others (for example, says, "I have enough money to buy gum but not a candy bar"; "Which pencil costs less?"; etc.).	2	1	0	DK	?
Start Ages 16+	23	Tells time by the half hour on analog clock (for example, 1:30, 2:00, etc.).	2	1	0	DK	?
	24	Makes telephone calls to others, using standard or cell phone.	2	1	0	DK	?
	25	Orders a complete meal in a fast-food restaurant. Scoring Tip: You may mark "N/O" for No Opportunity if the individual has never eaten at a fast-food restaurant.	2	1	0	DK N/O	?
	26	Carries or stores money safely (for example, in wallet, purse, money belt, etc.).	2	1	0	DK	?
	27	Tells time by 5-minute segments on analog clock (for example, 1:05, 1:10, etc.).	2	1	0	DK	?
	28	Obeys curfew parent or caregiver sets.	2	1	0	DK	?
	29	Watches or listens to programs for information (for example, weather report, news, educational program, etc.). Scoring Tip: You may mark "N/O" for No Opportunity if there is no TV or radio in the home.	2	1	0	DK N/O	?
	30	Counts change from a purchase.	2	1	0	DK	?
	31	Demonstrates computer skills necessary to carry out complex tasks (for example, word processing, accessing the Internet, installing software, etc.). Scoring Tip: You may mark "N/O" for No Opportunity if there is no computer in the home.	2	1	0	DK N/O	?
	32	Evaluates quality and price when selecting items to purchase.	2	1	0	DK	?
	33	Obeys time limits for breaks (for example, lunch or coffee breaks, etc.).	2	1	0	DK	?

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Daily Living, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Living in the Community, *continued*						Circle "?" If You Have a Question
34	Travels at least 5 to 10 miles to familiar destination (that is, bikes, uses public transportation, or drives self).	2	1	0	DK	?
35	Demonstrates understanding of right to complain or report legitimate problems when dissatisfied with services or situations.	2	1	0	DK	?
36	Notifies school or supervisor when he or she will be late or absent.	2	1	0	DK	?
37	Uses savings or checking account responsibly (for example, keeps some money in account, tracks balance carefully, etc.).	2	1	0	DK	?
38	Travels at least 5 to 10 miles to unfamiliar destination (that is, bikes, uses public transportation, or drives self).	2	1	0	DK	?
39	Earns money at part-time job (that is, at least 10 hours a week) for 1 year. Scoring Tip: Do not mark 1.	2	X	0	DK	?
40	Attempts to improve job performance after receiving constructive criticism from supervisor. Scoring Tip: You may mark "N/O" for No Opportunity if the individual has not held a job.	2	1	0	DK N/O	?
41	Manages own money (for example, pays most or all own expenses, uses checks or money orders for purchases as needed, etc.).	2	1	0	DK	?
42	Has held full-time job for 1 year. Scoring Tip: Do not mark 1.	2	X	0	DK	?
43	Budgets for monthly expenses (for example, utilities, rent, etc.).	2	1	0	DK	?
44	Applies for and uses personal credit card responsibly (for example, does not exceed credit limit, pays on time, etc.).	2	1	0	DK	?

13

Social Skills and Relationships

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Relating to Others							Circle "?" If You Have a Question
Start Ages 0–4	1	Looks at face of parent or caregiver.	2	1	0	DK	?
	2	Watches (that is, follows with eyes) someone moving by crib or bed for 5 seconds or more.	2	1	0	DK	?
	3	Shows two or more emotions (for example, laughs, cries, screams, etc.).	2	1	0	DK	?
	4	Smiles or makes sounds when approached by a familiar person.	2	1	0	DK	?
	5	Makes or tries to make social contact (for example, smiles, makes noises, etc.).	2	1	0	DK	?
	6	Reaches for familiar person when person holds out arms to him or her.	2	1	0	DK	?
	7	Shows preference for certain people and objects (for example, smiles, reaches for or moves toward person or object, etc.).	2	1	0	DK	?
	8	Shows affection to familiar persons (for example, touches, hugs, kisses, cuddles, etc.).	2	1	0	DK	?
	9	Imitates or tries to imitate parent's or caregiver's facial expressions (for example, smiles, frowns, etc.).	2	1	0	DK	?
	10	Moves about looking for parent or caregiver or other familiar person nearby.	2	1	0	DK	?
	11	Shows interest in children the same age, other than brothers or sisters (for example, watches them, smiles at them, etc.).	2	1	0	DK	?
Start Ages 5–15	12	Imitates simple movements (for example, claps hands, waves good-bye, etc.).	2	1	0	DK	?
	13	Uses actions to show happiness or concern for others (for example, hugs, pats arm, holds hands, etc.).	2	1	0	DK	?
	14	Shows desire to please others (for example, shares a snack or toy, tries to help even if not capable, etc.).	2	1	0	DK	?
	15	Demonstrates friendship-seeking behavior with others the same age (for example, says, "Do you want to play?" or takes another child by the hand, etc.).	2	1	0	DK	?
	16	Imitates relatively complex actions as they are being performed by another person (for example, shaving, putting on makeup, hammering nails, etc.).	2	1	0	DK	?
	17	Answers when familiar adults make small talk (for example, if asked, "How are you?" says, "I'm fine"; if told, "You look nice," says, "Thank you"; etc.).	2	1	0	DK	?
	18	Repeats phrases heard spoken before by an adult (for example, "Honey, I'm home"; "No dessert until you clean your plate"; etc.).	2	1	0	DK	?
	19	Uses words to express own emotions (for example, "I'm happy"; "I'm scared"; etc.).	2	1	0	DK	?
	20	Has best friend or shows preference for certain friends (of either sex) over others.	2	1	0	DK	?
	21	Imitates relatively complex actions several hours after watching someone else perform them (for example, shaving, putting on makeup, hammering nails, etc.).	2	1	0	DK	?
Start Ages 16+	22	Uses words to express happiness or concern for others (for example, says, "Yeah! You won"; "Are you all right?"; etc.).	2	1	0	DK	?
	23	Acts when another person needs a helping hand (for example, holds door open, picks up dropped items, etc.).	2	1	0	DK	?
	24	Recognizes the likes and dislikes of others (for example, says, "Chow likes soccer"; "Susie doesn't eat pizza"; etc.).	2	1	0	DK	?
	25	Shows same level of emotion as others around him or her (for example, does not downplay or overdramatize a situation, etc.).	2	1	0	DK	?
	26	Keeps comfortable distance between self and others in social situations (for example, does not get too close to another person when talking, etc.).	2	1	0	DK	?

