TITLE PAGE

Protocol Title:

A randomized, double-blind, placebo-controlled, multisite, Phase 3 study to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P) in children and adolescents with epilepsy with myoclonic-atonic seizures

Protocol Number: GWEP20238

Amendment Number: 2.0

Product Code: GWP42003-P (cannabidiol oral solution)

Brief Title:

A safety and efficacy study of cannabidiol oral solution (GWP42003-P) in children and adolescents with epilepsy with myoclonic-atonic seizures between 1 and 18 years of age, inclusive.

Phase: 3

Sponsor Name: Jazz Pharmaceuticals Inc. on behalf of GW Research Ltd.

Legal Registered Address: 3170 Porter Drive, Palo Alto, CA 94304.

Regulatory Agency Identifier Number(s)

IND: [redacted]

EudraCT: 2021-003094-61

Document Version and Approval Date: Amendment 2.0 (Version 4)

Refer to the final page of this protocol for electronic signature and date of approval.

INVESTIGATOR AGREEMENT

I have read the attached clinical study protocol entitled "A randomized, double-blind, placebo-controlled, multisite, Phase 3 study to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P) in children and adolescents with epilepsy with myoclonic-atonic seizures" and agree to abide by all provisions set forth therein.

I agree to comply with the ICH Harmonised Guideline on GCP, Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of participants during the study and for all study-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 the sponsor.

Site: _____

Print name: _____ Date: _____

Investigator (DD Month YYYY)

Signature: _____

Sponsor Authorization

Print name: _____ Date: _____

[redacted] Clinical Development or Designee (DD Month YYYY)

Signature: _____

Medical monitor name and contact information can be found in Appendix 1: Study Contacts.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2.0 (Version 4)	Refer to the final page of this protocol for electronic signature and date of approval.
Amendment 1.1 (Version 3)	25 August 2022
Amendment 01 (Version 2)	21 June 2022
Original Protocol (Version 1)	13 September 2021

Amendment 2.0

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in Amendment 2.0 was to ensure alignment of study procedures globally and to revise the statistical methodology per the CID meeting outcome with the FDA. Specific updates incorporated into Amendment 2.0 are listed below.

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page 10.1.2 Sponsor Contact Details	Updated sponsor name and address. Replaced “GW” with “the sponsor” throughout the document where applicable.	For clarification.
1.1 Synopsis 2.2 Study Rationale 2.3 Benefit/Risk Assessment 4.2 Scientific Rationale for Study Design 6.1 Study Intervention(s) Administered	Removed “OS (GWP42003-P)” as study IMP, where applicable.	For correction.
1.1 Synopsis 4.2 Scientific Rationale for Study Design	Primary aim for Part A updated to focus on efficacy.	For correction.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints	Reordered the key secondary and secondary objectives and endpoints for Part A and Part B.	To put a higher priority on the evaluation of important additional epilepsy-related improvement in global clinical symptoms (as directly reported by caregivers/participants) resulting from treatment with study medication.
1.1 Synopsis 3 Objectives and Endpoints 8.1.4 Participant eDiary 9.4.2 Primary Endpoint(s) 9.4.3.1 Key Secondary Endpoints [redacted]	Primary Endpoint for Part A and B revised to "Change in EMAS-associated seizure frequency during the treatment period compared to baseline" and similar changes made to other seizure frequency endpoints. Added the following secondary endpoint for Part A: "Proportion of participants who achieve ≥ 25%, ≥ 75%, and 100% reduction from baseline in EMAS-associated seizures over the 14-week treatment period." Added the following secondary endpoint for Part B: "Proportion of participants who achieve ≥ 25%, ≥ 75%, and 100% reduction in EMAS-associated seizures from baseline." Removed secondary and primary endpoint "Physical examination procedures" from Part A and Part B of objectives and endpoints. Removed the following secondary endpoint for Part B: "Change from baseline in number of EMAS associated seizure free days." [redacted]	For clarification.
1.1 Synopsis 3 Objectives and Endpoints 9 Statistical Considerations	Revised text for "Statistical Hypothesis;" "Sample Size Determination;" "Analysis Sets;" "Statistical Analyses;" "General Considerations;" "Primary, Secondary, [redacted];" and "Interim Analyses."	To change statistical considerations after consultation with the FDA as part of the FDA CID Program.
9.4.5 Safety Analysis	Updated text for "Clinical Laboratory Data" and "Vital Signs, ECG, Physical Examination and Other Safety Data."	For clarification.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis Part A and Part B 4.1 Overall Design	Added the following text "if participants discontinue treatment prematurely, they should be encouraged to complete the end of treatment visit and the taper period and remain in the study."	For clarification.
1.1 Synopsis 4.4 Number of Participants	Reduced maximum sample size from 240 to 120 and up to 60 per treatment arm.	To change study sample size after consultation with the FDA as part of the FDA CID Program.
	Revised to include "interim analyses when 60, 75, 90, and 105 participants are randomized."	To change study sample size and interim analysis after consultation with the FDA as part of the FDA CID Program.
1.1 Synopsis 5.1 Inclusion Criteria 5.2 Exclusion Criteria 6.8 Concomitant Therapy	Updated inclusion criterion #6, exclusion criterion #37, and third bullet point under concomitant therapy to shorten the required stability period on a ketogenic diet/epilepsy dietary therapy to ≥ 28 days prior to starting the baseline period. Revised inclusion criterion #7 to "Participant has failed ≥ 1 prior ASM due to inadequate seizure control." Revised EEG range to **≥ 2.5** to 6 Hz in inclusion criterion #8.	For flexibility and clarification in the enrollment of targeted study population.
1.2 Schema: Part A and Part B	Replaced both schema with the following updates: Part A: n≤~~120~~**60**, ~~AEDs~~**ASMs**, ~~CBD~~**GWP42003-P**, and ~~Dose optimized based on efficacy and safety~~ **Baseline ASMs (n ≤ 60).** Part B:~~ AEDs~~**ASMs**	For correction.
1.3 SoA	Removed body weight measurement at the end of Taper Period in Part A in consistency with Part B.	For correction.
	Specified "Section 8.1.4" under "PK blood" for reference.	For clarification.
	Corrected time between End of Taper Period and Safety FU Visit in Part B to 28 days instead of 32 days and day corrected to "376" instead of "380."	For correction.
2.1.2 Study Intervention Background	Included "other geographic expansion areas" along with US and EU as commercial markets for GWP42003-P.	For clarification.
4.1 Overall Design	Deleted "A safety follow-up visit (phone call) will be conducted 4 weeks after the end-of-taper visit."	To remove duplicated information.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Removed statement in inclusion criterion #4 that "At least 1 myoclonic-atonic seizure is mandatory and must be observed during the baseline period."	For flexibility in the enrollment of the targeted study population as the key requirement for myoclonic-atonic seizures can be based on medical history to confirm the diagnosis of EMAS with the existing inclusion criteria and does not need to be restricted to the baseline period. Note that independent confirmation of the EMAS diagnosis by the epilepsy consortium remains a requirement.
	Updated inclusion criterion #12 to include "≥ 25 days of daily Reminder Diary entries" instead of "≥ 25 days of entries."	To focus eligibility on completion of Reminder Diary.
5.2 Exclusion Criteria 6.8 Concomitant Therapy	Added "Is currently treated with Epidiolex/Epidyolex or recently received treatment with Epidiolex/Epidyolex within 28 days prior to screening (Part A Visit 1)" as exclusionary criterion # 31.	For clarity to avoid misinterpretation during audits/inspection.
	Revised and clarified exclusion criterion # 32 to exclude participants who experienced a lack of efficacy/poor tolerability to an adequate regimen of Epidiolex/Epidyolex and allow consideration of participants who discontinued treatment for reasons other than safety, tolerability, or lack of efficacy and previously received Epidiolex/Epidyolex ≥ 28 days prior to screening (Part A Visit 1) after consultation with medical monitor/sponsor.	
	Revised text under concomitant therapy for the following: • Any medication or vaccine… ~~or other previous or concomitant AEDs~~ that the participant is receiving within 3 months of Screening... • **Additionally,** ~~All~~ **all** ~~AED~~**ASMs**, antiepileptic therapies, and rescue medications taken during the participant's life ~~or receives during the study~~**(previous and/or current use)**..."	For clarification.
5.2 Exclusion Criteria	Removed exclusion criterion # 33 "treatment with general anesthetic in the 28 days prior to screening."	For flexibility in the enrollment of targeted study population.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention 8.2.1.1 C-SSRS	Updated definition of C-SSRS and the category of participants to which it applies, in exclusion criterion # 45. Specified age range of participants for using C-SSRS and added information regarding completion of C-SSRS.	For clarification.
6.7 Treatment of Overdose	Added wording "(when possible)" to the third bullet point.	For standardization.
7.1 Discontinuation of Study Intervention	Added new bullet point to include participants who decline "to continue receiving IMP or other protocol protocol-required therapies or procedures at any time during the study" as a reason for removal from IMP.	For consistency.
8.1.4 Participant eDiary	Added text "and 24 hours prior to Part A Visit 9 (or End of Treatment Visit if the participant discontinues treatment prior to Part A Visit 9)" for food eDiary completion.	For clarification.
[redacted]	[redacted]	[redacted]
10.1.2 Sponsor Contact Details	Replaced details for Pharmacovigilance Department - SAE Reporting (24-hour reporting) and updated Sponsor's Medical Expert details.	For correction.
10.1.3 Contract Research Organizations	Added missing information.	For correction.
10.2.5.1 The Epilepsy Study Consortium	Defined TESC.	For clarification.
10.4.2 Definition of SAE	Removed "positive COVID-19 test results" under SAE definition.	For correction.
Throughout	Editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Abbreviations: ASM = antiseizure medication; [redacted] CID = Complex Innovative Trial Design; COVID-19 = Coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; eDiary = electronic diary; EEG = electroencephalogram; EMAS = epilepsy with myoclonic-atonic seizures; EU = European Union; FDA = Food and Drug Administration; FU = follow-up; GW = GW Research Ltd; IMP = investigational medicinal product; OS = oral solution; PK = pharmacokinetic(s); SAE = serious adverse event; SoA = schedule of activities; *status epilepticus* = any seizure lasting 30 minutes or longer; TESC = The Epilepsy Study Consortium; US = United States.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A randomized, double-blind, placebo-controlled, multisite, Phase 3 study to investigate the efficacy and safety of cannabidiol oral solution (GWP42003-P) in children and adolescents with epilepsy with myoclonic-atonic seizures

Brief Title:

A safety and efficacy study of cannabidiol oral solution (GWP42003-P) in children and adolescents with epilepsy with myoclonic-atonic seizures between 1 and 18 years of age, inclusive.

Phase: 3

Indication: Treatment of seizures associated with epilepsy with myoclonic-atonic seizures (EMAS) syndrome in participants between 1 and 18 years of age, inclusive.

Study Rationale:

EMAS, also known as Doose syndrome, myoclonic-astatic epilepsy, or myoclonic-atonic epilepsy, is a childhood-onset idiopathic generalized seizure disorder. EMAS is characterized by multiple seizure types; however, myoclonic-atonic seizures are the hallmark seizure type and are mandatory for the diagnosis of EMAS.

There are no FDA-approved treatment options specifically for EMAS and its associated primary seizure types (ie, myoclonic-atonic and/or atonic and/or myoclonic seizures) and no clear consensus treatment guidelines for EMAS. Thus, there is a clear unmet need for the development of effective and well-tolerated treatments that target the primary seizures associated with EMAS.

Based on the results of several Phase 3 studies and open-label studies with GWP42003-P in the treatment of other pediatric epilepsy syndromes, GWP42003-P may be an appropriate candidate to investigate for the treatment of EMAS.

Therefore, the primary aim of Part A of the study is to assess the efficacy of GWP42003-P compared to placebo as an adjunctive treatment for children with EMAS. The primary aim of Part B of the study is to evaluate the long-term safety and tolerability of GWP42003-P in participants with EMAS.

Objectives and Endpoints:

Part A

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GWP42003-P compared with placebo in reducing the frequency of EMAS-associated seizures	• Change in EMAS-associated seizure frequency (myoclonic-atonic, atonic, tonic, clonic, or tonic-clonic) during the 14-week treatment period compared to baseline

Key Secondary	
• To evaluate the rate of treatment response to GWP42003-P compared with placebo in reducing the frequency of EMAS-associated seizures	• Proportion of participants who achieve ≥ 50% reduction from baseline in EMAS-associated seizures over the 14-week treatment period
• To evaluate the effect of GWP42003-P compared with placebo on caregiver impression of change	• CGIC score at Week 14
• To evaluate the effect of GWP42003-P in reducing the frequency of all seizure types compared with placebo	• Change in total seizure frequency during the 14-week treatment period compared to baseline
Secondary	
• To evaluate the effect of GWP42003-P compared with placebo on physician impression of change	• PGIC score at Week 14
• To evaluate the effect of GWP42003-P compared with placebo on additional antiepileptic measures from daily seizure diaries	• Proportion of participants who achieve ≥ 25%, ≥ 75%, and 100% reduction from baseline in EMAS-associated seizures over the 14-week treatment period • Proportion of participants who achieve ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction from baseline in total seizures over the 14-week treatment period • Change from baseline in number of EMAS-associated seizure-free days over the 14-week treatment period • Proportion of participants with ≥25% and ≥ 50% reduction in the number of days per week with myoclonic seizures during the treatment period • Time to baseline seizure frequency
• To evaluate the safety and tolerability of GWP42003-P compared with placebo	• Frequency of TEAEs over the 14-week treatment period • Laboratory tests • Vital signs • ECG • Tanner Staging • Change in: o C-SSRS ideation score o Number of suicide attempts in the C-SSRS

Part B

Primary	
• To evaluate the long-term safety and tolerability of GWP42003-P in participants with EMAS	• Frequency of TEAEs over the 48-week treatment period • Laboratory tests • Vital signs • ECG • Tanner Staging • Change in: o C-SSRS ideation score o Number of suicide attempts in the C-SSRS
Key Secondary	
• To evaluate long-term effect of GWP42003-P on seizure frequency and additional measures	• Change in EMAS-associated seizure frequency (myoclonic-atonic, atonic, tonic, clonic, or tonic-clonic) compared to baseline • Proportion of participants achieving ≥ 50% reduction in EMAS-associated seizures • CGIC score • Change in total seizure frequency compared to baseline
Secondary	
• To evaluate long-term effect of GWP42003-P on additional measures	• PGIC score • Proportion of participants who achieve ≥ 25%, ≥ 75%, and 100% reduction in EMAS-associated seizures from baseline • Proportion of participants who achieve ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction in total seizures from baseline • Proportion of participants with ≥ 25% and ≥ 50% reductions in the number of days per week with myoclonic seizures

Abbreviations: CGIC = Caregiver Global Impression of Change; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = 12-lead electrocardiogram; EMAS = epilepsy with myoclonic-atonic seizures; PGIC = Physician Global Impression of Change; TEAE = treatment-emergent adverse event.

Estimands (Part A Only)

The primary estimand for this study is defined by the following 3 components:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: change in EMAS-associated seizure frequency during the 14-week treatment period compared to baseline.
- Measure of IMP effect: change in EMAS-associated seizure frequency during the treatment period, regardless of any intercurrent events. This measure of effect follows the treatment policy strategy for handling intercurrent events.

The first key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: proportion of participants who achieve ≧ 50% reduction from baseline in EMAS-associated seizures over the 14-week treatment period.
- Measure of IMP effect: proportion of responders during the treatment period, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

The second key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: CGIC score at Week 14.
- Measure of IMP effect: CGIC score at Week 14, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

The third key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: change in total seizure frequency during the 14-week treatment period compared to baseline.
- Measure of IMP effect: change in total seizure frequency during the treatment period, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

Overall Design:

- This is a multisite, double-blind, randomized, placebo-controlled, parallel-group study (Part A) to evaluate the safety and efficacy of GWP42003-P compared to placebo as a treatment for children and adolescents with EMAS, followed by an open-label extension phase (Part B).

Part A:

- The duration of study participation in Part A is approximately 26 weeks, which includes a 1- to 3-week screening period, 4-week baseline observation period, 14-week dose-optimization treatment period, 10-day taper period, and a safety follow-up period (4 weeks after end-of-taper visit).
- After the informed consent/assent form has been signed, participants will be screened to enter the study from Day -49 to Day -35 (Visit 1) and commence a 28-day baseline period beginning at Day -28 (Visit 2), before returning for a randomization visit and treatment initiation (Day 1 [Visit 3]).
- IMP administration during the 14-week treatment period will follow a flexible titration schedule to enable optimization of dosage.
- Visits 4 to 6 will be conducted as phone visits; Visit 7 will be completed in clinic, and Visit 8 will be completed in clinic or at home visit. Participants will then return to the study site for an end of treatment visit (Day 99 [Visit 9]). If a participant withdraws from the study prematurely (ie, before the end of treatment visit) an early withdrawal visit will be conducted, and a safety follow-up phone call will occur 4 weeks after their last dose of IMP. If a participant discontinues IMP prematurely, they should be encouraged to complete the end of treatment visit and the taper period and remain in the study. Participants not continuing to Part B of the study will return to the study site again at the end of the 10-day taper period (Day 110 [Visit 10]) and complete a phone safety visit at the end of the follow-up period (Day 138 [Visit 11]).
- Part B will be available to participants who complete Part A of the study and continue to meet all eligibility criteria and to participants for whom the investigator feels continued treatment in Part B represents a favorable risk-benefit assessment. Rollover into Part B should occur on the same day as Part A Day 99 (Visit 9).
- Unscheduled phone visits can occur at any time throughout Part A, as needed.

Part B:

- Part B will evaluate the long-term safety, tolerability, [redacted] of GWP42003-P for a period of 48 weeks in participants with EMAS-associated seizures. All participants in Part B will receive GWP42003-P.
- The duration of study for Part B will be approximately 54 weeks, which includes a 48-week treatment period (including a 2-week blinded titration [or transition] period for all participants), 10-day taper period, and a safety follow-up period (4 weeks after end-of-taper visit).
- Part B will be available to participants who complete Part A of the study and continue to meet all eligibility criteria and to participants for whom the investigator feels continued treatment in Part B represents a favorable risk-benefit assessment.
- Participants who continue into Part B of the study will proceed without the Part A taper period (Visit 10) and follow-up visit (Visit 11). The Part A end of treatment visit (Visit 9) procedures/data will then be utilized for Visit 1 of Part B (ie, the same procedures should not be repeated at Visit 9 of Part A and Visit 1 of Part B). If the

participant is continuing to Part B, IMP should only be dispensed at Part B Visit 1. If the participant is not continuing to Part B, IMP for the taper period will be dispensed at Part A Visit 9, as required.

