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4 **Effect of Adjunctive Oral Cannabidiol (CBD) vs. Placebo on Convulsive**
5 **Seizure Frequency in Dravet Syndrome**
6 **Supplement 1**

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TITLE: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.

STUDY CODE: GWEP1424

EudraCT NUMBER: 2014-002939-34

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Study Code: GWEP1424
EudraCT Number: 2014-002939-34
Version 1 Date 22 Jul 14

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Investigator Agreement

I have read the attached protocol entitled "A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome", dated 22 Jul 14 and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the FDA regulations relating to good clinical practice and clinical trials and the European Union (EU) Clinical Trials Directive (2001/20/EC) and subsequent applicable regulatory/statutory instruments, or the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (ICH GCP) where the EU Directive does not apply and to complete a Form 1572 if required.

I am not aware that any conflicts of interest, financial or otherwise, exist for myself, my spouse [or legal partner] and dependent children and agree to confirm this in writing if required and update as necessary.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GW Research Ltd.

Center No: _____

Print Name: _____

Date: _____

Principal Investigator

(DD Month YYYY)

Signature: _____

GW Authorization 103

Print Name: **PPD** 104

Date: *05/16/14*

Clinical Manage 107

(DD Month YYYY)

Signature: _____

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1 PROTOCOL SYNOPSIS

Study Title	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.
Clinical Study Type	Phase Three Study
Indication	Dravet syndrome (DS)
Primary Objective	To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the maintenance period of the study in convulsive seizure frequency. The dose response effect between two GWP42003-P Dose Levels and placebo will also be explored. Convulsive seizures are defined as tonic-clonic, tonic, clonic or atonic and non-convulsive seizures as myoclonic, partial or absence.
Secondary Objective(s)	<ul style="list-style-type: none"> • To assess changes from baseline in non-convulsive seizure frequency, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, quality of life and conduct behavioral and cognitive assessments in patients taking GWP42003-P as an adjunctive treatment, when compared with placebo. • To assess the safety of both GWP42003-P doses when compared with placebo.
Study Design	<p>This study is a 1:1:1 randomized, double-blind, 14-week comparison of two Dose Levels of GWP42003-P versus placebo. The treatment period will consist of a two-week titration period followed by a 12-week maintenance period. The treatment period will be followed by a 10-day taper period and a four-week follow-up period. The study will aim to determine the efficacy, safety and tolerability of two Dose Levels of GWP42003-P compared with placebo. The High Dose Level will be as recommended by the Data Safety Monitoring Committee (DSMC) after assessment of safety and pharmacokinetic data from Part A of study GWEP1332. The Low Dose Level will be defined as 50% of the High Dose Level. Patients in the placebo group will be split into two equivalent cohorts: half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes. The first patient will not enroll into this study until the DSMC has reviewed the safety data from Part A of study GWEP1332.</p> <p>Following study completion, all patients will be invited to continue to receive GWP42003-P in an open label extension (OLE) study (under a separate protocol).</p>
Primary Endpoint	The primary endpoint is the mean percentage change from baseline in convulsive seizure frequency during the maintenance period (Day 15 to the end of the evaluable period) in patients taking GWP42003-P