14

Social Skills and Relationships, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Relating to Others, *continued*						Circle "?" If You Have a Question
27	Talks with others about shared interests (for example, sports, TV shows, summer plans, etc.).	2	1	0	DK	?
28	Starts small talk when meets people he or she knows (for example, says, "How are you?"; "What's up?"; etc.).	2	1	0	DK	?
29	Meets with friends regularly.	2	1	0	DK	?
30	Chooses not to say embarrassing or mean things or ask rude questions in public.	2	1	0	DK	?
31	Places reasonable demands on friendship (for example, does not expect to be a person's only friend or to have the friend always available, etc.).	2	1	0	DK	?
32	Understands that others do not know his or her thoughts unless he or she says them.	2	1	0	DK	?
33	Is careful when talking about personal things.	2	1	0	DK	?
34	Cooperates with others to plan or be part of an activity (for example, a birthday party, sports event, etc.).	2	1	0	DK	?
35	Demonstrates understanding of hints or indirect cues in conversation (for example, knows that yawns may mean, "I'm bored," or a quick change of subject may mean, "I don't want to talk about that"; etc.).	2	1	0	DK	?
36	Starts conversations by talking about things that interest others (for example, "Tyrone tells me you like computers"; etc.).	2	1	0	DK	?
37	Goes on group dates.	2	1	0	DK	?
38	Goes on single dates.	2	1	0	DK	?

Playing and Using Leisure Time							Circle "?" If You Have a Question
Start Ages 0–7	1	Responds when parent or caregiver is playful (for example, smiles, laughs, claps hands, etc.).	2	1	0	DK	?
	2	Shows interest in where he or she is (for example, looks or moves around, touches objects or people, etc.).	2	1	0	DK	?
	3	Plays simple interaction games with others (for example, peekaboo, patty-cake, etc.).	2	1	0	DK	?
	4	Plays near another child, each doing different things.	2	1	0	DK	?
	5	Chooses to play with other children (for example, does not stay on the edge of a group or avoid others).	2	1	0	DK	?
	6	Plays cooperatively with one or more children for up to 5 minutes.	2	1	0	DK	?
	7	Plays cooperatively with more than one child for more than 5 minutes.	2	1	0	DK	?
	8	Continues playing with another child with little fussing when parent or caregiver leaves.	2	1	0	DK	?
	9	Shares toys or possessions when asked.	2	1	0	DK	?
Start Ages 8–15	10	Plays with others with minimal supervision.	2	1	0	DK	?
	11	Uses common household objects or other objects for make-believe activities (for example, pretends a block is a car, a box is a house, etc.).	2	1	0	DK	?
	12	Protects self by moving away from those who destroy things or cause injury (for example, those who bite, hit, throw things, pull hair, etc.).	2	1	0	DK	?
	13	Plays simple make-believe activities with others (for example, plays dress-up, pretends to be superheroes, etc.).	2	1	0	DK	?

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Social Skills and Relationships, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

	Playing and Using Leisure Time, *continued*					Circle "?" If You Have a Question
	14	Seeks out others for play or companionship (for example, invites others home, goes to another's home, plays with others on the playground, etc.).	2	1	0	DK	?
	15	Takes turns when asked while playing games or sports.	2	1	0	DK	?
	16	Plays informal, outdoor group games (for example, tag, jump rope, catch, etc.).	2	1	0	DK	?
	17	Shares toys or possessions without being asked.	2	1	0	DK	?
	18	Follows rules in simple games (relay races, spelling bees, electronic games, etc.).	2	1	0	DK	?
	19	Takes turns without being asked.	2	1	0	DK	?
	20	Plays simple card or board game based only on chance (for example, Go Fish, Crazy Eights, Sorry™, etc.).	2	1	0	DK	?
	21	Goes places with friends during the day with adult supervision (for example, to a shopping mall, park, community center, etc.).	2	1	0	DK	?
Start Ages 16+	22	Asks permission before using objects belonging to or being used by another.	2	1	0	DK	?
	23	Refrains from entering group when nonverbal cues indicate that he or she is not welcome.	2	1	0	DK	?
	24	Plays simple games that require keeping score (for example, kickball, pickup basketball, etc.).	2	1	0	DK	?
	25	Shows good sportsmanship (that is, follows rules, is not overly aggressive, congratulates other team on winning, and does not get mad when losing).	2	1	0	DK	?
	26	Plays more than one board, card, or electronic game requiring skill and decision making (for example, Monopoly™, Cribbage, etc.).	2	1	0	DK	?
	27	Goes places with friends in evening with adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	2	1	0	DK	?
	28	Follows rules in complex games or sports (for example, football, soccer, volleyball, etc.).	2	1	0	DK	?
	29	Goes places with friends during the day without adult supervision (for example, to a shopping mall, park, community center, etc.).	2	1	0	DK	?
	30	Plans fun activities with more than two things to be arranged (for example, a trip to a beach or park that requires planning transportation, food, recreational items, etc.).	2	1	0	DK	?
	31	Goes places with friends in evening without adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	2	1	0	DK	?