- Participants who do not enroll in Part B at Visit 9 of Part A will be required to complete Part A and continue to an end-of-taper visit (Visit 10) and a follow-up visit (Visit 11).
- In order to maintain consistent exposure to IMP and maintain the integrity of the blind, participants will enter a 2-week blinded transition to Part B. Part B IMP will be titrated up to 10 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All participants will complete the transition and enter Part B taking GWP42003-P (Section 6.5 Part B) (Table 5).
- A safety follow-up visit (phone call) will be conducted 4 weeks after the end-of-taper visit. If a participant withdraws from the study prematurely (ie, before the end of treatment visit), an early withdrawal visit will be conducted, and a safety follow-up phone call will occur 4 weeks after their last dose of IMP. Participants who discontinue IMP prematurely should be encouraged to complete the end of treatment visit and taper period.

Schematics (Figure 1 for Part A and Figure 2 for Part B), presented in Section 1.2, depict the overall study design. A detailed outline of procedures and activities is provided in the Schedule of Activities (Table 1 for Part A and Table 2 for Part B).

Brief Summary:

The purpose of this study is to assess the change from baseline in seizure frequency of twice daily (BID) doses of cannabidiol (CBD; GWP42003-P) compared with placebo in children and adolescents with EMAS. Study details include:

Study Duration: Approximately 80 weeks (Part A: 26 weeks and Part B: 54 weeks)

Treatment Duration: Up to approximately 66 weeks for Part A and Part B (Part A up to 16 weeks including the taper period and Part B up to 50 weeks, including the taper period)

Visit Frequency: Weekly or monthly (study site visits, home visits, or phone visits). GWP42003-P is not available through an expanded access program.

Number of Participants:

Up to a maximum of 120 participants (up to 60 per treatment arm) will be randomized in Part A of this study.

Summary of Participant Eligibility

Male/female participants between 1 and 18 years of age, inclusive, with diagnosed EMAS with a minimum average frequency of ≥ 2 The Epilepsy Study Consortium-approved, countable, EMAS-associated seizures (myoclonic-atonic, atonic, tonic, clonic, or tonic-clonic) per week (≥ 8 seizures per month) at baseline, refractory to anticonvulsant treatment (failed ≥ 1 prior ASM) and treated with 1 or more ASMs on a stable regimen (≥ 28 days prior to starting the baseline period [Part A Visit 2]) or on a stable ketogenic diet/epilepsy dietary therapy (≥ 28 days prior to starting the baseline period [Part A Visit 2]) (Section 5.1 and Section 5.2).

Study Intervention(s)

GWP42003-P solution (100 mg/mL CBD in sesame oil with anhydrous ethanol (10% v/v), sweetener [sucralose], and strawberry flavoring).

Placebo solution (sesame oil) containing the excipients anhydrous ethanol (10% v/v), sweetener (sucralose), strawberry flavoring, and beta carotene.

Part A:

Participants will initiate IMP at a dose of 2.5 mg/kg BID (5 mg/kg/day morning and evening), and after 1 week, the dose will be increased to 5 mg/kg BID (10 mg/kg/day) as per randomization. Participants may then remain at this maintenance dose for 13 weeks.

For participants who are tolerating IMP at 10 mg/kg/day and require further reduction of seizures, dose escalation up to a maximum daily dosage of 20 mg/kg/day (in increments of 5 mg/kg/day [2.5 mg/kg BID] no more rapidly than every 7 days) may occur after Day 15 based on the investigator's assessment of safety and tolerability. If a dose becomes poorly tolerated in the investigator's opinion, the investigator may consider reducing the dose.

Part B:

Participants not entering Part B or who discontinue IMP early will down-titrate over a period of 10 days. Participants eligible to enter Part B will enter the blinded transition period. Part B GWP42003-P will be titrated to 10 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. For participants who are tolerating IMP at 10 mg/kg/day and require further reduction of seizures, dose escalation up to a maximum daily dosage of 20 mg/kg/day may occur after Day 15 based on the investigator's assessment of safety and tolerability. The IMP dose may be increased by increments of 2.5 mg/kg BID (5 mg/kg/day) no more rapidly than every 7 days, up to a maximum daily dosage of 20 mg/kg/day.

Assessments

The following assessments will be performed: informed consent/assent, eligibility check, medical history, epilepsy gene panel, demographics, physical examination, body weight, height, ECG, vital signs, electroencephalogram (if required) eligibility check, prior and concomitant medications recorded, electronic diary (eDiary) training, eDiary completion, questionnaires (C-SSRS, CGIC, PGIC, CGIC in Seizure Duration, [redacted] Treatment Credibility/Expectancy Questionnaire and Parent Version, [redacted], menstruation questions, tanner staging, and AE monitoring. Clinical laboratory tests including biochemistry, coagulation, hematology, urinalysis, pharmacokinetics, and pregnancy test will also be performed.

Statistical Considerations

[redacted]

[redacted]

Statistical Analyses for Primary/Secondary Endpoints

Part A:

- The analysis of the primary efficacy endpoint will utilize Bayesian methodology to borrow external data from the historical pivotal studies in DS, LGS, and TSC. Active treatment groups will be pooled across doses within each indication to achieve a single estimated historical treatment effect for each indication. A Bayesian hierarchical model that dynamically determines the amount of information to be "borrowed" from the historical studies in the estimation of the treatment effect in the EMAS population will be used.

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

- Primary endpoint analysis repeated using the following imputation methods for missing eDiary data during the treatment period only:
  - Any intermittent missing data for the number of seizures arising from unreported days in the eDiary will be imputed using the worst (highest number of seizures) of

the following for each participant: LOCF, NOCB and the mean daily number of seizures during the treatment period based on nonmissing data:

$$\frac{\text{Number of seizures}}{\text{Number of reported days in the eDiary}}$$

- For participants in the active arm who withdraw from the study due to an adverse event or lack of efficacy, missing eDiary data will be imputed as the baseline rate or the average seizure frequency during the treatment period, whichever is higher.

- To test the sensitivity of the results of the primary analysis to the degree of borrowing introduced by the dynamic borrowing prior, a model similar to the primary analysis model will explore a range of degrees of fixed borrowing of the historical data. More specifically, the variance of the Bayesian hierarchical distribution specified for the treatment effects across populations (Section 9.4.2) will be fixed across a set of values specified in the ADR ranging from very low (full borrowing) to very high (no borrowing). Summaries of the estimated treatment effect within each sensitivity analysis will be provided to assess the robustness of the primary analysis results to the degree of borrowing.

Part B:

All data collected during this part of the study will be summarized over time using appropriate descriptive statistics. Where baseline data are available from Part A, changes from baseline will also be presented as appropriate.

Interim Analyses

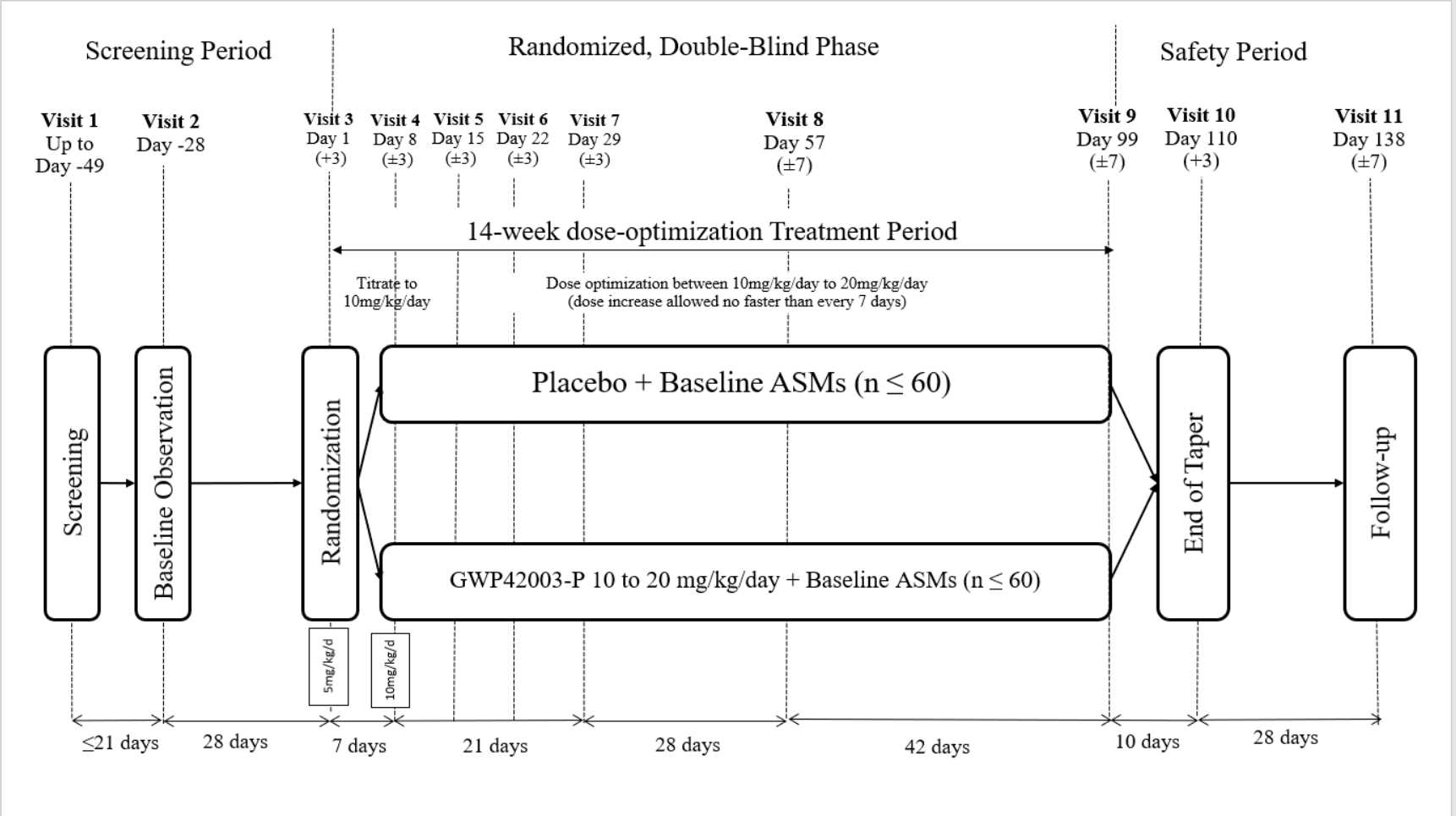
Interim analyses will be performed when 60, 75, 90, and 105 participants are randomized in Part A. The maximum sample size will be 120 randomized participants. The interim analyses or sample size updates will be based on the Goldilocks methodology in which Bayesian predictive probabilities are used to make sample size decisions.

Data Monitoring/Other Committee:

An IARC will be responsible for reviewing the data and providing recommendations based on the interim analyses of this study (see Section 9.5.1 for details).

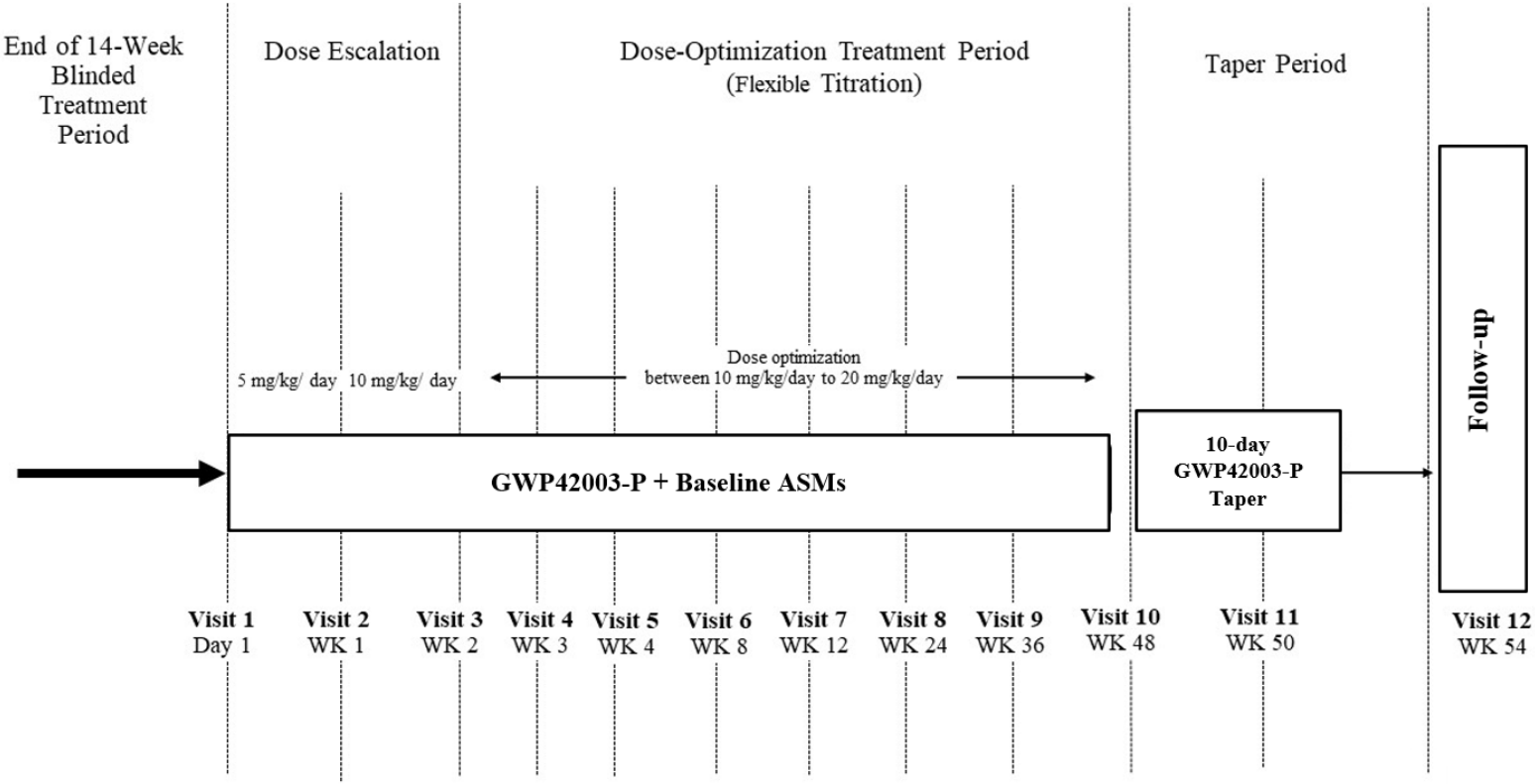
1.2. Schema

Figure 1: Study Schema: Part A



Abbreviations: ASMs = antiseizure medications; DRF = Diagnostic Review Form; eDiary = electronic diary; SIF = Seizure Identification Form; TESC = The Epilepsy Study Consortium.
Note: Additional information for dose titration is provided in Section 6.5 and Table 4.
Visit 2 will occur 14 to 21 days following Visit 1. Visit 2 cannot occur until the site has received final TESC approval of SIF/DRF and eDiary Seizure Classification Report.
Visit 3 will occur 28 days (+3 days) following Visit 2.

Figure 2: Study Schema: Part B



Abbreviations: ASMs = antiseizure medication; WK = week.
Note: Additional information for dose titration is provided in Section 6.5 and Table 5.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities: Part A

Study Period	Screening	Baseline Period	14-Week Dose-Optimization Treatment Period						EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	-	-	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**16**	**20**	
Day	**-49 to-35**	**-28**	**1**	**8**	**15**	**22**	**29**	**57**	**99**	**110**	**138**	
Visit Window (days)	-	-	**+3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**+3**	**±7**	
Visit Type	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Clinic***	**Clinic**	**Clinic**	**Phone**	
General Study Activities												
Informed consent/assent	X											
Demographics	X											
EEG	X											Section 5.1 and Section 8.1.2
Submission of SIF/DRF and eDiary Seizure Classification Report to TESC	X											Section 8.1.5 Visit 2 will occur after TESC approval of the SIF/DRF and eDiary Seizure Classification Report
Medical history	X											
Inclusion and exclusion criteria	X	X	X						X			Recheck before first dose of IMP. Part B eligibility will be confirmed before the participant rolls over to Part B, at Part A Visit 9

Table 1: Schedule of Activities: Part A

Study Period	Screening	Baseline Period	14-Week Dose-Optimization Treatment Period						EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	-	-	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**16**	**20**	
Day	**-49 to-35**	**-28**	**1**	**8**	**15**	**22**	**29**	**57**	**99**	**110**	**138**	
Visit Window (days)	-	-	+3	±3	±3	±3	±3	±7	±7	+3	±7	
Visit Type	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Clinic***	**Clinic**	**Clinic**	**Phone**	
Physical examination	X		X						X			Section 8.3.1 Includes measurement of height, length, and head circumference.
Serum pregnancy test	X											Section 8.3.5 May be performed more regularly if required by local regulations.
Urine pregnancy test			X						X			Section 8.3.5 Confirmed prior to first dose of IMP. May be performed more frequently if required by local regulations
Epilepsy gene panel			←==========→									Section 8.7. Optional, only completed once.
Body weight			X				X	X	X			Section 6.5 and Section 8.3.1.
Randomization			X									

Table 1: Schedule of Activities: Part A

Study Period	Screening	Baseline Period	14-Week Dose-Optimization Treatment Period						EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	
Week	-	-	0	1	2	3	4	8	14	16	20	
Day	-49 to-35	-28	1	8	15	22	29	57	99	110	138	
Visit Window (days)	-	-	+3	±3	±3	±3	±3	±7	±7	+3	±7	
Visit Type	Clinic	Phone	Clinic	Phone	Phone	Phone	Clinic	Clinic*	Clinic	Clinic	Phone	
IMP Administration												
eDiary Training	X											
Seizure Classification Training		X										
IMP and dosing eDiary training			X									
Dosing in clinic			X						X			
At home dosing			X	X	X	X	X	X	X	X		
IMP dosing frequency			2.5 mg /kg BID	5 mg/kg BID	5 or 7.5 mg /kg BID	5, 7.5, or 10 mg/kg BID				Reduce by 10% per day over 10 days		Section 6.5
eDiary Completion (Daily)	←==========									==========→		Section 8.1.4
eDiary Review		X	X	X	X	X	X	X	X	X		Section 8.1.4
IMP Dispensing			X				X	X	X			Section 8.11
IMP Return							X	X	X	X		
IMP Accountability							X	X	X	X		
IMP Dosing eDiary Compliance				X	X	X	X	X	X	X		Section 6.4

Table 1: Schedule of Activities: Part A

Study Period	Screening	Baseline Period	14-Week Dose-Optimization Treatment Period						EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	-	-	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**16**	**20**	
Day	**-49 to-35**	**-28**	**1**	**8**	**15**	**22**	**29**	**57**	**99**	**110**	**138**	
Visit Window (days)	-	-	+3	±3	±3	±3	±3	±7	±7	+3	±7	
Visit Type	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Clinic***	**Clinic**	**Clinic**	**Phone**	
Pharmacokinetics												
PK blood			X						X			Section 8.5 and Section 8.1.4
Safety and Tolerability												
CEQ-P	X											
Tanner Staging	X								X			
Menstruation question			X						X			Female participants only
CGIC	X								X			Memory aid only at Part A Visit 1
PGIC	X								X			Memory aid only at Part A Visit 1
[redacted]	[redacted]								[redacted]			[redacted]
[redacted]	[redacted]								[redacted]			
[redacted]	[redacted]								[redacted]			
[redacted]	[redacted]								[redacted]			
[redacted]	[redacted]								[redacted]			
Biochemistry & Coagulation	X		X				X	X	X			Section 8.3
Hematology	X		X				X		X			Section 8.3

Table 1: Schedule of Activities: Part A

Study Period	Screening	Baseline Period	14-Week Dose-Optimization Treatment Period						EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Week	-	-	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**16**	**20**	
Day	**-49 to-35**	**-28**	**1**	**8**	**15**	**22**	**29**	**57**	**99**	**110**	**138**	
Visit Window (days)	-	-	**+3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**+3**	**±7**	
Visit Type	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Clinic***	**Clinic**	**Clinic**	**Phone**	
Urinalysis	X		X						X			Section 8.3
ECG	X		X				X		X			Section 8.3.3
Vital signs	X		X				X	X	X	X		Section 8.3.2
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	
AE review	←==========										==========→	
Prior/concomitant medication review	←==========										==========→	

Abbreviations: AE = adverse event; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; [redacted] CEQ-P = Treatment Credibility/Expectancy Questionnaire and Parent Version; CGIC = Caregiver Global Impression of Change; CGIC SD = Caregiver Global Impression of Change in Seizure Duration; DRF = Diagnostic Review Form; ECG = 12-lead electrocardiogram; eDiary = electronic diary; EEG = Electroencephalogram; EOT = end of treatment; E/W = early withdrawal; IMP = investigational medicinal product; [redacted] PGIC = Physician Global Impression of Change; PK = pharmacokinetic; SIF = Seizure Identification Form; TESC = The Epilepsy Study Consortium; wks = weeks.