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	compared with placebo.
Secondary Endpoint(s)	<p>The following endpoints will be compared between the three treatment groups over the 12-week, double-blind maintenance period:</p> <ul style="list-style-type: none"> • Number of patients experiencing a >25% worsening, -25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline. • Number of patients who are convulsive seizure free. • Percentage changes from baseline in non-convulsive seizure frequency. • Change in types of seizures. • Changes from baseline in usage of rescue medication. • Changes from baseline in number of inpatient hospitalizations due to epilepsy. • Changes from baseline in Sleep Disruption 0–10 Numerical Rating Scale (0–10 NRS) score. • Changes from baseline in Epworth Daytime Sleepiness Scale (EDSS) score. • Changes from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score. • Changes from baseline in the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) score. • Change in cognitive function as measured with a cognitive assessment battery. • Caregiver Global Impression of Change (CGIC). <p>The safety profile of GWP42003-P compared with placebo will also be the assessed at each Dose Level by measuring:</p> <ul style="list-style-type: none"> • Adverse events (AEs). • Vital signs. • Physical examination parameters. • 12-lead Electrocardiogram (ECG). • Laboratory parameters. • Columbia-Suicide Severity Rating Scale (C-SSRS) score. • Cannabis Withdrawal Scale (CWS) score. • Abuse liability.
Sample Size	<p>A total of 120 patients will be enrolled to receive one of two Dose Levels of active investigational medicinal product (IMP) or placebo on a 1:1:1 basis (40 patients per treatment group). Patients in the placebo group will be split into two cohorts (20 receiving Low Dose Level dosing volumes and 20 receiving High Dose Level dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses</p>

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	<p>of efficacy.</p> <p>If it is assumed that patients in the placebo group will experience a mean reduction in convulsive seizure frequency of 10% (from baseline), this sample size of 40 patients per group will be sufficient to detect a difference of 40% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in convulsive seizures). This is based on a standard deviation of 63%, using a two-tailed 5% significance level and 80% power.</p>
<p>Summary of Patient Eligibility Criteria</p>	<p>Inclusion: Patients meeting the following criteria will be considered eligible for this study:</p> <ul style="list-style-type: none"> • Patient and/or parent(s)/legal representative must be willing and able to give informed assent/consent for participation in the study (see Section 15.2). • Patient and their caregiver must be willing and able (in the investigator's opinion) to comply with all study requirements. • Patient must be male or female aged between two and 18 years (inclusive). • Patient must have a documented history of DS which is not completely controlled by current antiepileptic drugs (AEDs). • Patient must be experiencing four or more convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the 28-day baseline observation period. • Patient must be taking one or more AEDs at a dose which has/have been stable for at least four weeks. • All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) must have been stable for four weeks prior to screening and patient and caregiver are willing to maintain a stable regimen throughout the study. • Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant to be notified of participation in the study. <p>Exclusion: The patient may not enter the study if ANY of the following apply:</p> <ul style="list-style-type: none"> • Patient has clinically significant unstable medical conditions other than epilepsy. • Patient has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or randomization, other than epilepsy. • Patient has clinically significant abnormal laboratory values, in the investigator's opinion, at screening or randomization. • Patient has clinically relevant abnormalities in the ECG measured at screening or randomization. • Patient has any concurrent cardiovascular conditions which will, in