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Social Skills and Relationships, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know

Adapting							Circle "?" If You Have a Question
Start Ages 1+	1	Changes easily from one at-home activity to another.	2	1	0	DK	?
	2	Says "thank you" when given something.	2	1	0	DK	?
	3	Changes behavior depending on how well he or she knows another person (for example, acts differently with family member than with stranger, etc.).	2	1	0	DK	?
	4	Chews with mouth closed.	2	1	0	DK	?
	5	Says "please" when asking for something.	2	1	0	DK	?
	6	Ends conversations appropriately (for example, says, "Good-bye"; "See you later"; etc.).	2	1	0	DK	?
	7	Cleans or wipes face and hands during and/or after meals.	2	1	0	DK	?
	8	Responds appropriately to reasonable changes in routine (for example, refrains from complaining, etc.).	2	1	0	DK	?
	9	Says that he or she is sorry for unintended mistakes (for example, bumping into someone, etc.).	2	1	0	DK	?
	10	Chooses not to taunt, tease, or bully.	2	1	0	DK	?
	11	Acts appropriately when introduced to strangers (for example, nods, smiles, shakes hands, greets them, etc.).	2	1	0	DK	?
	12	Changes voice level depending on location or situation (for example, in a library, during a movie or play, etc.).	2	1	0	DK	?
	13	Says he or she is sorry after hurting another's feelings.	2	1	0	DK	?
	14	Refrains from talking with food in mouth.	2	1	0	DK	?
	15	Talks with others without interrupting or being rude.	2	1	0	DK	?
	16	Accepts helpful suggestions or solutions from others.	2	1	0	DK	?
	17	Controls anger or hurt feelings when plans change for reason(s) that cannot be helped (for example, bad weather, car trouble, etc.).	2	1	0	DK	?
	18	Keeps secrets or confidences for longer than one day.	2	1	0	DK	?
	19	Says he or she is sorry after making unintentional mistakes or errors in judgment (for example, when unintentionally leaving someone out of a game, etc.).	2	1	0	DK	?
	20	Shows understanding that gentle teasing with family and friends can be a form of humor or affection.	2	1	0	DK	?
	21	Tells parent or caregiver about his or her plans (for example, what time he or she is leaving and returning, where he or she is going, etc.).	2	1	0	DK	?
	22	Chooses to avoid dangerous or risky activities (for example, jumping off high places, picking up a hitchhiker, driving recklessly, etc.).	2	1	0	DK	?
	23	Controls anger or hurt feelings when he or she does not get his or her way (for example, when not allowed to watch television or attend a party; when suggestion is rejected by friend or supervisor; etc.).	2	1	0	DK	?
	24	Follows through with arrangements (for example, if promises to meet someone, meets that person; etc.).	2	1	0	DK	?
	25	Stops or stays away from relationships or situations that are hurtful or dangerous (for example, being bullied or made fun of, being taken advantage of sexually or financially, etc.).	2	1	0	DK	?
	26	Controls anger or hurt feelings due to constructive criticism (for example, correction of misbehavior, discussion of test score or grade, performance review, etc.).	2	1	0	DK	?
	27	Keeps secrets or confidences for as long as needed.	2	1	0	DK	?
	28	Thinks about what could happen before making decisions (for example, refrains from acting impulsively, thinks about important information, etc.).	2	1	0	DK	?
	29	Is aware of potential danger and uses caution when encountering risky social situations (for example, binge drinking parties, Internet chat rooms, personal ads, etc.).	2	1	0	DK	?
	30	Shows respect for co-workers (for example, does not distract or interrupt others who are working, is on time for meetings, etc.).	2	1	0	DK	?

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Physical Activity

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Using Large Muscles							Circle "?" If You Have a Question
Start Ages 0–1	1	Holds head erect for at least 15 seconds when held upright in parent's or caregiver's arms.	2	1	0	DK	?
	2	Sits supported (for example, in a chair, with pillows, etc.) for at least 1 minute.	2	1	0	DK	?
	3	Sits without support for at least 1 minute.	2	1	0	DK	?
	4	Creeps or moves on stomach across floor.	2	1	0	DK	?
	5	Sits without support for at least 10 minutes.	2	1	0	DK	?
	6	Raises self to sitting position and sits without support for at least 1 minute.	2	1	0	DK	?
	7	Crawls at least 5 feet on hands and knees, without stomach touching floor.	2	1	0	DK	?
	8	Pulls self to standing position.	2	1	0	DK	?
	9	Crawls up stairs.	2	1	0	DK	?
	10	Takes at least two steps.	2	1	0	DK	?
	11	Stands alone for 1 to 3 minutes.	2	1	0	DK	?
	12	Rolls ball while sitting.	2	1	0	DK	?
	13	Climbs on and off low objects (for example, chair, step stool, slide, etc.).	2	1	0	DK	?
	14	Crawls down stairs.	2	1	0	DK	?
	15	Stands for at least 5 minutes.	2	1	0	DK	?
Start Ages 2–4	16	Walks across room; may be unsteady and fall occasionally.	2	1	0	DK	?
	17	Throws ball.	2	1	0	DK	?
	18	Walks to get around; does not need to hold on to anything.	2	1	0	DK	?
	19	Climbs on and off adult-sized chair.	2	1	0	DK	?
	20	Runs without falling; may be awkward and uncoordinated.	2	1	0	DK	?
	21	Walks up stairs, putting both feet on each step; may use railing.	2	1	0	DK	?
	22	Kicks ball.	2	1	0	DK	?
	23	Runs smoothly without falling.	2	1	0	DK	?
	24	Walks down stairs, facing forward, putting both feet on each step; may use railing.	2	1	0	DK	?
	25	Jumps with both feet off floor.	2	1	0	DK	?
Start Ages 5–6	26	Throws ball of any size in specific direction.	2	1	0	DK	?
	27	Catches beach ball-sized ball with both hands from a distance of 2 or 3 feet.	2	1	0	DK	?
	28	Walks up stairs, alternating feet; may use railing.	2	1	0	DK	?
	29	Pedals tricycle or other three-wheeled toy for at least 6 feet.	2	1	0	DK	?
		Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a tricycle or three-wheeled toy. However, if the individual has such a vehicle but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."			N/O		
	30	Jumps or hops forward at least three times.	2	1	0	DK	?
	31	Hops on one foot at least once without falling; may hold on to something for balance.	2	1	0	DK	?