Note: *Clinic or home nurse. For visits carried out remotely, home nurse assessments include collection/dispensation of IMP, blood samples, and vital signs.

Table 2: Schedule of Activities: Part B

Study Period	Dose Escalation		Dose Optimization Treatment Period (Flexible Titration)							EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**24**	**36**	**48**	**50**	**54**	
Day	**1**	**8**	**15**	**22**	**29**	**57**	**99**	**169**	**253**	**337**	**348**	**376**	
Visit Window (days)	-	±3	±3	±3	±3	±7	±7	±7	±7	±7	+3	±7	
Visit Type	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Clinic***	**Clinic**	**Clinic***	**Phone**	**Clinic**	**Clinic**	**Phone**	
General Study Activities													
Physical examination	X						X	X		X			Section 8.3.1 Includes measurement of height, length, and head circumference.
Urine pregnancy test	X									X			Section 8.3.5 Confirmed prior to first dose of GWP42003-P. May be performed more regularly if required by local regulations.
Body weight	X				X	X	X	X		X			Section 6.5 and Section 8.3.1

Table 2: Schedule of Activities: Part B

Study Period	Dose Escalation		Dose Optimization Treatment Period (Flexible Titration)							EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**24**	**36**	**48**	**50**	**54**	
Day	**1**	**8**	**15**	**22**	**29**	**57**	**99**	**169**	**253**	**337**	**348**	**376**	
Visit Window (days)	-	±3	±3	±3	±3	±7	±7	±7	±7	±7	+3	±7	
Visit Type	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Clinic***	**Clinic**	**Clinic***	**Phone**	**Clinic**	**Clinic**	**Phone**	
IMP Administration													
At home dosing	←═══════										═══→		
IMP dosing frequency	2.5 mg/kg BID	5 mg/kg BID	5 or 7.5 mg/kg BID	5, 7.5, or 10 mg/kg BID							Reduce by 10% per day over 10 days		Section 6.5
eDiary Completion (At Least Weekly)	←═══════									═══→	X		Section 8.1.4
eDiary review		X	X	X	X	X	X	X	X	X	X		Section 8.1.4
IMP Dispensing	X				X	X	X	X		X			Section 8.11
IMP return					X	X	X	X		X	X		
IMP accountability					X	X	X	X		X	X		
IMP dosing eDiary compliance		X	X	X	X	X	X	X	X	X	X		Section 6.4
Safety and Tolerability													
Tanner Staging	X									X			
Menstruation question	X									X			Female participants only.
CGIC							X	X		X			

Table 2: Schedule of Activities: Part B

Study Period	Dose Escalation		Dose Optimization Treatment Period (Flexible Titration)							EOT or E/W	Taper Period	Safety FU	Notes
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**24**	**36**	**48**	**50**	**54**	
Day	**1**	**8**	**15**	**22**	**29**	**57**	**99**	**169**	**253**	**337**	**348**	**376**	
Visit Window (days)	-	±3	±3	±3	±3	±7	±7	±7	±7	±7	+3	±7	
Visit Type	**Clinic**	**Phone**	**Phone**	**Phone**	**Clinic**	**Clinic***	**Clinic**	**Clinic***	**Phone**	**Clinic**	**Clinic**	**Phone**	
PGIC							X	X		X			
[redacted]							[redacted]	[redacted]		[redacted]			
[redacted]							[redacted]	[redacted]		[redacted]			
[redacted]							[redacted]	[redacted]		[redacted]			
[redacted]							[redacted]	[redacted]		[redacted]			
[redacted]							[redacted]	[redacted]		[redacted]			
Biochemistry & Coagulation	X				X	X	X	X		X			Section 8.3
Hematology	X				X		X			X			Section 8.3
Urinalysis	X				X		X			X			Section 8.3
ECG	X				X		X			X			Section 8.3.3
Vital signs	X				X	X	X	X		X	X		Section 8.3.2
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	
AE review	←==========→												
Prior/concomitant medication review	←==========→												

Abbreviations: AE = adverse event; BID = twice daily; [redacted]
C-SSRS = Columbia Suicide-Severity Rating Scale; CGIC = Caregiver Global Impression of Change; [redacted] E/W = early withdrawal; ECG = 12-lead electrocardiogram; EOT = end of treatment; FU = follow-up; IMP = investigational medicinal product; [redacted]
PGIC = Physician Global Impression of Change.
Note: *Clinic or home nurse. For visits carried out remotely, home nurse assessments include: collection/dispensation of IMP, blood samples, height, length, head circumference, and vital signs.
Note: Part B Visit 1 is the same as Part A Visit 9. Data collected at Part A Visit 9, will be considered as Part B Visit 1 data. Procedures completed at Part A Visit 9 should not be repeated at Part B Visit 1.

2. INTRODUCTION

2.1. Background

2.1.1. Disease Background

EMAS, also known as Doose syndrome, myoclonic-astatic epilepsy, or myoclonic-atonic epilepsy, is a childhood-onset primary generalized seizure disorder (Zempel 2014). EMAS is also classified as a developmental epileptic encephalopathy. Symptoms typically present between 1 to 6 years of age, with an estimated 24% of diagnosed children experiencing their first afebrile seizure between 1 and 2 years of age (Hinokuma 2020) (Neubauer 2005). EMAS represents up to an estimated 2.2% of childhood-onset epilepsies and has an approximate incidence rate of 1 in 10,000 children (Neubauer 2005).

EMAS is characterized by multiple seizure types (myoclonic-atonic, myoclonic, atonic, generalized tonic-clonic, atypical absences, and tonic seizures). However, myoclonic-atonic seizures are the hallmark seizure type and are mandatory for the diagnosis of EMAS (Hinokuma 2020) (Neubauer 2005). Myoclonic-atonic seizures are myoclonic seizures that are followed by atonic seizures, which result in drop attacks. Myoclonic seizures specifically produce quick, jerking movements (Hinokuma 2020), and atonic seizures cause patients to lose tone briefly, causing small drops of the head or trunk.

The majority of children with EMAS have normal development prior to onset of seizures (Moeller 2014) or exhibit only mild developmental/cognitive delays. Moreover, when well controlled, up to 90% of patients with EMAS can have normal or mild cognitive impairment (Oguni 1992).

Children with EMAS who develop tonic seizures and whose disease progresses to episodes of nonconvulsive *status epilepticus*, tend to have a poor prognosis that is often accompanied by significant developmental delays, cognitive impairment, intractable epilepsy, and intellectual disability (Oguni 1992) (Stephani 2006) (Wirrell 2018) (Hinokuma 2020). The most common cognitive effects associated with inadequately controlled seizures include deficits in processing speed, language, verbal learning, and memory (specifically phonological working memory in EMAS patients) (Doose 1992) (Kilaru 2007). Traditional ASM treatment can contribute to these cognitive deficits, which can be worsened by drug-drug interactions as many of these patients will be on 2 or more ASMs (Kilaru 2007). Many of the clinical features of EMAS are also common to LGS, although myoclonic-atonic seizures do not predominantly occur in LGS and patients with EMAS are typically developmentally normal with normal EEG background early in the course.

2.1.2. Study Intervention Background

GWP42003-P is the product code for the IMP, purified GWP42003-P, a CBD under development by the sponsor for the treatment of a number of conditions.

CBD is extracted from the *Cannabis sativa* L. plant as CBD BDS and purified by crystallization from solvent to produce the CBD active substance.

Nonclinical pharmacology studies conducted by the sponsor have identified antiepileptic, anti-inflammatory, neuroprotective, and antipsychotic activities for CBD.

A large body of nonclinical toxicity data on purified CBD and CBD BDS suggests a good safety profile for CBD and a wide safety margin between the proposed clinical dose of CBD and the dose at which toxicity is noted.

There is an adequate margin of safety for CBD at a daily dose of up to 25 mg/kg/day in a pediatric and adult population.

A single ascending-dose study has been conducted where 4 groups of 6 healthy participants received single oral doses of either 1500, 3000, 4500, or 6000 mg GWP42003-P (GWEP1544). Each single oral dose was well or moderately well tolerated.

The sponsor has performed a number of clinical studies to investigate a range of possible indications for GWP42003-P. These include 5 positive pivotal studies that have supported its commercialization in the US, EU, and other geographic expansion areas as an ASM.

2.2. Study Rationale

There are no FDA-approved treatment options specifically for EMAS and its associated primary seizure types (ie, myoclonic-atonic and/or atonic and/or myoclonic seizures) and no clear consensus treatment guidelines for EMAS. Drug resistance to ASMs in children with EMAS is common and patients typically fail an average of 5 ASMs (Doose 1970) (Oguni 1992). While several ASMs, including valproic acid, clobazam, clonazepam, and levetiracetam have been reported to be beneficial, none of these agents have been evaluated in randomized, controlled studies in patients with EMAS. Furthermore, most of these ASMs have also been associated with safety and tolerability issues, such as sedation, ataxia, and cognitive impairment (Menlove 2015). Valproic acid may have the best efficacy for controlling myoclonic seizures, but it is associated with additional safety and tolerability issues (eg, risk for hepatotoxicity, teratogenicity, alopecia, etc.). EMAS is considered challenging to treat and often requires patients to tolerate difficult-to-maintain ketogenic diets (Goldberg 2001). Despite all the treatment options with ASMs and ketogenic diet, 20 to 50% of patients will not respond to treatment and only 50% will become seizure free (Kelley 2010) (Helmstaedter 2020). Thus, there is a clear unmet need for the development of effective and well-tolerated treatments that target the primary seizures associated with EMAS.

Based on the results of several Phase 3 studies and open-label studies with GWP42003-P in the treatment of other pediatric epilepsy syndromes, GWP42003-P may be an appropriate candidate to investigate for the treatment of EMAS. Results of 5 Phase 3 randomized, double-blind, placebo-controlled studies show robust efficacy of GWP42003-P for treatment of seizures associated with LGS (Devinsky 2018a) (Thiele 2018), DS (Devinsky 2017) (Miller 2020), and TSC (Thiele 2020b). These effects were sustained with long-term therapy up to 1.5 years (Devinsky 2016). There is also strong preclinical (Gofshteyn 2017) (Hess 2016) and real-world evidence (Devinsky 2016) (Devinsky 2018b) (Szaflarski 2018) (Thiele 2020a) suggesting that GWP42003-P might have antiepileptic properties that target a broad range of seizure types.

GWP42003-P was also used in patients with treatment-resistant epilepsies other than those already approved by the FDA, including EMAS, as part of an investigator-initiated, FDA-authorized EAP. Interim safety and efficacy data collected as part of open-label studies of

the EAP uphold the finding that GWP42003-P produces clinically significant reductions in seizures when used as an add-on ASM treatment (McCagh 2009) (Wu 2020). Thus, there is extensive evidence supporting GWP42003-P as an effective therapy for the treatment of EMAS.

The primary aim of the current study is to assess the efficacy and tolerability of GWP42003-P compared to placebo as an adjunctive treatment for children with EMAS. Secondary aims of the study include assessment of treatment differences in safety throughout the treatment period, change from baseline in antiepileptic measures, and subjective impression of change.

While the study is designed to specifically test the effect of GWP42003-P on seizures, [redacted]

2.3. Benefit/Risk Assessment

Participants in the current study may experience some improvement of symptoms (beyond that of an assessment of their medical status) from participating in the study. Refer to Section 2.2 for details regarding antiseizure efficacy observed in previous epilepsy clinical studies with GWP42003-P, including patients with EMAS from the EAP. The risks of participation are primarily those associated with adverse reactions to the IMP, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with GWP42003-P may be found in the current approved version of the IB (GWP42003-P IB).

GWP42003-P is purified CBD, approved in the US as Epidiolex®, indicated for the treatment of seizures associated with LGS, DS, and TSC in patients 1 year of age and older and approved in the EU, indicated for the adjunctive treatment of seizures associated with LGS and DS, in conjunction with clobazam, in patients 2 years of age and older and for adjunctive treatment of seizures associated with TSC in patient 2 years of age and older. The most commonly reported side effects include somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor-quality sleep; infections; pyrexia; and vomiting. Serious side effects include hepatocellular injury, somnolence and sedation, suicidal behavior and ideation, hypersensitivity reactions, and withdrawal of ASMs. Further information is included in the latest GWP42003-P (Epidiolex) United States Prescribing Information and/or Summary of Product Characteristics.

Overall, based on the extensive clinical safety and efficacy results of GWP42003-P demonstrated across 5 Phase 3 studies, 2 open-label studies, and the EAP in the treatment of pediatric epilepsy syndromes, it is believed that GWP42003-P has a favorable benefit-risk profile for the treatment of EMAS.

3. OBJECTIVES AND ENDPOINTS

3.1. Part A

Primary	
• To evaluate the efficacy of GWP42003-P compared with placebo in reducing the frequency of EMAS-associated seizures	• Change in EMAS-associated seizure frequency (myoclonic-atonic, atonic, tonic, clonic, or tonic-clonic) during the 14-week treatment period compared to baseline
Key Secondary	
• To evaluate the rate of treatment response to GWP42003-P compared with placebo in reducing the frequency of EMAS-associated seizures	• Proportion of participants who achieve ≥ 50% reduction from baseline in EMAS-associated seizures over the 14-week treatment-period
• To evaluate the effect of GWP42003-P compared with placebo on caregiver impression of change	• CGIC score at Week 14
• To evaluate the effect of GWP42003-P in reducing the frequency of all seizure types compared with placebo	• Change in total seizure frequency during the 14-week treatment period compared to baseline
Secondary	
• To evaluate the effect of GWP42003-P compared with placebo on physician impression of change	• PGIC score at Week 14
• To evaluate the effect of GWP42003-P compared with placebo on additional antiepileptic measures from daily seizure diaries	• Proportion of participants who achieve ≥ 25%, ≥ 75%, and 100% reduction from baseline in EMAS-associated seizures over the 14-week treatment period • Proportion of participants who achieve ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction from baseline in total seizures over the 14-week treatment period • Change from baseline in number of EMAS-associated seizure-free days over the 14-week treatment period • Proportion of participants with ≥ 25% and ≥ 50% reduction in the number of days per week with myoclonic seizures during the treatment period

	• Time to baseline seizure frequency
• To evaluate the safety and tolerability of GWP42003-P compared with placebo	• Frequency of TEAEs over the 14-week treatment period • Laboratory tests • Vital signs • ECG • Tanner Staging • Change in: o C-SSRS ideation score o Number of suicide attempts in the C-SSRS
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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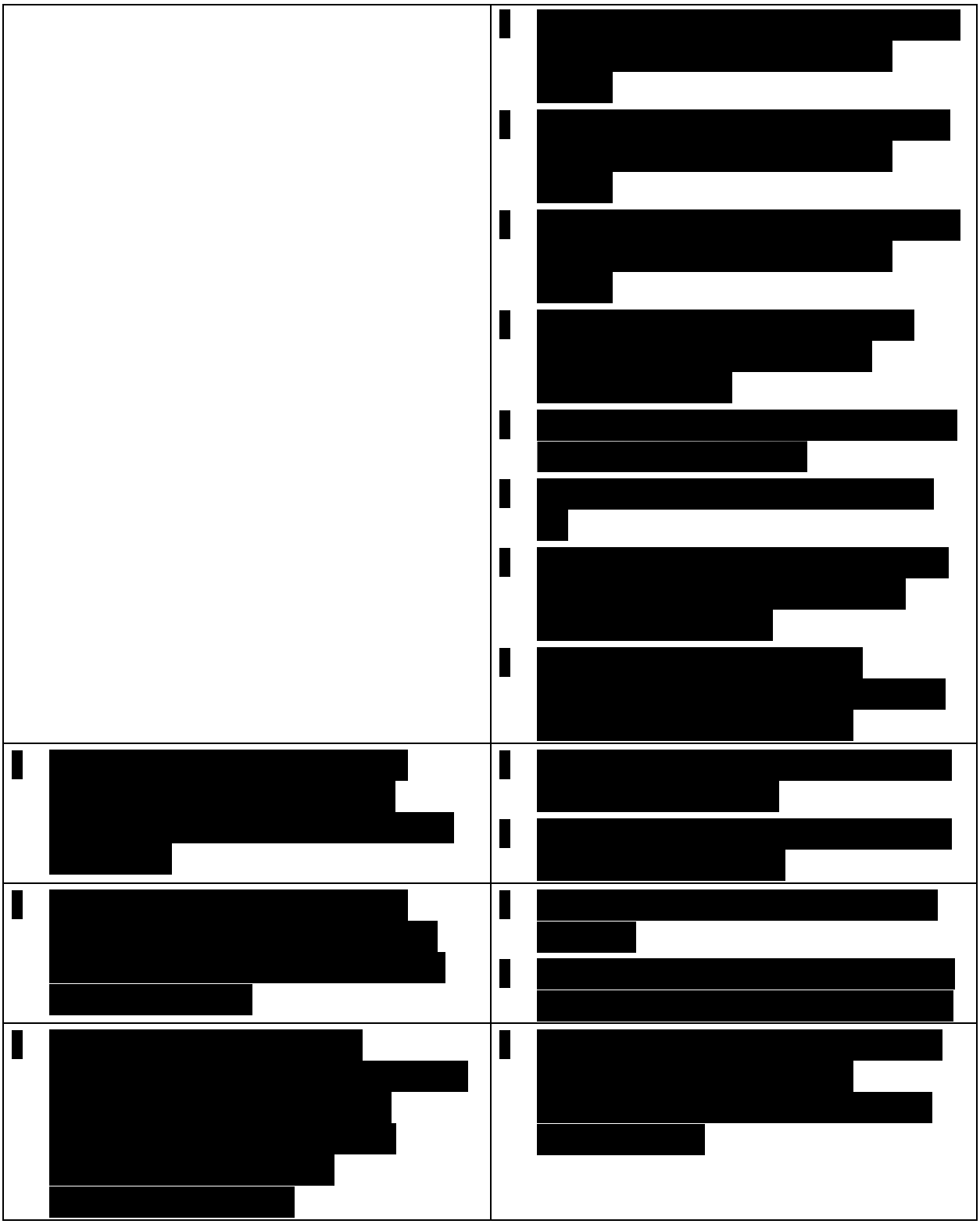


3.2. Part B

Primary	
• To evaluate the long-term safety and tolerability of GWP42003-P in participants with EMAS	• Frequency of TEAEs over the 48-week treatment period • Laboratory tests • Vital signs • ECG • Tanner Staging • Change in: o C-SSRS ideation score o Number of suicide attempts in the C-SSRS
Key Secondary	
• To evaluate long-term effect of GWP42003-P on seizure frequency and additional measures	• Change in EMAS-associated seizure frequency (myoclonic-atonic, atonic, tonic, clonic, or tonic-clonic) compared to baseline • Proportion of participants achieving ≥ 50% reduction in EMAS-associated seizures • CGIC score • Change in total seizure frequency compared to baseline
Secondary	
• To evaluate long-term effect of GWP42003-P on additional measures	• PGIC score • Proportion of participants who achieve ≥ 25%, ≥ 75%, and 100% reduction in EMAS-associated seizures from baseline • Proportion of participants who achieve ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction in total seizures from baseline • Proportion of participants with ≥ 25% and ≥ 50% reduction in the number of days per week with myoclonic seizures

Abbreviations: CBCL = Child Behavior Checklist; CBD = cannabidiol; CGIC = Caregiver Global Impression of Change; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = 12-lead electrocardiogram; eDiary = electronic diary; EMAS = epilepsy with myoclonic-atonic seizures; PGIC = Physician Global Impression of Change; *status epilepticus* = any seizure lasting 30 minutes or longer; TEAE = treatment-emergent adverse event.