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	<p>the investigator's opinion, interfere with the ability to assess their ECGs.</p> <ul style="list-style-type: none"> • Patient has a history or presence of alcohol or substance abuse within the last two years prior to the study or daily consumption of five or more alcohol-containing beverages. • Patient is currently using, or has in the past used, recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex[®]) within the three months prior to study entry and is unwilling to abstain for the duration of the study. • Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure due to postural changes. • Patient has ingested alcohol in the 24-hour period prior to the first study visit and/or is unwilling to abstain from drinking alcohol throughout the treatment period. • Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMPs (e.g., sesame oil). • Female patient is of child bearing potential or male patient's partner is of child bearing potential; unless willing to ensure that they or their partner use effective contraception, for example oral contraception, double barrier, intra-uterine device, during the study and for three months thereafter (however a male condom should not be used in conjunction with a female condom). • Female patient is pregnant, lactating or planning pregnancy during the course of the study and for three months thereafter. • Patient has been part of a clinical trial involving another IMP in the previous six months. • Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or affect the patient's ability to participate in the study. • Patient has significantly impaired hepatic function at screening (Visit 1) or randomization (Visit 2) (Alanine aminotransferase [ALT] >5 × upper limit of normal [ULN] or total bilirubin [TBL] >2 × ULN) OR the ALT or Aspartate aminotransferase (AST) >3 × ULN and (TBL >2 × ULN or international normalized ratio [INR] >1.5). <i>This criterion can only be confirmed once the laboratory results are available; patients randomized into the study who are later found not to meet this criterion should be withdrawn from the study.</i> • Following a physical examination the patient has any abnormalities that, in the opinion of the investigator, would prevent the patient from safe participation in the study.
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	<ul style="list-style-type: none"> • Patient is unwilling to abstain from donation of blood during the study. • There are plans for the patient to travel outside their country of residence during the study. • Patient has previously been randomized into this study. • Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS at screening.
Criteria for Withdrawal	<ul style="list-style-type: none"> • Administrative decision by the investigator or GW Research Ltd or Regulatory Authority. • Pregnancy. • Protocol deviation that is considered to potentially compromise the safety of the patient. • Withdrawal of patient consent/assent. • Withdrawal of parent(s)/legal representative consent. • Lost to follow-up. • Patient non-compliance. • AE which, in the investigator's opinion, compromises the safety of the patient continuing in the study. • ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$). • ALT or AST $>8 \times$ ULN. • ALT or AST $>5 \times$ ULN for more than two weeks. • ALT $>3 \times$ ULN or AST $>3 \times$ ULN and (TBL $>2 \times$ ULN or INR >1.5). • Any evidence of drug abuse or diversion. • Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.
Investigational Medicinal Product: Dosage, Regimen, Formulation and Mode of Administration	<p>GWP42003-P oral solution (100 mg/mL cannabidiol in sesame oil with anhydrous ethanol, added sweetener [sucralose] and strawberry flavoring).</p> <p>Placebo oral solution containing the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring.</p> <p>Dosage: Patients will titrate the IMP to the target Dose Level. Patients will then remain at this Dose Level for the duration of the treatment period of the study.</p> <p>The High Dose Level will be determined by the DSMC of Part A of study GWEP1332. The maximum dose considered will be 20 mg/kg/day.</p> <p>The Low Dose Level will be defined as 50% of the High Dose Level.</p>

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	IMP will be taken twice daily (morning and evening).
Control Group	The control group will receive placebo matching the assigned IMP Dose Level.
Procedures	<p>During Visit 1 (Day –28), the following assessments will be made: demographics, medical history (including seizure frequency over the last six months and voltage-gated sodium channel $\alpha 1$ subunit gene [<i>SCN1A</i>] mutation status), vital signs, postural blood pressure, physical examination (including height and body weight), ECG, C-SSRS (Children’s Baseline), and visit procedure-related AEs. If the mutation status of <i>SCN1A</i> is unknown, a blood sample will be taken for <i>SCN1A</i> analysis (this can be taken at any visit during the study). Clinical laboratory samples (urine [where possible] and blood) will be taken for hematology, biochemistry, urinalysis, a urine Δ^9-tetrahydrocannabinol (THC) screen and a serum pregnancy test (if appropriate). Patients or their caregivers will also be asked for information regarding concomitant medications and/or changes to medication (including AEDs). Eligible patients will then begin the 28-day baseline observation period. Patients or their caregivers will be issued with Interactive Voice Response System (IVRS) details and will be instructed on how to use it to record daily seizure information. Patients or their caregivers will also be given a paper diary to record usage of rescue medication, concomitant AEDs and AEs, and will be instructed on how to do so.</p> <p>At each subsequent clinic visit (Visits 2, 3, 4, 6 and 8), the following assessments will be made: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC (assessment not completed at Visit 2), cognitive assessment battery (Visits 2 and 8 only), QOLCE (Visits 2 and 8 only), C-SSRS (Children’s Last Visit) and the Vineland-II. Clinical laboratory samples (urine [where possible] and blood) will be taken for hematology, biochemistry and urinalysis. The patient’s IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen from Visit 2 onwards.</p> <p>After 28 (± 3) days, patients will return to the clinic at Visit 2 (Day 1). In addition to the above assessments, postural blood pressure and the CWS will be assessed and a test to detect THC and a pregnancy test, if appropriate, will also be performed. The investigator will assess the patient’s daily number of convulsive seizures from the patient’s IVRS data. Patients who have experienced four or more convulsive seizures (i.e., tonic-clonic, tonic, clonic or atonic seizures) during the baseline period and who meet all of the other inclusion and none of the exclusion criteria will be eligible to continue in the study. If a patient does not meet the eligibility criteria within this period, consideration</p>