18

Physical Activity, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Using Large Muscles, *continued*

						Circle "?" If You Have a Question
32	Climbs on and off high objects (for example, jungle gym, 4-foot slide ladder, etc.).	2	1	0	DK	?
33	Walks down stairs, alternating feet; may use railing.	2	1	0	DK	?
34	Runs smoothly, with changes in speed and direction.	2	1	0	DK	?
35	Rides bicycle with training wheels for at least 10 feet.	2	1	0	DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a bicycle. However, if the individual has a bike but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."		N/O			
36	Catches beach ball-sized ball (from at least 6 feet away) with both hands.	2	1	0	DK	?
37	Hops forward on one foot with ease.	2	1	0	DK	?
38	Skips at least 5 feet.	2	1	0	DK	?
39	Catches tennis or baseball-sized ball (from at least 10 feet away), moving to catch it if necessary.	2	1	0	DK	?
40	Rides bicycle with no training wheels without falling.	2	1	0	DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a bicycle. However, if the individual has a bike but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."		N/O			

Using Small Muscles

						Circle "?" If You Have a Question
Start Ages 0–4	1 Reaches for toy or object.	2	1	0	DK	?
	2 Picks up small objects (no larger than 2 inches on any side); may use both hands.	2	1	0	DK	?
	3 Moves object from one hand to the other.	2	1	0	DK	?
	4 Squeezes squeaky toy or object.	2	1	0	DK	?
	5 Picks up small object with thumb and fingers.	2	1	0	DK	?
	6 Removes object (for example, a block or clothespin) from a container.	2	1	0	DK	?
	7 Puts object (for example, a block or clothespin) into a container.	2	1	0	DK	?
	8 Turns pages of board, cloth, or paper book, one at a time.	2	1	0	DK	?
	9 Stacks at least four small blocks or other small objects; stack must not fall.	2	1	0	DK	?
	10 Opens doors by turning doorknobs.	2	1	0	DK	?
Start Ages 5–6	11 Unwraps small objects (for example, gum or candy).	2	1	0	DK	?
	12 Completes simple puzzle of at least two pieces or shapes.	2	1	0	DK	?
	13 Turns book or magazine pages one by one.	2	1	0	DK	?
	14 Uses twisting hand-wrist motion (for example, winds up toy, screws/unscrews lid of jar, etc.).	2	1	0	DK	?
	15 Holds pencil in proper position (not with fist) for writing or drawing.	2	1	0	DK	?
	16 Colors simple shapes; may color outside lines.	2	1	0	DK	?
	17 Builds three-dimensional structures (for example, a house, bridge, vehicle, etc.) with at least five small blocks.	2	1	0	DK	?
	18 Opens and closes scissors with one hand.	2	1	0	DK	?

19

Physical Activity, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/O** = No Opportunity

Using Small Muscles, *continued*

			Circle "?" If You Have a Question
19	Glues or pastes two or more pieces together (for example, for art or science projects, etc.).	2 1 0 DK	?
20	Uses tape to hold things together (for example, torn page, art project, etc.).	2 1 0 DK	?
21	Draws more than one recognizable form (for example, person, house, tree, etc.).	2 1 0 DK	?
	Scoring Tip: Mark a "2" if the individual draws two or more recognizable forms; mark a "1" if the individual draws one form; mark a "0" if the individual does not draw any recognizable forms.		
22	Makes recognizable letters or numbers.	2 1 0 DK	?
23	Draws circle freehand while looking at example.	2 1 0 DK	?
24	Uses scissors to cut across paper along a straight line.	2 1 0 DK	?
25	Colors simple shapes; colors inside the lines.	2 1 0 DK	?
26	Cuts out simple shapes (for example, circles, squares, rectangles, etc.).	2 1 0 DK	?
27	Uses eraser without tearing paper.	2 1 0 DK	?
28	Draws square freehand while looking at example.	2 1 0 DK	?
29	Draws triangle freehand while looking at example.	2 1 0 DK	?
30	Ties knot.	2 1 0 DK	?
31	Draws straight line using a ruler or straightedge.	2 1 0 DK	?
32	Unlocks dead-bolt, key, or combination locks that require twisting.	2 1 0 DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if there are no dead-bolt, key, or combination locks in the home.	N/O	
33	Cuts out complex shapes (for example, stars, animals, alphabet letters, etc.).	2 1 0 DK	?
34	Uses keyboard, typewriter, or touch screen to type name or short words; may look at keys.	2 1 0 DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if there is no computer in the home.	N/O	
35	Ties secure bow.	2 1 0 DK	?
36	Uses a keyboard to type up to 10 lines; may look at the keys.	2 1 0 DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if there is no computer in the home.	N/O	