Estimands (Part A Only)

The primary estimand for this study is defined by the following 3 components:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: change in EMAS-associated seizure frequency during the 14-week treatment period compared to baseline.
- Measure of IMP effect: change in EMAS-associated seizure frequency during the treatment period, regardless of any intercurrent events. This measure of effect follows the treatment policy strategy for handling intercurrent events.

The first key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: proportion of participants who achieve ≥ 50% reduction from baseline in EMAS-associated seizures over the 14-week treatment period.
- Measure of IMP effect: proportion of responders during the treatment period, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

The second key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: CGIC score at Week 14.
- Measure of IMP effect: CGIC score at Week 14, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

The third key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: change in total seizure frequency during the 14-week treatment period compared to baseline.
- Measure of IMP effect: change in total seizure frequency during the treatment period, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

4. STUDY DESIGN

4.1. Overall Design

This is a multisite, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of GWP42003-P compared to placebo as a treatment for children and adolescents with EMAS, followed by an OLE phase. The study will consist of 2 parts:

Part A:

The duration of study participation is approximately 26 weeks, which includes a 1- to 3-week screening period, 4-week baseline observation period, 14-week dose-optimization treatment period, 10-day taper period, and a safety follow-up period (4 weeks after end of taper visit).

After the ICF has been signed, participants will be screened to enter the study from Day -49 to Day -35 (Visit 1) and commence a 28-day baseline period beginning at Day -28 (Visit 2), before returning for a randomization visit and treatment initiation (Day 1 [Visit 3]).

On Day -28 (Visit 2), participants who continue to meet eligibility criteria will be contacted by phone and commence a 28-day baseline period, before returning for a randomization visit and treatment initiation (Day 1 [Visit 3]).

On Day 1 (Visit 3), participants will be randomized centrally in a 1:1 ratio to receive either GWP42003-P or matching placebo. Randomization will be stratified by clobazam use (on/off) and age of seizure onset (3 years of age and younger or older than 3 years of age).

IMP administration during the 14-week treatment period will follow a flexible titration schedule to enable optimization of dosage:

- Participants will be initiated on a dose of 2.5 mg/kg BID (5 mg/kg/day) on Day 1 (Visit 3), and after 1 week, the dose will be increased to 5 mg/kg BID (10 mg/kg/day) at the Day 8 (Visit 4) phone visit.
- For participants who are tolerating the IMP at 5 mg/kg BID (10 mg/kg/day) and require further reduction of seizures, investigators may choose to increase their dosage up to a maximum dosage of 10 mg/kg BID (20 mg/kg/day). The decision to titrate above 5 mg/kg BID (10 mg/kg/day) should be based on the observed efficacy, safety, and tolerability of the participant (including review of laboratory values) per the clinical judgement of the investigator.
- Starting at the Day 15 (Visit 5) phone visit, investigators have the option to titrate participants no more rapidly than 2.5 mg/kg BID (5 mg/kg/day) every 7 days, up to a maximum daily dosage of 20 mg/kg/day. The investigator will determine if further dose adjustments are warranted during unscheduled phone visits and/or scheduled clinic visits throughout the remainder of the 14-week treatment period. If dose change is warranted outside of a scheduled visit, the caregiver should be contacted by phone prior to making any dose increases above 10 mg/kg/day to assess the appropriateness of the dose increase based on the participant's reported clinical response and ensure the caregiver has received the updating dosing schedule reflecting the new target dose. This contact should be documented as an unscheduled phone visit in the eCRF.

- After Day 15 (Visit 5) phone visit, if in the investigator's opinion, a participant is experiencing a clinically meaningful improvement in EMAS-associated seizures, the investigator can choose to continue treatment at the participant's current dosage and may re-consider an increase in the dosage of IMP at either a later study visit, or at any time between study visits, as described above.
- If a participant reports any tolerability issues related to IMP, the investigator can also decrease a participant's current dosage. Dose decreases to below 10 mg/kg/day, based on safety and tolerability may occur at any time. Investigators should regularly monitor a participant's response to treatment and re-evaluate the need for adjustments to dosage (ie, increase, maintain, or decrease) at the next study visit, if applicable. The rationale for any dosage changes will be documented in the appropriate eCRF.

Participants will complete weekly scheduled phone visits at Day 8 (Visit 4), Day 15 (Visit 5), and Day 22 (Visit 6) and complete an in-clinic visit at Day 29 (Visit 7) and an in-clinic or home visit for review of symptoms and safety laboratory tests and to return/dispense IMP at Day 57 (Visit 8). Participants will then return to the study site for an end of treatment visit (Day 99 [Visit 9]). If a participant withdraws from the study prematurely (ie, before the end of treatment visit), an early withdrawal visit will be conducted, and a safety follow-up phone call will occur 4 weeks after their last dose of IMP. If a participant discontinues IMP prematurely, they should be encouraged to complete the end of treatment visit and the taper period and remain in the study.

Participants not continuing to Part B will return to the study site again at the end of the 10-day taper period (Day 110 [Visit 10]) and will complete a phone safety visit at the end of the follow-up period (Day 138 [Visit 11]).

Part B will be available to participants who complete Part A of the study and continue to meet all eligibility criteria and to participants for whom the investigator feels continued treatment in Part B represents a favorable risk-benefit assessment. Rollover into Part B should occur on the same day as Part A Day 99 (Visit 9).

Unscheduled phone visits can occur at any time throughout Part A, as needed.

AE, concomitant medication, and rescue medication eDiaries will be completed each day during the screening period, baseline observation period, treatment period, and taper period beginning at screening (Visit 1).

Seizure eDiaries will be completed each day during the screening period, baseline observation period, and treatment period beginning at screening (Visit 1).

IMP dosing eDiaries will be completed each day during the titration, treatment, and taper periods beginning at randomization (Visit 3).

Food eDiaries will be completed for approximately 24 hours prior to each visit where PK blood samples will be collected beginning approximately 24 hours prior to randomization (Visit 3).

Part B:

Part B will evaluate the long-term safety, tolerability, [redacted] of GWP42003-P for a period of 48 weeks in participants with EMAS-associated seizures. All participants in Part B will receive GWP42003-P.

The duration of study for Part B will be approximately 54 weeks, which includes a 48-week treatment period (including a 2-week blinded titration [or transition] period for all participants), 10-day taper period, and a safety follow-up period (4 weeks after end-of-taper visit).

Part B will be available to participants who complete Part A of the study and continue to meet all eligibility criteria and to participants for whom the investigator feels continued treatment in Part B represents a favorable risk-benefit assessment.

Participants who continue into Part B of the study will proceed without the Part A taper period (Visit 10) and follow-up visit (Visit 11). The Part A end of treatment visit (Visit 9) procedures/data will then be utilized for Visit 1 of Part B (ie, the same procedures should not be repeated at Visit 9 of Part A and Visit 1 of Part B). If the participant is continuing to Part B, IMP should only be dispensed at Part B Visit 1. If the participant is not continuing to Part B, IMP for the taper period will be dispensed at Part A Visit 9, as required.

Participants who do not enroll in Part B at Visit 9 of Part A will be required to complete an end-of-taper visit (Visit 10) and a follow-up visit (Visit 11).

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, participants will enter a 2-week blinded transition to Part B. Part B IMP will be titrated up to 10 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. All participants will complete the transition and enter Part B taking GWP42003-P (Section 6.5 Part B) (Table 5).

Investigators have the option to titrate participants no more rapidly than 2.5 mg/kg BID (5 mg/kg/day) every 7 days, up to a maximum daily dosage of 20 mg/kg/day.

After Part B Week 2 (Visit 3), for some participants in whom a more rapid titration from 10 to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day following consultation with the medical monitor and/or sponsor representative.

If any safety/tolerability issues, investigators can decide to maintain or decrease dosage.

After Part B Week 14 (Visit 7), serum transaminases and total bilirubin levels should be evaluated within 1 month following changes in GWP42003-P dosage and in medications that are known to impact the liver.

- As much as possible, laboratory assessments should be done centrally via IQVIA Mobile Health Solutions (if done locally, laboratory results should be filed in source documents and any abnormal and clinically significant results should be recorded as AEs)

A safety follow-up visit (phone call) will be conducted 4 weeks after the end-of-taper visit. If a participant withdraws from the study prematurely (ie, before the end of treatment visit), an early withdrawal visit will be conducted, and a safety follow-up phone call will occur 4 weeks after their last dose of IMP. Participants who discontinue IMP prematurely should be encouraged to complete the end of treatment visit and taper period.

Unscheduled phone visits can occur at any time during Part B, as needed.

During Part B, eDiaries will be completed at least weekly. No food eDiary is required for Part B.

Schematics (Figure 1 for Part A and Figure 2 for Part B), presented in Section 1.2, depicts the overall trial design. A detailed outline of procedures and activities is provided in the SoA

(Table 1 for Part A and Table 2 for Part B). More detailed information on treatment and study procedures is provided in Section 6 and Section 8, respectively.

4.2. Scientific Rationale for Study Design

EMAS is characterized by multiple seizure types (myoclonic-atonic, myoclonic, atonic, generalized tonic-clonic, atypical absences, and tonic seizures), with myoclonic-atonic seizures being the hallmark seizure type and mandatory for the diagnosis of EMAS (Hinokuma 2020) (Kelley 2010) (Neubauer 2005). There are no FDA-approved treatment options specifically for EMAS and its associated primary seizure types (ie, atonic and/or myoclonic seizures), and no clear consensus treatment guidelines for EMAS. Drug resistance to ASMs in children with EMAS is common and patients are typically exposed to and fail an average of 5 ASMs (Doose 1970) (Oguni 1992). While several ASMs have been reported to be beneficial, none of these agents have been evaluated in randomized, controlled studies in EMAS patient. Furthermore, most of these ASMs have also been associated with safety and tolerability issues, such as sedation, ataxia, and cognitive impairment (Menlove 2015). EMAS is considered challenging to treat, often requiring patients to tolerate difficult-to-maintain ketogenic diets (Goldberg 2001). Despite all the treatment options with ASMs and ketogenic diet, 20 to 50% of patients do not respond to treatment and only 50% become seizure-free (Helmstaedter 2020) (Kelley 2010). Thus, there is a clear unmet need for the development of effective and well-tolerated treatments that target the primary seizures associated with EMAS.

Based on the results of several Phase 3 studies and open-label studies with GWP42003-P in the treatment of other pediatric epilepsy syndromes, GWP42003-P may be an appropriate candidate to investigate for the treatment of EMAS. Results of 5 Phase 3 randomized, double-blind, placebo controlled studies show robust efficacy of GWP42003-P for treatment of seizures associated with LGS (Devinsky 2018a) (Thiele 2018), DS (Devinsky 2017) (Miller 2020), and TSC (Thiele 2020b). The anticonvulsant efficacy of GWP42003-P was durable as effects were sustained up to 1.5 years (Devinsky 2016).

GWP42003-P was also investigated in patients with other treatment-resistant epilepsies in the investigator initiated, FDA authorized EAP (including those with EMAS). Interim safety and efficacy results from the EAP uphold the finding that GWP42003-P produces clinically significant reductions in seizures when used as an add-on ASM treatment (McCagh 2009) (Wu 2020). Thus, there is direct evidence supporting that GWP42003-P can be an effective therapy for treatment of EMAS associated seizures.

Given the extensive clinical study results that have established the safety and efficacy profile of GWP42003-P as an anticonvulsant therapy and its potential to address the existing unmet need in the EMAS, the primary aim of Part A of the study is to assess the efficacy of GWP42003-P compared to placebo as an adjunctive treatment for children with EMAS. The primary aim of Part B of the study is to evaluate the long-term safety and tolerability of GWP42003-P in participants with EMAS.

The choice of a flexible dosing approach was based on results of the Phase 3 studies for DS, LGS, and TSC with GWP42003-P. These studies suggest that participants randomized to lower maximum dosages of GWP42003-P (eg, 10 mg/kg/day) experienced a similar magnitude of reductions in seizures to those treated with higher dosages of GWP42003-P (eg, 20, 25, and 50 mg/kg/day). Likewise, participants randomized to higher doses of GWP42003-P in clinical

studies report significantly greater side effects compared to those randomized to lower doses. However, given the variability in dose-response to GWP42003-P, it is possible that AEs observed with higher doses of GWP42003-P could be mitigated if participants are only titrated when clinically indicated. The choice of treatment length was determined based on previous studies of GWP42003-P, which have demonstrated that onset of treatment effect occurs rapidly (approximately within the 1 to 2 weeks of treatment) and maximum efficacy is attained at around 1 month of treatment. Based on these results, it is not scientifically warranted to extend the treatment phase past the length of historic studies (14 weeks).

4.2.1. Participant Input into Design

Representatives from patient organizations were consulted to ensure the patient and caregiver perspectives were implemented in the design of this clinical study.

4.3. Justification for Dose

The IMP, GWP42003-P, is FDA approved for the treatment of DS and LGS up to a maximum maintenance dosage of 20 mg/kg/day and for the treatment of TSC up to a recommended maintenance dosage of 25 mg/kg/day. It has also been prescribed by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies as part of the investigator initiated, FDA authorized EAP Investigational New Drug studies in daily dosages up to 50 mg/kg/day (median daily dosage of 25 mg/kg/day). Based on safety results from previous studies and because the current study is designed to allow for individualized dosing, a daily maximum dosage of 20 mg/kg/day GWP42003-P was selected.

All participants will be randomized to the IMP for administration during the 14-week treatment period that will follow a flexible titration schedule. Refer to Section 6.5 for details on dose modification.

Investigators may decrease daily dosage any time if a participant experiences intolerance. Participants whose dosage has been decreased can have their dosage increased again if the tolerability improves.

4.4. Number of Participants

In Part A, up to a maximum of 120 participants (up to 60 per treatment arm) will be randomly assigned to IMP (ie, randomized) in Part A of the study. The final sample size is dependent on the results from interim analyses when 60, 75, 90 and 105 participants are randomized (see Section 9.2 and Section 9.5 for sample size calculation assumptions).

Note: “Enrolled” means a participant’s or their caregiver’s agreement to participate in a clinical study following completion of the informed consent process.

4.5. End of Study Definition

The end of the study is defined as the date of the last participant’s final completed scheduled visit or last completed study assessment, whichever occurs last.

A participant is considered to have completed the entire study if he/she has completed all phases of Part A and Part B of the study including the last scheduled visit or the last scheduled

assessment shown in the SoA for Part B (Section 1.3). If a participant completes Part A and does not continue to Part B, he/she will be considered to have completed only Part A.

5. STUDY POPULATION

Investigators are responsible for confirming participant eligibility and will be required to maintain a log that includes limited information about all screened participants (initials, date of birth, and sex [as allowed per local regulations]) and outcome of screening.

Prospective approval of protocol deviations or waivers related to recruitment and eligibility criteria are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if ALL of the following criteria apply:

Age and Sex

1. Participant must be male or female between 1 and 18 years of age, inclusive, at the time of initial informed consent/assent.
2. Participant must weigh at least 10 kg.

Type of Participant

3. Participant has a current diagnosis of EMAS, also known as Doose syndrome, myoclonic-astatic epilepsy, or myoclonic-atonic epilepsy, consistent with the ILAE guidelines. Presence of myoclonic-atonic seizures is mandatory to support a diagnosis of EMAS as determined by medical history and independent approval by TESC.
4. Participant experiences a minimum average frequency of ≥ 2 TESC-approved, countable, EMAS-associated seizures (myoclonic-atonic, atonic, tonic, clonic, or tonic-clonic) per week (≥ 8 seizures per month), as reported in the baseline seizure eDiary from baseline (Part A Visit 2) until the evening prior to randomization (Part A Visit 3).
5. Participant's initial seizure onset occurred from ≥ 6 months to < 6 years of age, with normal or mildly impaired/delayed neurodevelopment reported prior to onset of seizures. During the first year of seizure onset, the majority of seizures experienced by the participant were myoclonic-atonic seizures or generalized tonic-clonic seizures as determined by medical history.
6. Participant is currently treated with 1 or more ASMs on a stable regimen (≥ 28 days prior to starting the baseline period [Part A Visit 2]) or on a stable ketogenic diet/epilepsy dietary therapy (≥ 28 days prior to starting the baseline period [Part A Visit 2]) and no changes to treatment are planned for the duration of the study.
7. Participant has failed ≥ 1 prior ASM due to inadequate seizure control.
8. Participant is able to provide a historical EEG report, which was performed within 12 months of screening (Part A Visit 1), or is willing to complete an EEG at screening (Part A Visit 1), that confirms a > 2.5 to 6 Hz generalized spike-and-slow-wave or polyspike-and-slow-wave pattern.

Sex and Contraceptive/Barrier Requirements

9. Contraceptive use by male and female participants should be consistent with Clinical Trial Facilitation Group guidelines and any applicable local regulations regarding the methods of contraception for those participating in clinical studies.