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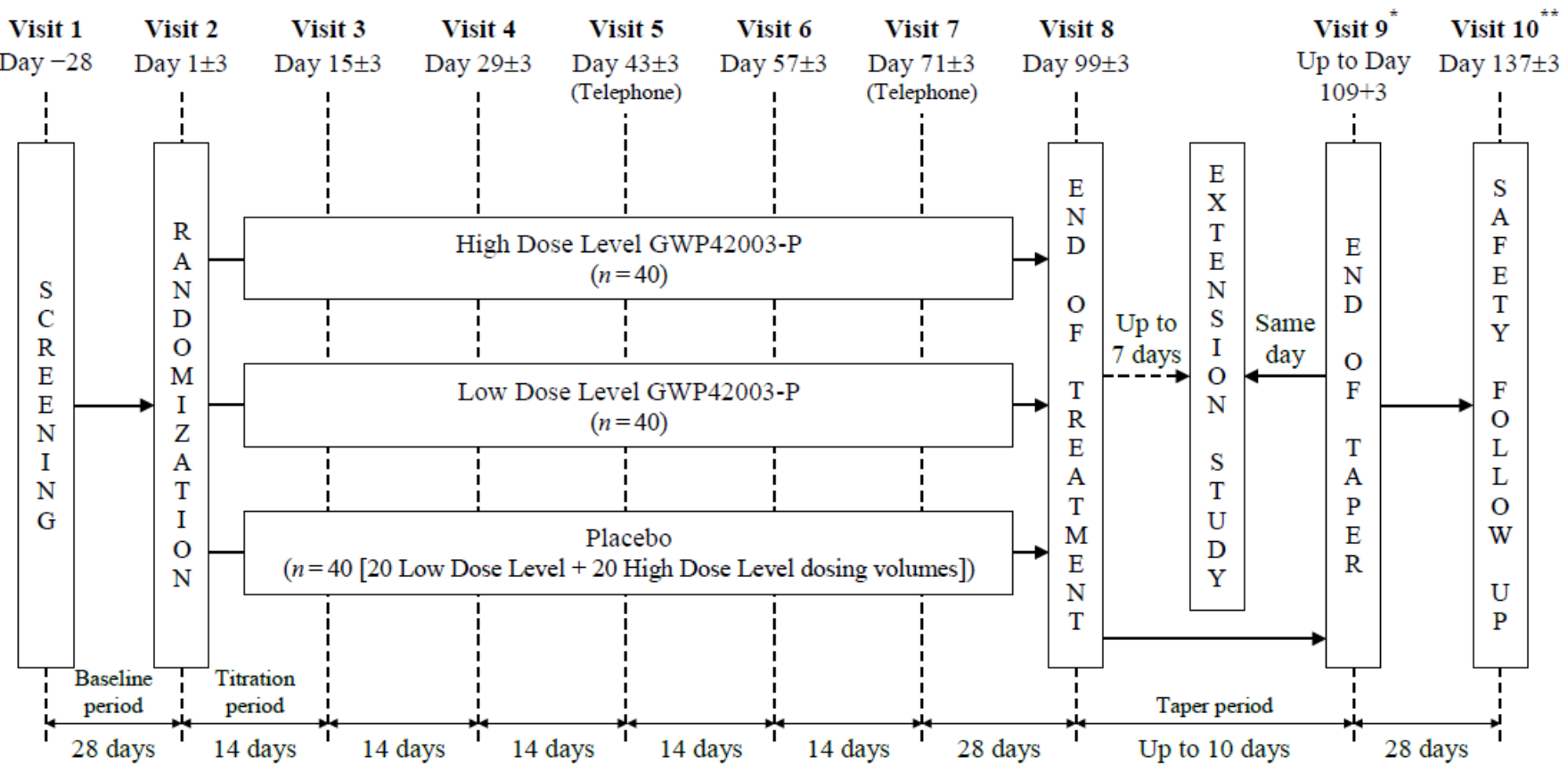
	<p>will be given to rescreen at a later date. Eligible patients will then be randomized to receive one of two Dose Levels of GWP42003-P or placebo in a 1:1:1 allocation ratio using the IVRS. Patients in the placebo group will be split into two equivalent cohorts; half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes.</p> <p>At Visit 2, caregivers will be asked to write a brief description of the patient's overall condition as a memory aid for the CGIC at subsequent visits or withdrawal.</p> <p>Patients will then receive sufficient IMP, as assigned by the IVRS, every 28 to 42 days for the 14-week treatment period. Each patient will take their first dose of IMP at Visit 2 (Day 1). Patients or their caregivers will be instructed on using the IVRS's daily dosing record, as well as how to record IMP dosing information in the paper diary.</p> <p>Patients will titrate to their target Dose Level using the regimen provided via the IVRS. If an unacceptable AE develops at any time during titration, dosing should initially be suspended or amended, as appropriate, until the event has resolved. After titration, patients should continue on a stable dosing regimen at the dose they achieved at the end of the titration period. If that dose becomes poorly tolerated during the post-titration period, the investigator may consider temporarily or permanently reducing the dose for the remainder of the study. However, where possible, the patient should be encouraged to return to the target dose.</p> <p>Patients will return to the clinic for further visits at Visit 3 (Day 15±3), Visit 4 (Day 29±3), Visit 6 (Day 57±3) and Visit 8 (Day 99±3). Adherence to the titration regimen and compliance will be assessed for safety reasons. Additional safety assessments will be made by telephone at Visit 5 (Day 43±3) and at Visit 7 (Day 71±3). During these calls, patients or their caregivers will be asked for information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to their medication (including AEDs).</p> <p>Visit 8 is the 'End of Treatment' visit and a test to detect THC and a pregnancy test (if appropriate) will be performed. The Caregiver Impression of IMP Palatability will also be assessed.</p> <p>At Visit 8, patients who have completed all of the scheduled study visits will be offered the option to enter an OLE study. Entry is to be on the same day as Visit 8 (Day 99) or within seven days of Visit 8. Patients not entering the OLE study at this visit will commence a taper period (down-titrating 10% per day for 10 days), and additional IMP will be dispensed, if required. Patients who require early termination prior to Visit 8 should also begin the taper period at the time the decision is made to discontinue (unless continued dosing is not possible due to an AE). The IVRS will generate the patient's daily IMP dosing volumes for the 10-day taper period, during which time IVRS and diary information will continue to be recorded. The taper period may be</p>