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Problem Behaviors Part 1

Response Options: 2 = Often, 1 = Sometimes, 0 = Never

Section A

					Circle "?" If You Have a Question
Start Ages 3+	1	Is overly dependent (that is, clings to caregiver, teacher, brother, or sister).	0	1	2	?
	2	Avoids others and prefers to be alone.	0	1	2	?
	3	Has eating difficulties (for example, eats too fast or too slowly, hoards food, overeats, refuses to eat, etc.).	0	1	2	?
	4	Has sleep difficulties (for example, sleepwalks, has frequent nightmares, sleeps significantly more or less than typical for his or her age).	0	1	2	?
	5	Refuses to go to school or work because of fear, feelings of rejection or isolation, etc.	0	1	2	?
	6	Is overly anxious or nervous.	0	1	2	?
	7	Cries or laughs too easily.	0	1	2	?
	8	Has poor eye contact (that is, does not look at or face others when speaking or spoken to).	0	1	2	?
	9	Is sad for no clear reason.	0	1	2	?
	10	Avoids social interaction.	0	1	2	?
	11	Lacks energy or interest in life.	0	1	2	?

Section B

					Circle "?" If You Have a Question
Start Ages 3+	1	Is impulsive (that is, acts without thinking).	0	1	2	?
	2	Has temper tantrums.	0	1	2	?
	3	Intentionally disobeys and defies those in authority.	0	1	2	?
	4	Taunts, teases, or bullies.	0	1	2	?
	5	Is inconsiderate or insensitive to others.	0	1	2	?
	6	Lies, cheats, or steals.	0	1	2	?
	7	Is physically aggressive (for example, hits, kicks, bites, etc.).	0	1	2	?
	8	Is stubborn or sullen.	0	1	2	?
	9	Says embarrassing things or asks embarrassing questions in public (for example, "You're fat," or "What's that big red thing on your nose?").	0	1	2	?
	10	Behaves inappropriately at the urging of others.	0	1	2	?

Section C

					Circle "?" If You Have a Question
Start Ages 3+	1	Sucks thumb or fingers.	0	1	2	?
	2	Wets bed or must wear diapers at night.	0	1	2	?
	3	Acts overly familiar with strangers (for example, holds hands, hugs, sits on lap, etc.).	0	1	2	?
	4	Bites fingernails.	0	1	2	?
	5	Has tics (that is, involuntary blinking, twitching, head shaking, etc.).	0	1	2	?

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Problem Behaviors Part 1, continued

Response Options: 2 = Often, 1 = Sometimes, 0 = Never

Section C, *continued*					Circle "?" If You Have a Question
6	Grinds teeth during the day or night.	0	1	2	?
7	Has a hard time paying attention.	0	1	2	?
8	Is more active or restless than others of same age.	0	1	2	?
9	Uses school or work property (for example, telephone, Internet access, office supplies, etc.) for unapproved personal purposes.	0	1	2	?
10	Swears.	0	1	2	?
11	Runs away (that is, is missing for 24 hours or longer).	0	1	2	?
12	Is truant from school or work.	0	1	2	?
13	Ignores or doesn't pay attention to others around him or her.	0	1	2	?
14	Uses money or gifts to "buy" affection.	0	1	2	?
15	Uses alcohol or illegal drugs during the school or work day.	0	1	2	?

Problem Behaviors Part 2

Response Options: 2 = Often, 1 = Sometimes, 0 = Never, S = Severe, M = Moderate

Section D							Circle "?" If You Have a Question
Start Ages 3+	1	Engages in inappropriate sexual behavior (for example, exposes self, masturbates in public, makes improper sexual advances, etc.).	0	1	2	S M	?
	2	Is obsessed with objects or activities (for example, constantly repeats words or phrases, is preoccupied with mechanical objects, etc.).	0	1	2	S M	?
	3	Expresses thoughts that do not make sense (for example, talks about hearing voices, seems delusional, etc.).	0	1	2	S M	?
	4	Has strange habits or ways (for example, makes repetitive noises, odd hand movements, etc.).	0	1	2	S M	?
	5	Consistently prefers objects to people (for example, pays more attention to objects than to people, etc.).	0	1	2	S M	
	6	Displays behaviors that cause injury to self (for example, bangs head, hits or bites self, tears at skin, etc.).	0	1	2	S M	?
	7	Destroys own or another's possessions on purpose.	0	1	2	S M	?
	8	Uses bizarre speech (for example, has conversations with self in public, speaks in phrases or sentences that have no meaning, repeats same word or phrase over and over, etc.).	0	1	2	S M	?
	9	Is unaware of what is happening around him or her (for example, seems to be in a "fog," stares blankly, etc.).	0	1	2	S M	?
	10	Rocks back and forth repeatedly.	0	1	2	S M	?
	11	Is unusually fearful of ordinary sounds, objects, or situations.	0	1	2	S M	?
	12	Remembers odd information in detail years later.	0	1	2	S M	?
	13	Is unable to complete a normal school or work day because of chronic pain or fatigue.	0	1	2	S M	?
	14	Is unable to complete a normal school or work day because of psychological symptoms.	0	1	2	S M	?