   Male participants:

   – Fertile male participants with partners of CBP must be willing to use a male barrier method of contraception in addition to a second method of acceptable contraception used by their female of CBP partners, from the time of screening (Part A Visit 1) until 3 months after the follow-up visit, as detailed in Section 10.5 (Appendix 5).

   Female participants of CBP:

   – Will not be pregnant or lactating and have a confirmed negative highly sensitive serum pregnancy test at screening (Part A Visit 1).

   – Must also have a confirmed negative urine pregnancy test prior to receiving their first dose of blinded IMP at Part A Visit 3.

   – Who are continuing to Part B must have a confirmed negative urine pregnancy test prior to receiving their first dose of open-label GWP42003-P at Part B Visit 1.

   – Must be willing to use a highly effective method of contraception from the time of signing the ICF until 3 months after the follow-up visit, as detailed in Section 10.5 (Appendix 5).

Informed Consent/Assent

10. Participant or participant's caregiver(s) (according to local laws) is/are willing and able to give signed informed consent/assent for participation in the study including compliance with the requirements and restrictions listed in the ICF and in Section 10.2.3.
11. Participant's caregiver(s) are willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.
12. Participant's caregiver completes ≥ 25 days of daily Reminder Diary entries during the first 28 days of the baseline period.

Part B Only:

13. Has completed Part A of this study.
14. Was compliant with all requirements of Part A (eg, dosing, seizure eDiary, visits/procedures), in the clinical judgement of the investigator and/or sponsor.

5.2. Exclusion Criteria

Participants are excluded from the study if ANY of the following criteria apply:

Medical Conditions

15. Has a history of psychogenic non-epileptic seizures that confounds the assessment of the primary efficacy measure.
16. Has clinically significant unstable medical condition(s), other than EMAS.
17. Has a clinically significant illness in the 28 days prior to screening (Part A Visit 1) or randomization (Part A Visit 3), other than epilepsy, which in the opinion of the investigator could affect seizure frequency.
18. Has presence of focal seizures or persistent focal epileptiform discharges on EEG.
19. Has a history of infantile spasms.
20. Has moderate to severe neurocognitive and/or developmental delay prior to seizure onset.
21. Has a progressive neurological condition.
22. Has known or suspected hypersensitivity to cannabinoids or any of the excipients of GWP42003-P such as sesame oil.
23. Is unwilling or unable to remain stable on concurrent ASMs throughout the study.
24. Has, in the opinion of the investigator, clinically significant abnormalities in the ECG measured at screening (Part A Visit 1), or any concurrent cardiovascular conditions, which will interfere with the ability to read their ECGs.
25. Has significantly impaired hepatic function at the screening visit (Part A Visit 1) or prior to dosing, defined as any of the following:
    - ALT or AST > 5 × ULN
    - TBL (serum total bilirubin) > 1.5 × ULN or INR > 1.5. Note that for participants diagnosed with Gilbert's disease, TBL > 3.0 × ULN and/or direct bilirubin > 1 × ULN are exclusionary.
    - 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%).
    - Elevated ALT or AST at screening (Part A Visit 1), should be discussed with the medical monitor prior to randomization (Part A Visit 3); the medical monitor may allow for a confirmatory re-draw prior to randomization.

    This criterion can only be confirmed once the laboratory results are available.
26. Has clinically significant impaired renal function at screening (Part A Visit 1), as evidenced by an estimated glomerular filtration rate (Schwartz equation) < 60 mL/min.

27. Is a female participant of CBP, who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for 3 months thereafter.
28. Participant has any known or suspected history of alcohol or substance use disorder.
29. Any clinically significant abnormalities identified following a physical examination or laboratory assessments of the participant that, in the opinion of the investigator, would jeopardize the safety of the participant if they take part in the study.
30. Participant has any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the participant, other participants, or site staff at risk because of participation in the study, may influence the result of the study, or may affect the participant's ability to take part in the study.

Prior Therapy

31. Is currently treated with Epidiolex/Epidyolex or recently received treatment with Epidiolex/Epidyolex within 28 days prior to screening (Part A Visit 1).
32. Has experienced a lack of efficacy and/or poor tolerability to an adequate treatment regimen of Epidiolex/Epidyolex based on medical history and the clinical judgment of the investigator. Participants who discontinued treatment for reasons other than safety, tolerability, or lack of efficacy and previously received Epidiolex/Epidyolex ≥ 28 days prior to screening (Part A Visit 1) may be eligible for the study after consultation with the medical monitor and/or sponsor representative.
33. Has a change in anticonvulsant therapies within 28 days of starting the baseline period (Part A Visit 2), including ASMs or settings on vagal nerve stimulator.
34. Has any planned clinical interventions or intends to change any or all medications that may impact seizures during the study.
35. Has undergone surgery for epilepsy in the 6 months prior to screening (Part A Visit 1).
36. Is being considered for epilepsy surgery or any procedure involving general anesthesia during the study.
37. Has initiated a ketogenic diet within 28 days prior to starting the baseline period (Part A Visit 2). Participants who are stable on a ketogenic diet for ≥ 28 days and willing to remain on a stable epilepsy dietary therapy (eg, ketogenic diet, Atkins diet, low glycemic index diet) during the study, are eligible for inclusion.
38. Has initiated felbamate within 12 months prior to screening (Part A Visit 1). Participants who are stable on a felbamate for ≥ 12 months are eligible for inclusion.
39. Is currently being treated with or had previously (within 3 months prior to screening [Part A Visit 1]) received intravenous immunoglobulin treatment or plasma exchange for the treatment of seizures.

Prior/Concurrent Clinical Study Experience

40. Has participated in a clinical study involving administration of an IMP (new chemical entity) or medical device (eg, vagal nerve stimulator) within 28 days prior to screening (Part A Visit 1).
41. Has previously been randomized, completed, or withdrawn from this study.

Alcohol and Drugs

42. Is currently using a drug of abuse or current nonprescribed use of any prescription drug.
43. Is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications, products, or supplements (botanical or synthetic) within 28 days prior to screening (Part A Visit 1).
44. Mother (if breastfeeding the participant) is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications, products, or supplements (botanical or synthetic) within 28 days of screening (Part A Visit 1).

Other Exclusions

45. History of suicidal behavior, current suicidal risk as determined from history, or presence of active suicidal ideation as indicated by a positive response to Item 4 or Item 5 on the C-SSRS. The C-SSRS criterion applies only to participants 4 to 18 years of age.
46. Is unwilling or unable to comply with all study requirements, including accurate eDiary completion.
47. Participants who, in the opinion of the investigator (or designee), should not participate in this study.
48. Has travel planned outside their country of residence during the study, unless the participant has confirmation that the IMP is permitted in the destination country and all stops along the way.

Part B Only:

49. Has significantly impaired hepatic function at Part A Visit 9, defined as any of the following:
    - ALT or AST > 5 × ULN
    - TBL (serum total bilirubin) > 1.5 × ULN or INR > 1.5. Note that for participants diagnosed with Gilbert's disease, TBL > 3.0 × ULN and/or direct bilirubin > 1 × ULN are exclusionary.
    - 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%). The medical monitor may allow for a confirmatory re-draw prior to rollover.

50. Meets any exclusion criteria at Part B Visit 1.

5.3. Lifestyle Considerations

Note: Restrictions that apply to the period before the first admission are described in Section 5.1 and Section 5.2.

5.3.1. Meals and Dietary Restrictions

The caregiver will record the date, time, and meal type (eg, high-fat meal [dairy or meat], standard meal [fruit or vegetable], or other [if not fitting into one of the categories above]) for all meals consumed by the participant within 24 hours prior to PK collection.

5.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently randomly assigned to the IMP. Documentation of screening failures will be collected and recorded in the eCRF. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, AEs, and any SAE.

5.4.1. Rescreening

Participants who do not meet the criteria for participation in this study (screen failure), or who could not be randomized within the screening/baseline window for logistical reasons, may be rescreened once at the discretion of the investigator or designee and after consultation with the medical monitor and/or sponsor representative. Rescreened participants must first be registered as screen failures in the eCRF and subsequently registered as rescreens in the eCRF. Once the participant is registered as rescreened, a new screening window will begin. For all rescreens, all screening procedures, including ICF, must be repeated. Sites should discuss planned rescreens with the medical monitor prior to rescreening (Part A Visit 1).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any IMP or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 3: Study Interventions

ARM Name	GWP42003-P	Placebo
Intervention Name	GWP42003-P	Placebo
Type	Drug	Drug
Dose Formulation	CBD dissolved in the excipients sesame oil and anhydrous ethanol (10% v/v), with sweetener (sucralose), and strawberry flavoring	The excipients sesame oil and anhydrous ethanol (10% v/v), with sweetener (sucralose), strawberry flavoring, and beta carotene
Unit Dose Strength(s)	100 mg/mL CBD	n/a
Dosage Level(s)	5 mg/kg/day (2.5 mg/kg BID) up to a maximum of 20 mg/kg/day	0.05 mL/kg/day up to a maximum of 0.2 mL/kg/day
Route of Administration	Oral	Oral
Use	Experimental	Placebo comparator
IMP or non-IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	IMP will be provided in bottles with syringes for administration. Each bottle will be labeled as required per country requirement.	IMP will be provided in bottles with syringes for administration. Each bottle will be labeled as required per country requirement.
Current/Former Names or Alias	Cannabidiol	n/a

Abbreviations: BID = twice daily; CBD = cannabidiol; IMP = investigational medicinal product; n/a = not applicable; OS = oral solution.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only participants randomized to receive IMP in the study may receive IMP and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally

controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

For self-administration of IMP, participants/caregivers will be provided with bottle(s) containing the oral dosing solution along with oral syringes. Participants/caregivers will be trained, during Visit 3 at the study site, to self-administer IMP orally or with gastrostomy or nasogastric tubes BID (eg, morning and evening) preferably about the same time each day, consistently with or without food. Participants/caregivers will be provided with clear instructions for the dose escalation and taper dosing periods of the study via a printed dosing schedule and will record usage of IMP as part of the IMP dosing eDiary to aid in compliance.

Where required by local regulations, IMP may be dispensed more frequently than outlined in the schedule of assessments by completion of an unscheduled dispensing visit.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the pharmacy manual or other specified location.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

All participants will be centrally assigned to randomized IMP using an IRT (RTSM). Before the study is initiated, the log-in information and directions for the IRT will be provided to each site. Refer to Section 8.1.3 for details on the IRT.

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

The IMP will be dispensed at the study visits summarized in the SoA (Section 1.3).

Returned IMP should not be re-dispensed to the participants.

6.3.2. Blinding

At the start of Part A, participants will be randomly assigned in a 1:1 ratio to receive GWP42003-P or matching placebo. Investigators will remain blinded to each participant's assigned IMP throughout the course of the study.

Participants entering Part B of the study, will first complete a 2-week blinded titration phase. Following the blinded titration phase, participants will start open-label treatment with GWP42003-P.

6.3.2.1. Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' IMP assignment is warranted. Participant safety must always be the first consideration in making such a determination. Unblinding for any other reason will be considered a protocol deviation. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's IMP assignment unless this could delay

emergency treatment of the participant. If a participant's IMP assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

Sponsor safety staff may unblind the IMP assignment for any participant with an SAE. The study team will remain blinded to IMP assignment. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report may be sent to investigators in accordance with local regulations and/or sponsor policy. Reason for unblinding and date must be recorded/documented appropriately per study documentation process.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive IMP directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the IMP dosing eDiary. The dose of IMP and study participant identification will be confirmed at the time of dosing.

Compliance with IMP will be reviewed during phone visits by direct questioning and review of completed IMP dosing eDiary. However, IMP compliance cannot be fully assessed during phone visits since bottle(s) will not be returned. Possible deviation(s) from the prescribed dosing regimen should be discussed with the caregiver (eg, re-training provided) and documented in the source documents.

Compliance with IMP will be assessed at each visit where IMP is returned, as part of accountability assessment. Compliance will be assessed by direct questioning, counting returned bottle(s), review of completed IMP dosing eDiary, measurement of the IMP used from each bottle compared to expected usage, etc. during the site visits and documented in the source documents and eCRF. Significant deviation(s) from the prescribed dosage regimen should be recorded as protocol deviations as outlined within the pharmacy manual.

A record of the quantity of IMP dispensed to and administered by each participant must be maintained and reconciled with IMP and compliance records. IMP start and stop dates, including dates for IMP dosing delays and/or dose adjustments, will also be recorded.

6.5. Dose Modification

Body weight will be used to calculate the IMP dose. Body weight will be confirmed prior to IMP dose calculation. If a visit is being done at home, the last available clinic weight will be used to calculate the dose.

Refer to the "CBD Dose Adjustment" section of the current approved GWP42003-P IB for detailed information regarding potential drug interactions and associated dose modifications.

Part A:

On Day 1 (Visit 3) of treatment with IMP, participants will be initiated on a dose of 2.5 mg/kg BID (5 mg/kg/day), and after 1 week, the dose will be increased to 5 mg/kg BID (10 mg/kg/day) at the Day 8 (Visit 4) phone visit.

For participants who are tolerating the IMP at 5 mg/kg BID (10 mg/kg/day) and require further reduction of seizures, investigators may choose to increase their dosage up to a maximum dosage

of 10 mg/kg BID (20 mg/kg/day). The decision to titrate above 5 mg/kg BID (10 mg/kg/day) should be based on the observed efficacy, safety, and tolerability of the participant (including review of laboratory values) per the clinical judgement of the investigator.

Starting at the Day 15 (Visit 5) phone visit, investigators have the option to titrate participants no more rapidly than every 7 days by an additional 2.5 mg/kg BID (5 mg/kg/day) up to a maximum daily dosage of 20 mg/kg/day. The investigator will determine if further dose adjustments are warranted during unscheduled phone visits and/or scheduled phone or clinic visits throughout the remainder of the 14-week treatment period. If dose change is warranted outside of a scheduled visit, the caregiver should be contacted by phone prior to making any dose increases above 10 mg/kg/day to assess the appropriateness of the dose increase based on the participant's reported clinical response and ensure the caregiver has received the updated dosing schedule reflecting the new target dose. This contact should be documented as an unscheduled phone visit in the eCRF.

After the Day 15 (Visit 5) phone visit, if in the investigator's opinion, a participant is experiencing a clinically meaningful improvement in EMAS-associated seizures, the investigator can choose to continue treatment at the participant's current dosage and may re-consider an increase in the dosage of IMP at either a later study visit, or at any time between study visits, as described above.

If a participant reports any tolerability issues related to IMP, the investigator can also decrease a participant's current dosage. Dose decreases to below 10 mg/kg/day, based on safety and tolerability may occur at any time. The caregiver should be contacted by phone prior to making any dose decreases below 10 mg/kg/day. Investigators should regularly monitor a participant's response to treatment and re-evaluate the need for adjustments to dosage (ie, increase, maintain, or decrease) at the next study visit, if applicable. Dose decreases below 10 mg/kg/day may occur in decrements of 2.5 or 5 mg/kg/day based on the clinical judgment of the investigator.

Table 4: Possible Range of Investigational Medicinal Product Doses During the 14-Week Treatment Period of Part A

Day	Morning Dose (mg/kg)	Evening Dose (mg/kg)	Total Daily Dose (mg/kg/day)
1-7	2.5	2.5	5
8-14	5	5	10
15-21	5 or 7.5	5 or 7.5	10 or 15
22-56	5, 7.5, or 10*	5, 7.5, or 10*	10, 15, or 20*
57-84	5, 7.5, or 10*	5, 7.5, or 10*	10, 15, or 20*
85-98	5, 7.5, or 10*	5, 7.5, or 10*	10, 15, or 20*

***** The maximum dosage (or dosage equivalent) that could be administered by this point or subsequent points.
Note: The dose ranges in the table serve as guidance only. Slight differences in dosage timing are allowed.

At the End of Treatment visit for Part A, participants who complete the treatment period, continue to meet all Part B eligibility criteria, and for participants whom the investigator feels continued treatment in an extension trial represents a favorable risk-benefit assessment for the participant will be offered the option to enroll in Part B.

Part B

Participants eligible to participate in Part B of the study will not be required to complete the Part A taper period (Visit 10) or follow-up visit (Visit 11). The Part A end of treatment visit (Visit 9) procedures/data should be utilized for Visit 1 of Part B (ie, the same procedures should not be repeated at Visit 9 of Part A and Visit 1 of Part B). If the participant is continuing to Part B, the IMP should only be dispensed at Part B Visit 1. If the participant is not continuing to Part B, the IMP for the taper period will be dispensed at Part A Visit 9, as required.

In order to maintain consistent exposure to IMP and maintain the integrity of the blind, participants will enter a 2-week blinded titration (or transition) to Part B. Part B IMP will be increased to 10 mg/kg/day whilst blinded IMP is simultaneously tapered down to zero. If a participant completes Part A on a dose < 10 mg/kg/day and continues into Part B, they can transition to Part B and remain at a lower GWP42003-P dosage following approval from the medical monitor and/or sponsor representative. After Week 2 (Visit 3), investigators will then have the option to titrate participants no more rapidly than every 7 days by an additional 2.5 mg/kg BID (5 mg/kg/day) up to a maximum daily dosage of 20 mg/kg/day (Table 5).

After Week 2 (Visit 3), it is recommended that the GWP42003-P dosage should be increased no more rapidly than 5 mg/kg/day (2.5 mg/kg BID) every 7 days. However, for some participants in whom a more rapid titration from 10 to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day following consultation with the medical monitor and/or sponsor representative.

If any safety/tolerability issues, investigators can decide to maintain or decrease dosage.

Table 5: Cross-Titration Scheme from End of 14-Week Treatment Period in Part A to Start of Part B

Study Part/ Visit	Visit Type	Study Day	GWP42003-P 10 mg/kg/day			GWP42003-P 15 mg/kg/day			GWP42003-P 20 mg/kg/day			Placebo		
			Blinded (mg/kg/ day)	OL (mg/kg/ day)	Total Dose (mg/kg/ day)	Blinded (mg/kg/ day)	OL (mg/kg/ day)	Total Dose (mg/kg/ day)	Blinded (mg/kg/ day)	OL (mg/kg/ day)	Total Dose (mg/kg /day)	Blinded (mg/kg/ day)	OL (mg/kg /day)	Total Dose (mg/kg /day)
Part A Visit 9	C	99	10	0	10	15	0	15	20	0	20	0	0	0
Part B Visit 1	C	1–7	5	5	10	10	5	15	15	5	20	0	5	5
Part B Visit 2	P	8–14	0	10	10	5	10	15	10	10	20	0	10	10
Part B Visit 3	P	15–21	-	10 or 15	10 or 15	0	10 or 15	10 or 15	5	10 or 15	15 or 20	0	10 or 15	10 or 15
Part B Visit 4	P	22–28	-	10, 15, or 20	10, 15, or 20	-	10, 15, or 20	10, 15, or 20	0	10, 15, or 20	10, 15, or 20	0	10, 15, or 20	10, 15, or 20

Abbreviations: C = clinic; OL = open-label; P = phone.

6.6. Continued Access to Study Intervention After the End of the Study

There is no plan to provide continued access to IMP after the end of the study.