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	<p>interrupted if the patient wishes to enter the OLE study within the seven days of Visit 8.</p> <p>Following completion or cessation of the taper period, patients will return to the clinic for Visit 9 ('End of Taper Period' Visit) where the following assessments will be made: vital signs, physical examination (including height and body weight), C-SSRS (Children's Last Visit) and CWS. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). For patients not entering the OLE study, Visit 9 should occur 10 (+3) days after Visit 8 (i.e., on Day 109[+3]). For patients who delay entry into the OLE study, Visit 9 should occur on the day the patient enters the OLE study and within seven days of Visit 8 (i.e., up to Day 106), to allow the patient to enter the OLE study within this timeframe.</p> <p>A safety follow-up visit (Visit 10) is required for patients who do not enter the OLE study or who withdraw from the study early. This visit should occur four weeks after Visit 9 (i.e., on Day 137±3), or withdrawal from treatment, and can be conducted by telephone. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).</p> <p>For patients not entering the OLE study, safety telephone calls will be made weekly (±3 days) from Visit 9 until Visit 10.</p> <p>Patients who enter the OLE study on Day 99 will not attend Visits 9 or 10.</p> <p><u>Monitoring of Drug Abuse Liability (for patients 12 years of age and older):</u></p> <p>During the routine collection of AEs in this study, if AEs are reported which can illuminate an abuse potential signal (specific AEs detailed in Section 9.1.15.1.1), then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussion of the event(s) with the patient/caregiver.</p> <p>The second trigger that will require the investigator or study coordinator to discuss abuse potential signals with the patient/caregiver is drug accountability issues regarding overuse of the IMP or missing bottles.</p> <p>Irrespective of the above, all patients/caregivers will be interviewed at their final dosing visit (Visit 8/9) or withdrawal visit and a Study Medication Use and Behavior Survey will be completed by the investigator or study coordinator.</p> <p>A formal Adjudication Committee will be appointed and assigned to this initiative to classify triggered cases. The Adjudication Committee will meet on a periodic basis to review and assess all of the information</p>
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	collected on triggered cases.
Statistical Considerations	<p>The following endpoints will be described and compared between the three treatment groups, using appropriate statistical methods, over the 12-week, double-blind maintenance period:</p> <ul style="list-style-type: none"> • Mean percentage change from baseline in the frequency of convulsive seizures. • Number of patients experiencing a >25% worsening, -25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline. • Number of patients who are convulsive seizure free. • Percentage change from baseline in non-convulsive seizure frequency. • Change in types of seizures. • Change from baseline in use of rescue medication. • Change from baseline in number of inpatient hospitalizations due to epilepsy. • Change from baseline in Sleep Disruption 0–10 NRS score. • Change from baseline in EDSS score. • Change from baseline in QOLCE score. • Change from baseline in cognitive assessment battery. • Change from baseline in Vineland-II score. • CGIC. <p>All statistical tests will be two-tailed and carried out at the 5% level of significance.</p> <p>All safety data will be summarized using appropriate statistical methods.</p>
Sponsor	<p>GW Research Ltd Porton Down Science Park Salisbury Wiltshire SP4 0JQ</p>