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2 RATIONALE

This clinical protocol amendment 2 (will be incorporated into the protocol creating Clinical Protocol Version 3, Date 20 September 2016) addresses the following issue(s):**Compliance with U.S. Regulatory Requirements**

In order to comply with requests received from the United States Food and Drug Administration (FDA), the protocol has been amended as follows:

2.1.1 Extend Age Range in the Pilot Phase; Second Cohort

As the pivotal trial involves patients from 1 month to 24 months, the age range in cohort 2 of the pilot phase will be extended from 6 months to 24 months to 1 month to 24 months. The inclusion criterion has been updated.

2.1.2 Clarification of Allowable Changes in Concomitant Medications

The FDA suggested that allowing increased doses of patients' infantile spasm (IS) therapy may make the treatment effects of GWP42003-P difficult to interpret. The following clarifications have therefore been made:

- During the pilot and pivotal phase, every effort should be made to keep the patient's current IS therapy stable; current therapy may be tapered, in response to AEs, at the discretion of the investigator.
- Increases in the dose of existing concomitant AEDs or commencement of new AEDs are not allowed during the pilot or pivotal phases.
- During the OLE, in response to AEs or if there are symptoms of toxicity due to a suspected drug-drug interaction, the investigator may adjust the dose of GWP42003-P or other concomitant AEDs following discussion with the GW medical monitor.
- In Section 8.3, text has been added to prohibit any increases to existing AEDs or commencement of new AEDs during the pilot or pivotal phase.

2.1.3 Utilization of Central Video Electroencephalography Readings

The FDA queried how the central video-electroencephalography (EEG) reader would be used in practice. They stated that, for enrollment, the study should use a single expert central reader to adjudicate the presence of hypsarrhythmia and wanted to understand the process for disagreements between local and central EEG readings. In response to this, the following clarifications have been made within the protocol:

- Provided details of the Central Reader in Appendix 2.3.
- Stated that the retrospective assessment of the video-EEGs by the central reader will be considered final.

2.1.4 Statistical Considerations

To clarify how dropouts/missing data will be handled in the analyses, Section 13.6.2.2 has been updated:

- Details of sensitivity analyses due to missing data and handling of patients potentially receiving rescue medication will be fully detailed in the statistical analysis plan prior to unblinding.

2.1.5 Data Safety Monitoring Committee

The protocol has been updated to include:

- Statement that ad hoc meetings of the Data Safety Monitoring Committee will take place based on new or unexpected safety signals.

2.2 Inclusion/Exclusion Criteria

- Clarification that approved IS therapies include therapies that have been approved in the United States or Europe.
- Clarification that if a patient has a QT interval, corrected for heart rate with Bazett's formula (QTcB) of > 460 msec on ECG, the investigator should repeat the ECG 3 times and contact the GW medical monitor, prior to screen failure or entry into the pilot/pivotal phase.

- The previous use of the terms “enrolled/randomized” for patients entering the pilot/pivotal phases conflicted with the definition of an enrolled patient in the clinical protocol (which is that any patient whose parent(s)/legal representative has provided written informed consent to take part in the trial). Therefore, the protocol wording has been updated as follows to avoid any misunderstanding :
    - Any patient who has previously been included in the pilot or pivotal phase of this trial will be excluded.
    - Confirmation of elevations in transaminase levels will be required prior to screen failure or entry into the pilot or pivotal phase.

2.3 Withdrawal Criteria

Following questions from investigators regarding the QTcB withdrawal criterion, the following clarification has been included:

- If a patient has a QTcB of 500 msec or greater on ECG, or a shift from baseline of 60 msec or greater, the ECG should be repeated 3 times. If the QTcB criteria are confirmed then the patient should be withdrawn from the trial.
- Clarification that any requirement to increase the dose of concomitant AED(s) or add in new AED(s) may result in the patient being withdrawn from the trial.

2.4 Procedures

The following changes have been made:

- During a UK site visit, the site asked whether laboratory results prior to screening could be taken into account to reduce the amount of blood that needs to be taken. In line with this, the protocol now states that to minimize the volume of blood required, serum biochemistry and hematology results from samples analyzed up to 3 days prior to Visit 1 may be used. The samples must be analyzed at the same local laboratory that is being used for the clinical laboratory aspects of the trial.
- To allow limited rescreening of patients, a statement has been included such that, in exceptional circumstances, rescreening may be allowed following discussions with the GW medical monitor.

2.5 Changes to Information Recorded in the Paper Diary

The following changes have been made to reduce unnecessary caregiver burden:

- Epilepsy interventions will not be recorded in the paper diary, only concomitant AEDs and rescue medications.
- Only the drug name and dose level of each rescue medication administration will be required, not the number of times administered each day.

2.6 Minor Corrections and Clarifications

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

- Addition of transaminases into the abbreviations list for ALT and AST since GW approved global abbreviations list now allows both aminotransferase and transaminase in reference to these enzymes.
- Addition of statistical analysis plan into the abbreviations list.
- Updated information has been provided on completed GW studies, Expanded Access Program and Compassionate Use programs.
- Complete edit/reordering of the information presented within sections 13.6.2.2 through to 13.6.3.3 to ensure the relevant text correctly applies to each section.
- Alignment of wording between trial objectives, trial endpoints and statistical endpoints.
- The list of contract research organizations, clinical and bioanalytical laboratories and central EEG reader has been updated with current details.
- Clarification of the days where safety checks should be made during IMP dosing in pilot, pivotal and open-label extension phases.
- Reference list has been updated to include new reference (GWEP1544 CSR) and updated citations for CBD Investigator Brochure (Edition 9) and US FDA CFR Title 21.
- A copy of the Vineland-II questionnaire has been included for reference.
- Minor spelling/grammatical corrections have been made to improve consistency but these are not captured within this amendment document.