6.7. Treatment of Overdose

For this study, any dose of IMP > 20 mg/kg within a 24-hour period may be considered an overdose, based on investigator's or sponsor's discretion.

In the event of overdose, the participant should be treated symptomatically (supportive management) according to local guidelines and in line with the current approved version of the IB.

In the event of an overdose, the investigator should:

- Closely monitor the participant for any AE/SAE including any laboratory abnormalities as clinically indicated.
- Contact the medical monitor as soon as possible.
- Evaluate the participant to determine, in consultation with the medical monitor (when possible), whether the IMP should be interrupted or whether the dose should be reduced.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Instructions on missed doses and/vomiting will be included in a separate pharmacy manual.

6.8. Concomitant Therapy

Caution should always be exercised when allowing administration of concomitant therapies according to the individual profile and clinical risk-benefit assessment. Key restrictions on concomitant therapies that apply to the period before screening and during the study are briefly summarized below. Additional restrictions and details are described further in Section 5.1 and Section 5.2.

- Current treatment with 1 or more ASMs or a vagal nerve stimulator are allowed; change in anticonvulsant therapies (including ASMs or vagal nerve stimulator settings) are not permitted within 28 days of starting the baseline period (Part A Visit 2), and no changes to these therapies should be planned for the duration of the study.
- Previous treatment with felbamate within 12 months prior to screening (Part A Visit 1) is prohibited. However, participants who are stable on felbamate for ≥ 12 months are eligible.
- Current therapy with ketogenic diet/epilepsy dietary therapy is allowed as long as dietary therapy has been stable (≥ 28 days prior to starting the baseline period [Part A Visit 2]) and no changes to therapy are planned for the duration of the study.

- Current therapy with Epidiolex/Epidyolex or recent treatment with Epidiolex/Epidyolex within 28 days prior to screening (Part A Visit 1) is not permitted.
- Previous treatment with Epidiolex/Epidyolex that resulted in a lack of efficacy and/or poor tolerability is prohibited. However, participants who discontinued treatment for reasons other than safety, tolerability, or lack of efficacy and previously received Epidiolex/Epidyolex ≥28 days prior to screening (Part A Visit 1) may be eligible for the study after consultation with the medical monitor and/or sponsor representative.
- Current use or recent use (within 28 days prior to screening [Part A Visit 1]) of recreational or medicinal cannabis, cannabinoid-based medications, products, or supplements (botanical or synthetic) is prohibited.
- If the study participant is being breastfed, current use or recent use (within 28 days prior to screening [Part A Visit 1]) by the mother of recreational or medicinal cannabis, cannabinoid-based medications, products, or supplements (botanical or synthetic) is prohibited.

Any vaccination related to SARS-CoV-2 (COVID-19) that was received within the last 12 months prior to screening (Part A Visit 1) or during the study should be recorded as concomitant medication. The information recorded should include the vaccine manufacturer and the dates of administration; differing start and end dates if more than 1 dose is received.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving within 3 months of screening (Part A Visit 1) or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Additionally, all ASMs, antiepileptic therapies, and rescue medications taken during the participant's life (previous and/or current use) will be recorded in the eCRF and reviewed at each subsequent visit.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

It is possible that GWP42003-P oral solution may modify the metabolism of other drugs (including other ASMs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P oral solution and other concurrently administered drugs. **Detailed information on potential drug interactions can be found in the current approved GWP42003-P IB in the "CBD Dose Adjustment" section.**

Concomitant ASM dose reductions are permitted on clinical grounds (eg, due to AEs or transaminase elevations not meeting withdrawal criteria specified in Section 7.1) following discussion with the medical monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants have the right to withdraw from the IMP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator can withdraw a participant(s) from IMP, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1 and Section 7.2.

7.1. Discontinuation of Study Intervention

Reasons for removal from IMP include any of the following:

- Participants may decline to continue receiving IMP or other protocol-required therapies or procedures at any time during the study.
  - Participants who choose to discontinue IMP or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, and in agreement with the sponsor, the participants should remain in the respective part of the study to ensure safety surveillance and collection of outcome data. Specifically, participants who discontinue IMP prematurely in Part A of the study will not be enrolled in Part B.
  - The investigator is to discuss with the participant the appropriate processes for discontinuation from IMP or other protocol-required therapies. The investigator must discuss with the participant the possibilities for continuation of activities described in the SoA (Table 1 and Table 2) and must document this decision in the eCRF.
- Decision by investigator.
- Decision by sponsor.
- Withdrawal by participant/caregiver/legal representative.
- Lack of efficacy.
- Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects participant safety, as determined by the investigator (or designee).
- Protocol deviation that is considered to potentially compromise the safety of the participant.
- Noncompliance with IMP.
- Noncompliance with study assessments.
- Pregnancy.
- Liver Chemistry - Discontinuation of IMP for abnormal liver tests is required by the investigator when a participant meets one of the following conditions outlined or in

the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

  - 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%).
  - ALT or AST > 8 × ULN.
  - ALT or AST > 5 × ULN for > 2 weeks.
  - ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).
  - Note: Refer to Section 10.6 (Appendix 6) for information on follow up for clinically significant liver results.

- Any evidence of drug abuse or diversion.
- Suicidal behavior or Serious suicidal ideation during the treatment period, defined as Item 4 or Item 5 on the C-SSRS.
- An AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe administration of IMP to the participant in the study.

7.2. Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or compliance reasons.

- The participant will be permanently discontinued both from the IMP and from the study at that time.
- If a participant is withdrawn from the study, the study monitor will be informed immediately. If there is a medical reason for withdrawal, the participant will be followed up by the investigator until satisfactory health has returned.
- All efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.
- Participants withdrawing due to an AE should be followed up according to Section 10.4.4. All information should be reported on the applicable eCRF pages (refer to Section 8). A safety follow-up visit should take place ±7 days after last dose of IMP (refer to Table 1 and Table 2). If withdrawing participants decline to give a reason for withdrawal of consent, the investigator must respect the participant's wishes.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Reasons for removal of a participant from the study are:

- Decision by investigator.
- Decision by sponsor.
- Lack of efficacy.
- AE.
- Withdrawal by participant/caregiver/legal representative.
- Death.
- Lost to follow up.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and/or is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get the IMP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.2.9.

8. STUDY ASSESSMENTS

Study procedures and their timing are summarized in the SoA (Section 1.3).

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed in the source records and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and confirmation of eligibility or record reasons for screening failure, in the eCRF as applicable.
- Safety/Laboratory/analyte results that could unblind the study will not be reported to investigational sites or other blinded personnel until the study has been unblinded.

8.1. General Assessments

8.1.1. Demographics

At screening (Part A Visit 1), the following information will be obtained for each participant: age, sex, race, ethnic origin (if allowed per local regulation or if otherwise supported by the scientific rationale).

8.1.2. Medical History

Full medical history, including perinatal history, and EEG report (historical EEG report can be used to determine eligibility at screening if performed within the past 12 months prior to screening [Part A Visit 1]) will be obtained during screening and is defined as any condition or disease that meets any of the following criteria:

- May affect the condition under study.
- Including complete seizure history, developmental history, lifetime history of epilepsy, history of *status epilepticus*, and any hospitalizations.
- Is ongoing on entry into the study.
- Has occurred within 1 year prior to screening (Part A Visit 1).
- Suspected or confirmed COVID-19 infection (or other significant communicable diseases) within 1 year prior to screening (Part A Visit 1).
- Information required for TESC confirmation of EMAS diagnosis and/or seizure classification, including but not limited to lifetime imaging history, EEG history, genetic testing history, etc.
- Gastrostomy or nasogastric tube placement.
- Prior cannabis use.

- Historical vaccinations.

8.1.3. Interactive Response Technology

The IRT (RTSM) will be used to assign participants to treatment groups, manage IMP supply, and to provide treatment allocation information in the event of participant unblinding. The RTSM will be integrated with Rave electronic data capture.

A member of the study team must register in the eCRF at each clinic visit in order to:

- Obtain a participant's number at screening (Part A Visit 1).
- Randomize a participant (Part A Visit 3).
- Obtain dispensing information on day of visit (Part A Visits 3, 7, 8, and 9; Part B Visits 1, 5, 6, 7, 8, and 10). If required for home health visits, dispensing information may be obtained 1 day prior to visit.
- Provide completion/taper/premature termination information (after Part A Visit 3).

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

8.1.4. Participant eDiary

An eDiary will be completed throughout the study, until the end of the taper period (Part A Visit 10; Part B Visit 11) or early withdrawal visit (Part A Visit 9; Part B Visit 10). If the participant is provided with a site-provisioned eDiary, the device must be returned to the site at the last clinic visit. A back-up plan to record eDiary data will be in place in case of any device failure.

Caregivers will record the following information in the eDiary:

- AEs, concomitant medications, rescue medication, and seizures (including type, number, and days with *status epilepticus*) beginning at screening (Part A Visit 1).
- Food eDiary module beginning approximately 24 hours prior to randomization (Part A Visit 3) and 24 hours prior to Part A Visit 9 (or End of Treatment Visit if the participant discontinues treatment prior to Part A Visit 9) – details of each meal consumed by the participant within approximately 24 hours prior to **PK collection**, including the date, time, and meal type:
  - High fat meal (dairy or meat)
  - Standard meal (fruit or vegetable)

Other (if not fitting into one of the categories above)

- IMP dosing eDiary module beginning at randomization (Part A Visit 3) – IMP usage, including dose time, volume administered, and consistency of IMP dosing with respect to mealtimes.

Caregivers will be instructed to immediately contact the investigator by phone to discuss any changes in their child's health (possible AEs), changes in concomitant medications, including ASMs, use of rescue medication, and days with *status epilepticus* or potential new seizure types.

All eDiary entries will be reviewed and discussed with the caregiver for verification during participant phone or clinic visits. This review will be documented in the source and eCRF.

- For the AE, concomitant medication, and rescue medication eDiaries, details on AEs, changes in concomitant medications, including ASMs and use of rescue medication will be recorded within the source documents and eCRF.
- For the seizure eDiary, any days with *status epilepticus* will be recorded in the source and reported as an SAE; any potential new seizure types will be recorded in the source and reported to TESC for adjudication. New seizure types may be added to the eCRF as expected seizure types following TESC approval.

8.1.5. Confirmation of EMAS Diagnosis and Seizure Classification

To ensure accurate diagnosis of EMAS according to ILAE criteria (International League Against Epilepsy 2012) (Trinka 2015), investigators will collect lifetime developmental and lifetime seizure history during screening (Part A Visit 1) using the SIF/DRF and eDiary Seizure Classification Report.

Caregivers will begin reporting seizures to the seizure eDiary immediately following screening (Part A Visit 1) and will continue reporting seizures to the seizure eDiary for the remainder of the study.

The investigator will submit the completed SIF/DRF and eDiary Seizure Classification Report directly to TESC within 24 hours (1 business day) of screening (Part A Visit 1), where possible. TESC may ask the investigator for additional information to assist in their decision. The Epilepsy Study Consortium decision will be made within 14 days of receipt of all required information and written approval of the SIF/DRF and eDiary Seizure Classification Report must be received by the investigator before the baseline (Part A Visit 2) can occur.

At baseline (Part A Visit 2), the investigator will contact the caregiver by phone for seizure classification training (eg, to review TESC-approved eDiary Seizure Classification Report and train the caregiver to identify, count and report the participant's TESC-approved seizures to the seizure eDiary). Only seizures reported from the start of baseline (Part A Visit 2) will be used for the participant's baseline seizure count.

Only seizures that are recognizable and countable will be reported by caregivers for this study. The following ILAE seizure subtypes may be collected in the eDiary:

- Primary endpoint EMAS-associated seizures:
  - Myoclonic-atonic
  - Atonic
  - Tonic
  - Clonic
  - Tonic–clonic
- Secondary endpoint seizures:
  - Myoclonic seizures

  - Total Seizures (primary endpoint seizures and other seizures)

- *Status epilepticus* (any seizure lasting 30 minutes or longer)
  - Convulsive *status epilepticus*
  - Non-convulsive *status epilepticus*

8.1.6. Investigational Medicinal Product Accountability

Records of IMP accountability will be maintained according to Section 6.2 and Section 6.4.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. Questionnaires and Assessments Completed at Scheduled Visits

Non-investigator/physician-facing questionnaires should be completed by the main caregiver. The questionnaires will be captured using an electronic system. The same person should complete the questionnaires/assessments throughout the study to maintain consistency. If the main caregiver is not available at the appropriate visit, then this information can be captured over the telephone, ideally on the day of the visit or otherwise within ± 7 days. Because participants in this study are expected to be experiencing varying degrees of cognitive impairment or delay related to their seizure history, only completion of caregiver-facing questionnaires are expected for this study.

Investigator/physician-facing questionnaires should be completed by the appropriate rater and data will be recorded in an electronic system, ideally on the day of the visit or otherwise within ± 7 days. The same person should complete the questionnaires/assessments throughout the study to maintain consistency.

The participant's age at Part A Visit 1 will be used to determine which questionnaires should be completed for the duration of the trial. Questionnaires should only be administered to study participants who satisfy minimum age requirements at screening (Part A Visit 1). Questionnaires completed during screening (Part A Visit 1) will be considered as baseline.

Questionnaires should be completed prior to any invasive procedures (eg, blood draws, ECG, EEG, etc.) that may affect the caregiver's responses to the questionnaires.

Questionnaires will only be administered if a translation is available in the caregiver's native language.

8.2.1.1. Columbia-Suicide Severity Rating Scale (4 Years of Age and Older)

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

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. During screening (Part A Visit 1), questions will be in relation to lifetime experiences, and all subsequent questioning will be in relation to the last assessment (since last visit).

The C-SSRS is to be completed by the investigator or his/her qualified delegate at every visit as indicated in the SoA (Section 1.3); "qualified delegate" is defined as anyone who has completed the C-SSRS training within the past 2 years or has continually administered the C-SSRS assessments throughout this study since obtaining the training certificate. The survey should be completed by the same assessor, where possible, throughout the study.

The C-SSRS will be used for participants aged 4 to 18 years (inclusive). If a participant is unable to provide adequate responses, the C-SSRS may be administered to the participant's caregiver to obtain responses on behalf of the participant.

8.2.1.2. Caregiver Global Impression of Change

The CGIC, will be performed for all participants. At screening (Part A Visit 1), the participant's caregiver will be asked to write a brief description of the participant's overall condition as a memory aid for the CGIC at subsequent visits. It is preferred that the same person performs this assessment at each visit throughout the study and should take less than 5 minutes to complete.

8.2.1.3. Physician Global Impression of Change

The PGIC will be performed for all participants and should take less than 5 minutes to complete. At screening (Part A Visit 1), the investigator will be asked to write a brief description of the participant's overall condition as a memory aid for the PGIC at subsequent visits. It is preferred that the same investigator performs this assessment at each visit throughout the study.

8.2.1.4. Caregiver Global Impression of Change in Seizure Duration

The caregiver will be asked to assess the average duration of the participant's seizures at screening (Part A Visit 1) (ie, prior to commencement of IMP) as a memory aid for subsequent visits. It is preferred that the same person performs this assessment at each visit throughout the study and should take less than 5 minutes to complete.

[redacted]

[redacted]

8.2.1.9. Treatment Credibility/Expectancy Questionnaire – Parent Version

CEQ-P is a self-rated measure addressing the parents' expectancy and credibility about the treatment. CEQ-P consists of 6 items: 3 items regarding credibility and 3 items regarding expectancy. To meet the requirements of the original version of CEQ-P, items 1, 2, 3, and 5 are scored on a 9-point scale, while items 4 and 6 are scored on an 11-point scale. Items 4 and 6 are

recoded to a 9-point scale before summarizing the scales. The CEQ-P will only be administered if a translation is available in the caregiver's native language and should take 5 minutes to complete.

8.2.1.10. Menstruation

Caregivers will be asked if the female participant is menstruating, and details will be recorded as part of their randomization visit (Part A Visit 3); any changes in normal cycles will be captured at Part A Visit 9 (Day 99)/Part B Visit 1 and Part B Visit 10.

8.2.1.11. Tanner Staging

The pubic hair growth (both sexes), genital (males only), and breast (females only) development of all adolescent participants (ie, 10 to 17 years of age at the time the ICF is signed, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will be assessed by the investigator or his/her qualified delegate using Tanner Staging (Carel 2008). The participants will undergo a discreet physical examination and be assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male participants only), and Breasts (female participants only).

Once a participant reaches a score of V (ie, 5), the examination need not be performed again.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.3.1. Physical Examinations

A physical examination (including height, length, head circumference, and weight) will be performed at the time points specified in the SoA (see Section 1.3).

8.3.2. Vital Signs

Vital signs will be measured in a supine position after 5 minutes rest in a quiet setting without distractions (eg, television, mobile phones) and will include body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. As part of screening procedures and at each clinic visit, blood pressure and pulse rate will also be taken after 2 minutes in a standing position (if it is possible for the participant to stand), following supine measurements. All measurements will be performed singly and repeated once if outside the relevant clinical reference range. Blood pressure must be recorded using the same arm throughout the study, where possible.

Additional vital signs measurements may be taken during the study, if clinically indicated.

8.3.3. Electrocardiograms

ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT interval with Bazett correction intervals.

An ECG will be performed after 5 minutes in a supine position. A physician must review the ECG in a timely manner and any clinically significant abnormal findings considered to indicate

significant medical history or AEs must be recorded appropriately on the eCRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

8.3.4. Clinical Safety Laboratory Assessments

See Section 10.3 (Appendix 3) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

In participants with clinical risk factors for hepatocellular injury, re-assessment of laboratory safety parameters (biochemistry, coagulation, urinalysis, and hematology), including review of results should be completed up to 14 days prior to randomization (Part A Visit 3) to verify eligibility for the study. The investigator should use his/her clinical judgement along with screening assessments and consider the participant's risk factors to determine whether to re-check biochemistry and coagulation during the baseline period. Possible risk factors include but are not limited to concurrent use of valproic acid or ketogenic diet, a recent infection or illness, a history of elevated liver enzymes, elevated liver enzymes during the previous study visit, or any other relevant signs or symptoms that could indicate the participant is experiencing abnormal liver function. If re-assessment of laboratory parameters (biochemistry, hematology, urinalysis, and coagulation) is completed within 14 days of randomization (Part A Visit 3), testing at randomization (Part A Visit 3) does not need to be performed.

In the absence of clinical risk factors, per the clinical judgement of the investigator, re-assessment of laboratory parameters are not required. The laboratory results from Part A Visit 1 will serve as Part A baseline values. Part A Visit 9 laboratory results will serve as Part B baseline values.

*Re-assessment of biochemistry and coagulation at Part A Day 57 (Visit 8) is required if there has been an adjustment to the participant's dose of IMP following Part A Day 29 (Visit 7) and/or the participant is on concurrent valproic acid and/ or participant had elevated transaminases during previous visits.

The investigator must review the laboratory report, document this review, and record any clinically significant changes (in the investigator's opinion) occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values normalize, return to baseline, or are no longer considered clinically significant by the investigator or medical monitor or until values stabilize.