Figure 1-1 Study Design and Treatment Schema

182 * For patients not entering the OLE study at Visit 8. Patients who opt not to enter the OLE study must have weekly (□3 days) safety telephone calls until Visit 10.

183 ** For patients not entering the OLE study; can be conducted by telephone.

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396 Illuminate an Abuse Potential Signal (for Patients 12
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List of Abbreviations

AE	Adverse Event
AEDs	Antiepileptic drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBD	Cannabidiol
CGIC	Caregiver Global Impression of Change
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CWS	Cannabis Withdrawal Scale
DS	Dravet syndrome
DSMC	Data Safety Monitoring Committee
EC	Ethics Committee
ECG	12-lead Electrocardiogram
EDSS	Epworth Daytime Sleepiness Scale
EEG	Electroencephalogram
EU	European Union
GCP	Good Clinical Practice
GW	GW Research Ltd
GWP	GW Pharma Ltd
IB	Investigator Brochure
ICH GCP	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat
IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward

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MMRM	Mixed-Effect Model Repeated Measures
0–10 NRS	0–10 Numerical Rating Scale
OLE	Open label extension
PI	Principal Investigator
PP	Per Protocol
PVD	Pharmacovigilance Department
QOLCE	Quality of Life in Childhood Epilepsy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
<i>SCN1A</i>	Voltage-gated sodium channel α 1 subunit gene
SMEI	Severe Myoclonic Epilepsy in Infancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
THC	Δ^9 -tetrahydrocannabinol
ULN	Upper limit of normal
Vineland-II	Vineland Adaptive Behavior Scales, Second Edition
VNS	Vagus Nerve Stimulation