2 RATIONALE

This clinical protocol amendment 1 (will be incorporated into the protocol creating Clinical Protocol Version 2, Date 31 May 2016) addresses the following issue(s):**Compliance with U.S. Regulatory Requirements**

In response to comments received from the United States Food and Drug Administration (FDA), the protocol has been amended as follows:

2.1.1 Revised Clinical Phase and Overall Design

The trial phase has been revised from phase 2 to phase 3, and the design has been updated to reflect this. The trial will now comprise an initial open-label safety study comprising 2 cohorts of 5 patients (pilot phase), followed by a phase 3 efficacy study (pivotal phase). The 1 year open-label extension (OLE) will be open to patients who complete either phase.

Due to this change, the trial title, objectives, endpoints and patient numbers have been adjusted accordingly.

2.1.2 Use of a Data Safety Monitoring Committee

As the trial involves a vulnerable pediatric population, an independent data safety monitoring committee (DSMC) will be used. The DSMC will be used throughout the study and will consider safety of the patients, and confirm doses and dose regimens to be investigated in the pivotal phase. If required, following DSMC review, adjustment of doses and dose regimens will also take place following the first cohort of 5 patients in the pilot phase.

2.1.3 Addition of a Pilot Phase to Confirm Safety

Due to the lack of safety data in infants under 2 years of age, safety will be confirmed in a small group of patients in a hospital environment (pilot phase) before proceeding to the pivotal investigations. Therefore, the trial will be performed as 2 separate phases (pilot and pivotal) which will be run sequentially. All patients in the pilot phase will receive GWP42003-P (open-label) while all patients in the pivotal phase will be randomly allocated to GWP42003-P (1 of 2 dose levels) or matching placebo in a double-blind manner. As infants younger than 6 months are particularly vulnerable, all patients in the pilot phase will be over 6 months of age. The pivotal phase will only be enrolled after the DSMC

has reviewed data from the pilot phase and has confirmed that there are no safety issues.

Due to the rapid titration of the investigational medicinal product (IMP), all patients in the pilot phase will remain in the clinic as inpatients during the 4-day titration period. In both phases, compulsory clinic-based assessments will take place at the end of the titration period (i.e., Day 4) and OLE transition period (i.e., Day 19). In addition, daily safety checks will be made during the first week of IMP dosing during the pilot and pivotal phases (i.e., Days 1–7) and during the first week of OLE IMP dosing (i.e., Days 16–22).

2.1.4 Discussion of Approved Treatments for Infantile Spasms Prior to Enrollment

Due to the ethical issues regarding the enrollment of patients who have not failed all approved infantile spasms (IS) treatments, all approved therapies and treatment options must be discussed with the caregiver before the patient is considered for the trial.

2.1.5 Evaluation of Clinical Response and Continued Benefit

As it is unclear what length of treatment is optimal for IS, patients will be evaluated for clinical response by video-electroencephalogram (video-EEG) after 1 month of treatment and approximately every 3 months thereafter during the OLE phase. In addition, as only patients who show evidence of benefit should continue to be treated with GWP42003-P during the OLE phase, any patients who do not will be withdrawn from the trial. Patients who have not demonstrated complete resolution of IS, but have shown some benefit of treatment, may remain in the trial, but may receive other concomitant medications during the OLE phase. The option of withdrawing from the trial will be discussed with caregivers at each visit.

2.1.6 Clarification of Video-EEG Evaluation

The protocol has been updated to clarify that it is important for at least one full sleep-wake cycle to be observed in each video-EEG assessment. In addition, any video-EEG findings considered to represent an adverse event must be documented on the case report form.

2.1.7 Monitoring Plasma Levels of Concomitant Antiepileptic Drugs

Since potential drug-drug interactions are still being evaluated for GWP42003-P, concomitant antiepileptic drug (AED) levels will be checked with clinical laboratory evaluation, as clinically indicated by symptoms of toxicity. In addition, as the risk of hepatotoxicity with valproate may be high in the proposed patient population, the protocol provides guidance for investigators to pay particular attention to liver enzyme levels in patients who are taking valproate.

2.1.8 Clarification of Cannabidiol Metabolites

The protocol has been updated to clarify that the following metabolites of CBD will be assessed:

- 6-hydroxy-cannabidiol (6-OH-CBD).
- 7-hydroxy-cannabidiol (7-OH-CBD).
- 7-carboxy-cannabidiol (7-COOH-CBD).

2.2 Duration of Open-label Extension Phase

The 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.

2.3 Clarification of Procedures Following the Investigator's Decision to Discontinue GWP42003-P During the Open-label Extension Phase

The protocol has been updated to clarify that the investigator may consider discontinuing IMP during the OLE phase if the patient has become spasm-free and that the patient's parent(s)/legal representative will be encouraged to allow the patient to remain in the trial to complete the remaining assessments (up to 1 year). Instructions are provided regarding the discontinuation process as well as on restarting GWP42003-P in cases of relapse.

2.4 Revised Eligibility Criteria

The eligibility criterion excluding patients who have received an IMP within the 3 months prior to the screening visit has been revised to clarify that IMP relates to any product received as part of a clinical trial (as opposed to the off-label use

of a licensed drug). In addition, due to the urgency of establishing effective treatment in this patient population, the minimum time required before these patients may be considered eligible for this trial has been changed to 5 half-lives prior to the screening visit. Similarly, the minimum time required before patients who have used cannabis/cannabinoids has been reduced to 1 month prior to the screening visit.