If clinically significant values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.3 (Appendix 3), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results would be captured as AEs and appropriate follow-up actions/measures taken, if needed.

Blood sample volume requirements and processing procedures will be detailed in a separate laboratory manual; the maximum cumulative amount of blood taken in any 4-week period,

including PK blood samples, will be 2.55 mL/kg of body weight and will not exceed a total of 50 mL within any 8-week period (Howie 2011), taking into account possible repeat tests. The participant/caregiver must be advised that it may not be safe for the participant to undertake further blood tests within 1 month of any study-related blood draws and to inform the investigator if they suffered any blood loss during the 1-month period leading up to a planned blood draw.

8.3.5. Pregnancy Testing

Refer to Section 5.1 inclusion criteria for pregnancy testing entry criteria.

Pregnancy testing (serum or urine) should be conducted for women of CBP as detailed in the SoA (Section 1.3).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

ASMs are associated with an increased risk of suicidal ideation or behavior.

Participants with EMAS may occasionally develop suicidal ideation or behavior.

Participants being treated with IMP should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of IMP, or at the time of dose changes, either increases or decreases. All factors contributing to suicidal ideation or behavior should be evaluated and consideration should be given to discontinuation of the IMP.

Baseline assessment of suicidal ideation and behavior will be monitored during the study using C-SSRS or clinical interview if C-SSRS is not appropriate.

8.4. Adverse Events, Serious Adverse Events and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.4 (Appendix 4).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs or SAEs, considered related to the IMP or study procedures, or that caused the participant to discontinue the IMP until resolution or the event is considered stable (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4 (Appendix 4).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs*, including SAEs, will be collected from the signing of the ICF until the follow-up visit (Visit 11 for Part A and Visit 12 for Part B) as specified in the SoA (Section 1.3) or end of the participant's participation in the study.

Medical occurrences that begin before the start of IMP but after obtaining informed consent/assent will be reported as non-TEAE.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of becoming aware of the SAE as indicated in Section 10.4 (Appendix 4). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor.

* For the participant's expected seizure types, these do not routinely require documentation as AEs. However, any clinically significant worsening, including a clinically significant change in the pattern or severity of seizures from baseline, must be documented as an AE.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 10.4.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.4.4.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it

along with the IB/package insert and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the ICF has been signed and until 3 months after the follow-up visit (Part B Visit 11 or Part A Visit 12 [if the participant does not continue to Part B]).

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant pregnancy.

The investigator is not obliged to actively monitor for any pregnancies that commence more than 3 months after the follow-up visit. However, if the investigator becomes aware of a new pregnancy outside this time limit, then they should report it as above. The sponsor PVD will follow-up for all pregnancy outcomes.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner (after obtaining the necessary signed informed consent/assent from the female partner) will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate for 6 months after birth, and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue IMP or be withdrawn from the study.

8.4.6. Adverse Events of Special Interest

See Section 10.4.3.

8.5. Pharmacokinetic Assessments

PK assessments will only be performed for Part A of the study. Plasma samples will be collected from all participants for measurement of plasma concentrations of CBD and its major metabolites as specified in the SoA (Section 1.3) as follows:

- Pre-dose (within 60 minutes prior to the morning dose of IMP).

- Post-dose (3 hours [±1 hour]) following morning dose of IMP).

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of CBD and its major metabolites.

IMP concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

The maximum amount of blood taken for PK analysis will be approximately 4 mL.

Caregivers will record the date, time, and meal type (eg, high fat meal [dairy or meat], standard meal [fruit or vegetable] or other [if not fitting into one of the categories above]) for all meals consumed by the participant within 24 hours prior to PK collection.

Analysis of all PK samples will be conducted at a central bioanalytical laboratory and additional details are provided in the laboratory manual.

8.6. Pharmacodynamic Assessment

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics Assessment

In Part A, samples for epilepsy gene panel analysis will be collected at the time point indicated in the SoA (Section 1.3), if the participant/caregiver/legal representative provides consent/assent.

Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

Details on processes for collection, shipment, storage, and destruction of these samples can be found in a separate laboratory manual. No genetic samples will be retained following the analysis.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.10. Healthcare Resource Utilization

Healthcare resource utilization parameters are not evaluated in this study.

8.11. Special Circumstances

During special circumstances (eg, COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. In cases where participants are not able to perform all protocol-defined assessments due to special circumstances, the investigator must discuss with the medical monitor potential mitigation approaches.

For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Visits may be done by a telephone call, other means of virtual contact or home visit, if appropriate.
- Participant and/or clinician-rated outcomes assessments may be done by videoconference, telephone call, other means of virtual contact, if possible.
- An alternative approach for IMP dispensing, secure delivery, and collection may be sought.
- Visits may take place in a different location than defined in the protocol. If this is not feasible, then the visit may take place virtually with documentation of the means of communication (eg, phone call or videoconference).
- Biological samples may be collected and analyzed at a different location than defined in the protocol. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until shipping/processing.
- If it is not possible to collect the biological samples or safety assessments (eg, ECG, vital signs) within the interval predefined in the protocol (see the SoA [Section 1.3]), then the interval may be extended up to a maximum duration of 7 days.
- If a safety assessment cannot be performed within the modified window, the investigator must review the benefit-risk for participant continuation in the study and record this in the medical records.

The rationale (eg, the specific reasons behind the changes) and outcome of the discussion with the medical monitor will be documented in the medical record. Information on how each visit was performed will be recorded in the eCRF.

9. STATISTICAL CONSIDERATIONS

[redacted]

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	All participants who sign the ICF.
Randomized	All Enrolled participants who are randomized to IMP. This analysis set will be used to summarize randomized participants in the participant disposition summary table.
Part A ITT	All participants in Part A who are randomized, receive at least 1 dose of IMP during Part A, and have post-baseline efficacy data. Participants will be analyzed according to their randomized treatment group. The Part A ITT analysis set is the primary analysis set for all efficacy endpoints in Part A.
Part A Safety	All randomized participants who are exposed to IMP. Participants will be analyzed according to the IMP they receive.
Part B Safety	All participants who enter Part B and receive at least 1 dose of IMP during Part B will be included.

Abbreviations: ICF = informed consent form; IMP = investigational medicinal product; ITT = intention to treat.

9.4. Statistical Analyses

The interim analysis SAP, SAP and ADR will be finalized prior to the first interim analysis and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned methodology.

9.4.1. General Considerations

Unless stated otherwise, continuous data will be summarized using descriptive statistics comprising the number of participants with data to be summarized (n), mean, SD, median,

minimum (min), and maximum (max). Categorical variables will be summarized by the frequency and proportion of participants falling into each category.

For plasma concentration data and PK parameters, geometric mean, CV, and geometric CV will also be computed.

Unless stated otherwise, baseline is defined as the last record or measurement collected prior to the first dose of IMP on Day 1 (Part A Visit 3). Baseline for Part B is the same as the baseline for Part A.

9.4.2. Primary Endpoint(s)

Part A:

The primary efficacy endpoint is EMAS-associated seizure frequency (myoclonic-atonic, atonic, tonic, clonic, or tonic clonic) over the 14-week treatment period.

The primary estimand for this study is defined by the following 3 components:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: change in EMAS-associated seizure frequency during the 14-week treatment period compared to baseline.
- Measure of IMP effect: change in EMAS-associated seizure frequency during the treatment period, regardless of any intercurrent events. This measure of effect follows the treatment policy strategy for handling intercurrent events.

The analysis of the primary efficacy endpoint will utilize Bayesian methodology to borrow external data from the historical pivotal studies in DS, LGS, and TSC. Active treatment groups will be pooled across doses within each indication to achieve a single estimated historical treatment effect for each indication. A Bayesian hierarchical model that dynamically determines the amount of information to be "borrowed" from the historical studies in the estimation of the treatment effect in the EMAS population will be used (Viele 2014).

For the primary efficacy analysis, a single Bayesian hierarchical linear model will be applied as specified in the interim analysis SAP, SAP, and ADR to the 4 populations (DS, LGS, TSC, and EMAS). The model will include a population-specific intercept, a population-specific treatment effect, an adjustment for prespecified baseline covariates (log baseline seizure frequency, age at onset of seizures, and clobazam use), and a shared residual error. Prior distributions are prespecified for each of the model parameters. A Bayesian hierarchical distribution is specified for the treatment effects across populations, in which each study-specific treatment effect has a normal distribution centered on a grand overall treatment effect. A prior on the variance of this distribution will be specified to induce dynamic borrowing of the data from the previous pivotal trials in DS, LGS and TSC, in which the degree of similarity of the EMAS observed data relative to the historical data influences the magnitude of borrowing. Markov-Chain Monte Carlo methods will be used to estimate the Bayesian posterior distribution for parameters in the primary analysis model. Statistical inference and hypothesis testing will be conducted on the EMAS-specific treatment effect parameter corresponding to the primary efficacy hypothesis (ie, ratio of the change in seizure frequency between GWP42003-P and placebo). Complete details will be provided in the interim analysis SAP, SAP, and ADR.

Part B:

No primary efficacy endpoint is defined for Part B of the study. The primary objective for Part B is to evaluate the long-term safety and tolerability of GWP42003-P, evaluated by assessing the frequency of TEAEs; laboratory tests; vital signs; ECGs; Tanner Staging, and C-SSRS results. Data will be presented as per Section 9.4.5.

9.4.2.1. Missing Data

To ensure consistency with the previous pivotal trials in DS, LGS and TSC, missing data will be imputed using methodology implemented in the previous pivotal trials. More specifically, for participants missing seizure data due to withdrawal or intercurrent events, a 28-day average is imputed for each participant as

$$\frac{\text{Number of seizures recorded in the period for participant}}{\text{Number of days that seizure data was recorded for participant in the period}} \times 28$$

The change in seizure frequency from baseline is calculated using the imputed value.

9.4.2.2. Sensitivity Analyses

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

- Primary endpoint analysis repeated using the following imputation methods for missing eDiary data during the treatment period only:
  - Any intermittent missing data for the number of seizures arising from unreported days in the eDiary will be imputed using the worst (highest number of seizures) of the following for each participant: LOCF, NOCB, and the mean daily number of seizures during the treatment period based on nonmissing data:

$$\frac{\text{Number of seizures}}{\text{Number of reported days in the eDiary}}$$

  - For participants in the active arm who withdraw from the study due to an adverse event or lack of efficacy, missing eDiary data will be imputed as the baseline rate or the average seizure frequency during the treatment period, whichever is higher.
- To test the sensitivity of the results of the primary analysis to the degree of borrowing introduced by the dynamic borrowing prior, a model similar to the primary analysis model will explore a range of degrees of fixed borrowing of the historical data. More specifically, the variance of the Bayesian hierarchical distribution specified for the treatment effects across populations (Section 9.4.2) will be fixed across a set of values specified in the ADR ranging from very low (full borrowing) to very high (no borrowing). Summaries of the estimated treatment effect within each sensitivity analysis will be provided to assess the robustness of the primary analysis results to the degree of borrowing.

9.4.3. Secondary Endpoint(s)

The following endpoints will be compared by treatment group over the treatment period:

9.4.3.1. Key Secondary Endpoints

- Proportion of participants who achieve ≥ 50% reduction from baseline in EMAS-associated seizures
- CGIC score.
- Change in total seizure frequency compared to baseline
- Change in EMAS-associated seizure frequency compared to baseline (Part B only)

Part A:

The first key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: proportion of participants who achieve ≥ 50% reduction from baseline in EMAS-associated seizures over the 14-week treatment period.
- Measure of IMP effect: proportion of responders during the treatment period, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

The second key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: CGIC score at Week 14.
- Measure of IMP effect: CGIC score at Week 14, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

The third key secondary estimand for this study is defined as follows:

- Target population: participants with EMAS-associated seizures who have not achieved adequate control from other ASMs.
- Endpoint: change in total seizure frequency during the 14-week treatment period compared to baseline.
- Measure of IMP effect: change in total seizure frequency during the treatment period, regardless of any intercurrent events. This measure of effect follows a treatment policy strategy for handling intercurrent events.

For the first key secondary endpoint, a binary indicator for response (at least a 50% reduction from baseline in seizure frequency over the 14-week treatment period) equaling either 1 or 0, a single Bayesian hierarchical logistic regression model will be applied to the 4 populations (DS,

LGS, TSC, and EMAS). The model will take a form similar to the primary analysis model. Complete details will be provided in the ADR.

For CGIC, a Bayesian hierarchical ordinal logistic regression model will be applied to the 4 populations. This model will take a form similar to the primary analysis model and will be detailed in the ADR.

Change in total seizure frequency will be analyzed in the same way as the primary endpoint. Full details will be provided in the ADR.

Part B:

Key secondary endpoints for Part B (long term) will be descriptive, with no formal statistical inference, and will be summarized by treatment group over time, using appropriate summary statistics.

9.4.3.2. Other Secondary Efficacy Endpoints

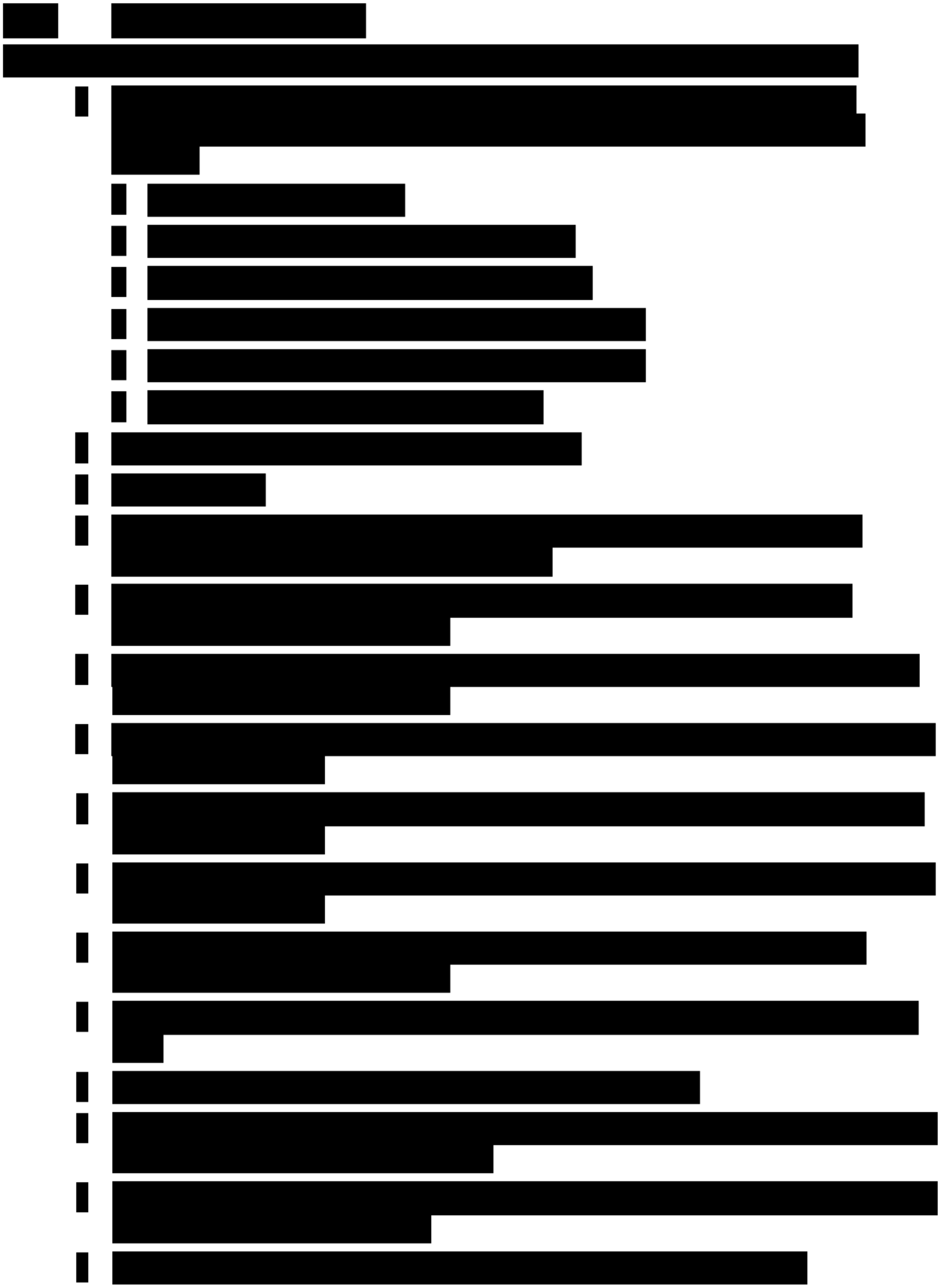
- PGIC score
- Proportion of participants who achieve ≥ 25%, ≥ 75%, and 100% reduction from baseline in EMAS-associated seizures
- Proportion of participants who achieve ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction from baseline in total seizures
- Change from baseline in number of EMAS-associated seizure-free days (Part A only)
- Time to baseline seizure frequency (Part A only)
- Proportion of participants with ≥ 25% and ≥ 50% reduction in the number of days per week with myoclonic seizures during the treatment period

Secondary endpoints will be summarized by treatment group over time using appropriate descriptive statistics for Part A and Part B.

9.4.3.3. Safety Secondary Endpoints (Part A Only):

- Frequency of TEAEs over the 14-week treatment period
- Laboratory tests
- Vital signs
- ECG
- Tanner Staging
- Change in
  - C-SSRS ideation score
  - Number of suicide attempts in the C-SSRS

Safety data for Part A will be presented as per Section 9.4.5.



9.4.5. Safety Analysis

Safety data will be summarized using appropriate descriptive statistics.

9.4.5.1. Treatment Compliance and Extent of Treatment Exposure

Treatment compliance and exposure to treatment will be summarized.

9.4.5.2. 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 produced by preferred term and System Organ Class for the safety analysis set. The number of participants reporting at least 1 AE will be provided.

The following summaries will be produced:

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

9.4.5.3. Clinical Laboratory Data

Clinical laboratory data at each visit, along with the change from baseline and percent change from baseline to each post-baseline visit will be summarized for the safety analysis set using appropriate summary statistics. Categorical shift tables will also be presented, showing the numbers of participants with values outside the normal range.

9.4.5.4. Vital Signs, ECG, Physical Examination and Other Safety Data

Vital signs, ECG, physical examination, and C-SSRS data will be summarized for the safety analysis set at screening, baseline, and each time point during the treatment period using appropriate descriptive statistics. Changes from baseline to each post-baseline visit will also be summarized for vital signs and ECG.

9.4.6. Other Analysis

Following completion of Part A of the study, data will be cleaned and an analysis of all Part A data will be conducted. The SAP will describe the planned analyses in greater detail.

9.5. Interim Analyses

Interim analyses will be performed when 60, 75, 90, and 105 participants are randomized in Part A. The maximum sample size will be 120 randomized participants. The interim analyses or sample size updates will be based on the Goldilocks methodology (Broglio 2014) (Saville 2014) in which Bayesian predictive probabilities are used to make sample size decisions. Complete details of the interim analyses will be provided in the interim analysis SAP and ADR.

9.5.1. Interim Analysis Review Committee

An independent statistician will perform the interim analysis and the IARC will make one of 3 possible recommendations to the sponsor: 1) stop accrual for expected success and conduct the primary analysis after all randomized participants have 14-week follow-up; 2) a nonbinding recommendation to stop the study for futility; or 3) continue enrolling to the next interim analysis or maximum sample size. A full detailed description of how the interim analyses will be conducted (eg, logistics, results delivery) will be documented in an IARC charter.

Blinding

In order to maintain study blinding, the interim analyses will be conducted by an unblinded statistical team independent from the day-to-day operational team. Enrollment will not be paused during the interim analysis. Interim analyses results will be shared only with the IARC, which will make a recommendation to the sponsor according to the prespecified adaptive algorithm. The sponsor will be provided the general IARC recommendation regarding sample size, but not the details of the interim analysis (eg, model results, treatment effects, posterior probabilities).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Study Contacts

10.1.1. Investigator Details

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

10.1.2. Sponsor Contact Details

Pharmacovigilance Department — SAE Reporting (24-hour reporting):	**AEreporting@jazzpharma.com** **ClinicalSafety@jazzpharma.com** **Or via fax to 1-800-974-7405**
Sponsor:	Jazz Pharmaceuticals Inc. on behalf of GW Research Ltd 3170 Porter Drive, Palo Alto, CA 94304
Sponsor's Medical Expert:	[redacted] Tel: [redacted] E-mail: [redacted]
24-hour Emergency Contact details and Clinical Project Manager:	Please refer to the Sponsor and Related Contact Details form in the study site file.
Clinical Study Supplies:	Jazz Pharmaceuticals Inc. on behalf of GW Research Ltd Tel: +44 (0) 1795 435 029 Fax: +44 (0) 1795 475 439

10.1.3. Contract Research Organizations

Contract Research Organization and Clinical Site

[redacted]

Clinical Laboratory

[redacted]

[redacted]

Testing Lab:

[redacted]

Bioanalytical Laboratory

[redacted]

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH Guidelines including ICH E6(R2).
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Protocol amendments must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent/assent documents. The IRB/IEC and regulatory authorities must be informed of all amendments and give approval for any substantial amendments, except for changes necessary to eliminate an immediate hazard to study participants. 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 the sponsor.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Note that in some regions this may be the sponsor's responsibility.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR (if applicable), ICH guidelines, the IRB/IEC, European Directive 2001/20/EC (including amendments since 2001), Directive 2005/28/EC for clinical studies (if applicable), and all other applicable local regulations.

10.2.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.2.3. Informed Consent/Assent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to withdraw at any time. Participants or their caregivers will be required to sign a study-specific statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, General Data Protection Regulation, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent/assent was obtained, and the date the written consent/assent was obtained, before the participant completes any protocol-specific screening procedures or any IMPs are administered. The authorized person obtaining the informed consent/assent must also sign and date the ICF.

- If in the investigator's opinion, a participant lacks the cognitive capacity to provide assent, this should be documented in the participant's source documents and consent should be obtained from the caregiver in accordance with local regulations.
- For participants who are able to provide assent, the caregiver must also provide written consent in accordance with local regulations.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study per IRB/IEC requirements.
- A copy of the completed ICF(s) must be provided to the participant.

10.2.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the sponsor.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent/assent.
- The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors, clinical study monitors, or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.2.5. Committees Structure

10.2.5.1. The Epilepsy Study Consortium

An independent The Epilepsy Study Consortium (TESC) will be instated to confirm EMAS diagnosis and verify the ILAE seizure types of screened participants prior to start of the baseline period (Part A Visit 2). See Section 8.1.4 and Section 8.1.5.

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

10.2.6. Dissemination of Clinical Study Data

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

10.2.7. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the study eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the Quality Tolerance Limits and remedial actions taken will be summarized in the Clinical Study Report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the clinical monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.2.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in a source data verification plan.

- The investigator must maintain accurate documentation (attributable, legible, contemporaneous, original, accurate and complete, consistent, enduring, and available [ALCOA+] source data) that supports the information entered in the eCRF.
- Study monitors will perform (on-site or remotely) ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.2.9. Study and Site Start and Closure

10.2.9.1. First Act of Recruitment

The first act of recruitment is when the first participant signs the ICF and will be the study start date.

10.2.9.2. Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further IMP development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Planned target number of participants achieved earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.2.10. Publication Policy

- All information concerning the IMP and operations of the sponsor such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the sponsor and not previously published is considered confidential by the sponsor and shall remain the sole property of the sponsor. The investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the sponsor.
- The raw data generated by a site from this study may be obtained from the sponsor by the site or the investigator on request. Should they wish, investigators are allowed to conduct their own analyses on data generated at their own site and are permitted to present or publish such information in accordance with the relevant terms set out in the clinical study agreement. No single site publication may precede a multisite publication.
- All publications, eg, manuscripts, abstracts, oral/slide presentations, or book chapters based on this study, must be submitted to the sponsor Medical Affairs Department and, as applicable, the sponsor Publication Committee for corporate review before release. To ensure adequate time for the sponsor 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 principal investigators must then incorporate all reasonable comments made by the sponsor into the publication.
- The sponsor 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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.3. Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the central laboratory, wherever possible.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP administration and/or response evaluation. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results must be recorded in the source documents. All abnormal, clinically significant lab results obtained locally would be captured as AE's and appropriate follow-up actions/measures taken, if needed.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Refer to Section 8.3.4 for more detail.

Table 6: Protocol-required Laboratory Tests

Biochemistry (Serum)	**Hematology (Whole Blood)**	**Urinalysis (Urine)[a,b,d]**	**Hormone Panel (Serum) (CBP only)**
ALT Albumin ALP AST Calcium Creatinine[e] Creatine Kinase Direct bilirubin GGT Potassium LDL cholesterol HDL cholesterol LDH Total cholesterol Sodium TBL Total protein Urea (blood urea nitrogen) Glucose Chloride Triglycerides Inorganic phosphate IGF-1	Hematocrit Hemoglobin MCV MCH Platelets RBC count WBC count with automated differential Neutrophils[c] Lymphocytes[c] Monocytes[c] Eosinophils[c] Basophils[c]	Blood Glucose Nitrites pH Protein WBCs Specific gravity Ketones Urobilinogen Bilirubin Pregnancy test (human chorionic gonadotropin) (female participants of CBP only)	Pregnancy test (human chorionic gonadotropin)
	Coagulation INR		**Other** Genetic testing

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBP = childbearing potential; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; IGF-1 = insulin-like growth factor-1; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; TBL = total bilirubin; WBC = white blood cell.
Note: Investigators must document their review of each laboratory safety report.

[a] Analyzed at the study site using an automated analyzer/urine dipstick.
[b] In accordance with clinical laboratory or local standard procedures, urine microscopy/sediment examinations will only be performed if there is an abnormality in urinalysis.
[c] Absolute and % of total WBC will be measured.
[d] Urinalysis will be completed where urine collection is possible.
[e] Estimated glomerular filtration rate will be calculated using the Schwartz equation.

10.4. Appendix 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

10.4.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, starting at any time from informed consent/assent through the follow-up visit, whether or not considered related to the IMP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) occurring at any time from informed consent/assent through the follow-up visit.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, biochemistry, coagulation, or urinalysis) or other safety assessments (eg, electrocardiogram, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/serious AE (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. *Status epilepticus*. 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. *Status epilepticus* is defined as any seizure lasting 30 minutes or longer.
h. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. – Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of IMP dependency or IMP abuse.

10.4.3. Adverse Events of Special Interest

AEs of special interest for this study include:

- Drug-induced liver injury

- Pneumonia
- Rash
- Seizure worsening (increased frequency or severity of seizures or new emergent seizure types).

10.4.4. Recording and Follow up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor PVD in lieu of completion of the required form. • There may be instances when copies of medical records for certain cases are requested by the sponsor PVD through eCRF queries. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor PVD. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
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 (ie, month and year or, in exceptional circumstances, just year). When the actual start date becomes known the eCRF must be updated to replace the previously recorded date.
Outcome
The outcome of the event must be recorded accurately and classified into one for the following categories: • Recovered/resolved. • Recovered/resolved with sequelae. • Not recovered/not resolved. • Fatal.
Action Taken with Study Treatment
The action taken with study treatment must be recorded accurately and classified into one of the following categories: • Not applicable. • Dose Not Changed. • Dose Increased. • Dose Reduced. • Dose Interrupted.

- Drug Withdrawn.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Other measures to evaluate AEs and SAEs may be utilized (eg, National Cancer Institute Common Terminology Criteria for Adverse Events).

Assessment of Causality

- The investigator is obligated to assess the relationship between IMPs and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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".
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor PVD. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor PVD.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor

to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- Any ongoing SAEs should be followed up until resolution, wherever possible.
- Any AEs considered related to the IMP by the investigator or the sponsor should be followed up until resolution or the event is considered stable.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor PVD with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE to the sponsor PVD within 24 hours of receipt of the information.
- The investigator is not obliged to actively monitor for any new SAEs that occurred after the 14 days post final dose follow-up visit. However, if the investigator becomes aware of any deaths or a new IMP-related SAE occurring within 28 days of the final dose of IMP, these should be reported to the sponsor PVD.
- Any other problem discovered after 14 days post dose which is deemed to be an unexpected safety issue and is likely to have an impact on participants who have taken part in the study must be treated as an SAE and reported to the sponsor PVD as described below. The sponsor PVD may request safety follow-up information after the final study visit in order to investigate a potential safety issue.

10.4.5. Reporting of SAEs

SAE Reporting to the Sponsor Pharmacovigilance Department

- All SAEs occurring during the study must be reported to the sponsor with any other supporting information and recorded in the AE section of the eCRF.
- All SAEs must be reported directly to the sponsor PVD within 24 hours of discovery or notification of the event, through recording in the eCRF.
- After the study is completed, and following database lock, the eCRF system will be locked to prevent the entry of new data or changes to the existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the eCRF system has been locked, the site should still report this information to the sponsor PVD.
- Contacts for SAE reporting can be found in Section 10.1.2.

10.4.6. Urgent Safety Measures

The sponsor and investigator may take appropriate urgent safety measures in order to protect the participants of a clinical study against any immediate hazard to their health or safety. If such measures need to be taken by the investigator, they must notify the sponsor immediately or at least within 24 hours of awareness. The sponsor will report urgent safety measures to regulatory authorities within 24 hours of awareness, wherever possible, and will provide a written report to the regulatory authorities and IRB/IEC within 3 days.

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

Female Participants of Nonchildbearing Potential (NCBP)

Female participants in the following categories are considered as NCBP:

1) Participants who are premenarchal.
2) Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

3) Postmenopausal female with documentation of cessation of menses for ≥ 12 consecutive months without an alternative medical cause.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Female Participants of Childbearing Potential

Female participants are considered of childbearing potential (fertile):

- From the time of menarche until becoming postmenopausal (ie, documentation of cessation of menses for ≥ 12 consecutive months without an alternative medical cause) unless permanently sterile (as described above as NCBP).

Infertile Male Participants

A man is considered infertile when permanently sterile following bilateral orchidectomy, or any other documented cause of infertility.

Fertile Male Participants

A man is considered fertile after puberty unless permanently sterile as described above.

10.5.2. Contraception Guidance

CONTRACEPTIVES[a], ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.* • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral tubal occlusion. • Azoospermic partner (vasectomized or due to a medical cause).

Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been *confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a) Contraceptive use by male or female participants should also be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c.) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.6. Appendix 6: Liver Safety: Actions and Follow-up Assessments

All investigational sites are required to submit to the sponsor PVD the laboratory results for any participant after randomization that meets the criteria for the selected laboratory parameters as follows:

- 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%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for > 2 weeks.
- ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).

These reports must be sent to the sponsor PVD using the fax number or by e-mail for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the participant's baseline laboratory results with all reports to the sponsor PVD.

Abnormal values in AST and/or ALT with or without concurrent 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 as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, INR, full blood count (and differential count), eosinophil counts, ALP, and GGT levels, creatine kinase levels, detailed history, and physical examination. Participants should be followed with frequent (every 48 to 72 hours) repeat clinical laboratory assessments and any other appropriate assessments until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

Elevations in ALT or AST > 3 × ULN **or** TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours' notice of abnormal results. If the participant is no longer at the investigational site, repeat assessments may be performed at a local laboratory and the results sent to the sponsor PVD.

Refer to Section 7 for study withdrawal/discontinuation criteria.

10.7. Appendix 7: Abbreviations and Definitions

List of Abbreviations and Definitions of Terms

AE	Adverse event
ADR	Adaptive Design Report
ASM	Antiseizure medication (former terminology was antiepileptic drug [AED])
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDS	Botanical Drug Substance
BID	Twice daily
[redacted]	[redacted]
C	Clinic
[redacted]	[redacted]
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CBP	Childbearing potential
CEQ-P	Treatment Credibility/Expectancy Questionnaire and Parent Version
CFR	Code of Federal Regulations
CGIC	Caregiver Global Impression of Change score
[redacted]	[redacted]
CID	Complex Innovative Trial Design
COVID-19	Coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
Day 1	The day a participant first receives IMP in this study.
DRF	Diagnostic Review Form
DS	Dravet syndrome
E/W	Early withdrawal
EAP	Expanded access program
EC	Ethics Committee
ECG	12-lead electrocardiogram
eCRF	Electronic case report form

eDiary	Electronic diary
EAP	Expanded access program
EEG	Electroencephalogram
EMAS	Epilepsy with myoclonic-atonic seizures
End of study	Date of the last participant's final completed scheduled visit or last completed study assessment, whichever occurs last
Enrolled participant	Any participant who has provided written informed consent/assent to take part in the study
EOT	End of treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
E/W	Early withdrawal
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GW	GW Research Ltd
HDL	High-density lipoprotein
[redacted]	[redacted]
IARC	Interim Analysis Review Committee
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
ILAE	International League Against Epilepsy
IMP	Investigational medicinal product; term used to describe both investigational active product and reference therapy (placebo).
INR	International normalized ratio; a calculation made to standardize prothrombin time.
Investigator	Study principal investigator or a formally delegated study physician.
IRB	Institutional Review Board
IRT	Interactive Response Technology

ITT	Intention to Treat
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LGS	Lennox Gastaut syndrome
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
N/A	Not applicable
NCBP	Nonchild bearing potential
NOCB	Next observation carried backward
OL	Open-label
OLE	Open-label extension
OS	Oral solution
P	Phone
Participant	Any participant enrolled in the study.
[redacted]	[redacted]
[redacted]	[redacted]
PGIC	Physician Global Impression of Change
PK	Pharmacokinetic(s)
PVD	Pharmacovigilance department
RBC	Red blood cell
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Screen failure	Participants who consent/assent to participate in the clinical study but are not subsequently randomized
Status epilepticus	Any seizure lasting 30 minutes or longer
SIF	Seizure Identification Form
SoA	Schedule of activities
Start of the study	The date the first participant signs the informed consent/assent form
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event

TESC	The Epilepsy Study Consortium
Treatment duration	The length of time the IMP will be administered.
Study duration	The maximum length of time a participant can be in the study.
Study intervention	Investigational medicinal product(s), marketed product(s), or placebo, intended to be administered to a study participant per protocol.
TSC	Tuberous sclerosis complex
ULN	Upper limit of normal
US	United States
WBC	White blood cell
wks	Weeks

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1.1 (Version 3)	25 August 2022
Amendment 01 (Version 2)	21 June 2022
Original Protocol (Version 1)	13 September 2021

Amendment 1.1 (25 August 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in Amendment 1.1 was to ensure alignment between study procedures and Italy Regulatory Agency guidance. Specific updates incorporated into Amendment 1.1 are listed below. Minor editorial changes are not presented.

Section # and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities (SoA)	SoA: Part B: added physical examination for Week 14 (Month 3 visit) and Week 24 (Month 6 visit) study visits.	To have closer timelines for physical examination in Part B of the study.
	SoA: Part A and Part B: under column for "Notes" specified that height, length, and head circumference will be measured during physical examination.	To clarify that where physical examination appears now or was added, assessments for height, length, and head circumference will also occur.
	SoA: Part A and Part B: removed row for "Height/length."	For clarity since details regarding assessments for height, length, and head circumference during physical examination were included under column for "Notes."
	SoA: Part B Table Note: Text added specifying that "height, length, and head circumference will be collected at remote visits."	To clarify that these measurements will be collected during remote visits.
2.3 Benefit/Risk Assessment	Added a link to Section 2.2 (Study Rationale).	To outline the potential benefits of GWP42003-P.
	Added statement regarding favorable benefit-risk profile of GWP42003-P.	

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	#2: An additional inclusion criterion specifying "minimum body weight required for eligibility" has been added.	To keep the blood volume within the maximum limits allowed during the study.
5.2 Exclusion Criteria	#25: Specified estimated glomerular filtration rate (Schwartz equation) < 60 mL/min.	To provide clarification per Health Authority request.
8.3.1 Physical Examinations	Specified that height, length, and head circumference will be collected during physical examinations.	
Table 6	Footnote "e" added to specify that estimated glomerular filtration rate will be calculated using the Schwartz equation.	

Amendment 01 (21 June 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in Amendment 01 was to ensure alignment between study procedures and Medicines and Healthcare products Regulatory Agency guidance. Specific updates incorporated into Amendment 01 are listed below. Minor editorial changes are not presented.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Revised the erroneous "yes" to "no" to accurately indicate that a Data Monitoring Committee (DMC) will not be utilized in this study.	To clarify no DMC will be employed in this study.
2.2 Study Rationale, 4.2 Scientific Rationale for Study Design, and 4.3 Justification for Dose	Revised description of the expanded access program (EAP) to indicate it was initiated by the investigator and authorized by the Food and Drug Administration.	To describe the nature of the EAP.
5.2 Exclusion Criteria	Revised exclusion criterion for serum total bilirubin (TBL) from ≥ 2 × upper limit of normal (ULN) to > 1.5 × ULN. Also specified exclusionary TBL (> 3 × ULN) and/or direct bilirubin	To update TBL and direct bilirubin exclusion criteria, particularly as they relate to participants with Gilbert's disease.

Section # and Name	Description of Change	Brief Rationale
	(> 1 × ULN) for participants diagnosed with Gilbert's disease.	
6.5 Dose Modification	Inserted reference to the "CBD Dose Adjustment" section of the current approved GWP42003-P Investigator's Brochure (IB).	To provide reference to the IB, where detailed information regarding potential drug interactions and associated dose modifications may be found.
6.8 Concomitant Therapy	Added details regarding key restrictions on concomitant therapies. Also inserted reference to the "CBD Dose Adjustment" section of the current approved GWP42003-P IB.	To clarify restrictions regarding concomitant medications and provide reference to the IB, where detailed guidance on potential drug interactions may be found.
10.5.1 Definitions (in Appendix 5: Contraceptive and Barrier Guidance)	Added definition of postmenopausal female.	To provide clarity regarding the definition of postmenopausal status.

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