2.5 Clarification of Withdrawal Criterion

Due to the potential impact on the intention to treat population, the criterion regarding withdrawal of patients who do not continue to meet the eligibility criteria has been revised to clarify that patients must be withdrawn only if there are safety concerns; patients may be withdrawn if the concerns are non-safety related.

2.6 Revised Pharmacokinetic Blood Sampling Times

Since safety blood samples will be taken on Day 4 and Day 19, the proposed pharmacokinetic (PK) blood sampling times have been revised to ensure that the maximum amount of blood taken will not exceed a total of 50 mL within the initial 8-week period of the trial. Additionally, PK sampling will only take place during the pivotal phase.

2.7 Removal of Caregiver Impression of IMP Palatability Questionnaire

The Caregiver Impression of IMP Palatability questionnaire has been removed from the trial, as minimal feedback is expected in this patient population as it will be difficult to determine due to the age of the patients.

2.8 Removal of THC Testing

Δ^9-tetrahydrocannabinol (THC) testing has been removed from the trial, to reduce the burden on the patient and caregiver. Furthermore, rapid decision making and treatment is needed for this patient population, and this testing would add additional complexity while being of minimal benefit in this patient population.

2.9 Citation of Recently Disseminated Data

The protocol has been updated to include citations of GWP42003-P safety and efficacy data presented at the American Epilepsy Society 69th Annual Meeting[1,2].

2.10 Patient Confidentiality

The protocol has been updated to clarify that all video-EEG recordings will be kept confidential and secure, and that the patient's anonymity must be maintained if data are presented.

2.11 Minor Corrections and Clarifications

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

- Only patients who complete the pilot or pivotal phase will have the opportunity to continue to the OLE phase; those who withdraw early are ineligible.
- Since absorption of topical mammalian target of rapamycin (mTOR) inhibitors is lower than oral formulations, only oral mTOR inhibitors may not be used.
- The eligibility criterion regarding breastfeeding has been combined with the criterion regarding abstention.
- The physical description of the IMP has been updated to "clear, colorless to yellow solution".
- The information to be recorded in the paper diary has been added to the synopsis for clarity.
- The full 4-week safety follow-up period concludes with the safety follow-up visit.
- Caregivers will record IMP intake in the paper diary but will not be required to record the volume of IMP administered on each treatment day.
- The assessments listed as bullet points in Section 9.1.1.2 (Visit 2 [Day 1]) must be conducted prior to receiving the first dose of IMP.

- The timings of any PK blood draws must be recorded, as well as IMP dosing time and the timing of concomitant AEDs and feeds/meals around the time of PK sampling.
- Vital signs and clinical laboratory samples must be assessed/collected on Day 4.
- In the OLE phase, all visit days and visit windows are in relation to Visit 2.
- Medical history includes prior and current seizures/spasms.
- The laboratory manual should be referred to for analysis of clinical laboratory samples.
- Since local laboratories will be used, all laboratory results must be documented on the case report form.
- The dose and number of times rescue medication is given each day will be recorded in the paper diary.
- The patient's parent(s)/legal representative would voluntarily withdraw the patient (rather than the patient withdrawing themself, due to their age).
- All statistical analyses will be conducted at the 5% level of significance.
- The end of the evaluable period for the OLE phase is defined as the last day on which a study-related assessment was undertaken during the OLE phase as opposed to the last day on which the study IMP was taken.
- Participation in the trial would not delay initiation with the next recognized IS therapy if the patient had failed all recognized IS therapies at enrollment.
- IMP will not be dispensed at the end of OLE treatment/withdrawal visit unless required for the taper period.
- Investigator Global Impression of Change (IGIC) is updated to Physician Global Impression of Change (PGIC) for consistency with other GW trials.
- Only a patient number will be used (screening numbers will not be utilized).

- Definition of status epilepticus has been added. Additionally, convulsive and non-convulsive status epilepticus events are considered to be medically significant and should be reported to the sponsor as medically significant serious adverse events.
- The caregiver should return the completed caregiver diary following the safety follow-up visit.
- Guidance regarding transaminase levels, laboratory testing and withdrawals.
- Preliminary data from the recently completed GW trial GWEP1332 (Dravet) added.
- Daily safety checks (Day 2 to 7 [inclusive] and Day 16 to 22 [inclusive]) to be made daily (including weekends, if possible), and where applicable they will be incorporated into scheduled visits (e.g., Day 4 and Day 19).
- Provision for transaminase levels to be repeat tested prior to enrollment /randomization/withdrawal, in case of elevated levels as specified in the exclusion criterion and the withdrawal section.

3 IMPLEMENTATION OF THE AMENDMENT

The changes detailed in this amendment will be issued as Clinical Protocol Version 2, Date 31 May 2016. It will be kept in the trial master file (TMF) at GW as well as in each investigational site file and, if applicable, pharmacy site file.

Section 4 (Presentation of Amended Text) is not included in this amendment document. The justification is as follows; Version 1 of the GWEP15100 Clinical Protocol was used for an initial submission to the FDA. Following feedback from the FDA significant changes have been made to protocol Version 1, including conversion of the trial from phase 2 to phase 3, increasing the trial's complexity. Due to the significant number of changes an agreement has been reached between GW Clinical Quality Assurance, Medical Writing and the Clinical Operations departments that the full details of all the amended text will not be documented here, but a summary of, and the rationale for, the changes will be outlined in Section 2 above. For documentation purposes, a track changed