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Definition of Terms

Term	Definition
Baseline	The 28-day period from screening (Visit 1 [Day -28]) to randomization (Visit 2 [Day 1]).
Day 1	The day a patient first receives investigational medicinal product or placebo.
End of treatment	Completion of the treatment period (Visit 8 [Day 99]) or withdrawal.
End of study	Completion of the Clinical Study Report.
High Dose Level	The maximum target dose of GWP42003-P as determined by the Data Safety Monitoring Committee of study GWEP1332 Part A (up to 20 mg/kg/day), or equivalent volume of placebo.
IMP	Investigational Medicinal Product (Study Medication). Used to describe both investigational active product and reference therapy (placebo).
INR	International Normalized Ratio is a calculation made to standardize prothrombin time.
Investigator	Study Principal Investigator or a formally delegated study physician.
Low Dose Level	50% of the High Dose Level of GWP42003-P, or equivalent volume of placebo.

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2 OBJECTIVES

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2.1 Primary

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To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the maintenance period of the study in convulsive seizure frequency. The dose response effect between two GWP42003-P Dose Levels and placebo will also be explored. Convulsive seizures are defined as tonic-clonic, tonic, clonic or atonic and non-convulsive seizures as myoclonic, partial or absence.

2.2 Secondary

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- To assess changes from baseline in non-convulsive seizure frequency, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, quality of life and conduct behavioral and cognitive assessments in patients taking GWP42003-P as an adjunctive treatment, when compared with placebo.
- To assess the safety of both GWP42003-P doses when compared with placebo.

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3 BACKGROUND AND RATIONALE

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3.1 Disease

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Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy in Infancy (SMEI), is a rare form of severe epilepsy with onset in early childhood. It has an incidence of less than one per 40,000 and accounts for 1.4% of epilepsies in children aged <15 years^{1, 2, 3}. DS is characterized by a variety of treatment-resistant seizures (febrile and afebrile, generalized and unilateral, clonic or tonic-clonic) that occur in the first year of life and has a poor cognitive prognosis. Onset usually occurs between four and eight months of age and manifests typically as a prolonged (>15 min) clonic, generalized or unilateral convulsive seizure, often triggered by fever, that can evolve into status epilepticus^{4, 5, 6}. After a typical period of two weeks to two months, further febrile seizures occur and afebrile seizures also appear. In addition to convulsive seizures, other seizure types appear between the ages of one and four years, including myoclonic seizures, focal seizures, atypical absences and obtundation statuses (in which consciousness is impaired). Significant developmental delay becomes apparent from the second year onwards and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common. Beyond five years of age, convulsive seizures decrease but persist and occur mainly in sleep. Myoclonic and absence seizures tend to disappear and focal seizures either persist or decrease. Although psychomotor development and behavior tend to improve over time, cognitive impairment persists throughout the patient's lifetime^{4, 5, 6}.

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Myoclonic seizures are a defining characteristic of DS and can be massive, predominantly involving axial muscles, or erratic/segmental, which are mainly limited to the distal limbs and face. Massive myoclonic seizures are often associated with electroencephalogram (EEG) paroxysms and can be variable in intensity, with outcomes ranging from falling (drop attack) to causing only small, saccadic movements of the head, shoulders or trunk^{4, 5, 6}. Erratic myoclonic seizures do not have an EEG correlate and are typically mild in intensity, although they can affect fine motor coordination. Some patients with DS experience both massive and erratic myoclonic seizures, yet these seizures can be absent in some DS patients. Such cases are defined as "borderline" SMEI and may have different EEG features to typical SMEI, although the course and outcome of the disease remain the same^{2, 6, 7}.

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Genetic analyses have revealed that more than 70% of patients with DS have mutations in the voltage-gated sodium channel $\alpha 1$ subunit gene (*SCN1A*)^{8, 9, 10, 11, 12, 13}. *SCN1A* encodes the pore-forming subunit of the Na_v1.1 voltage-gated sodium

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channel and there are currently more than 700 published *SCN1A* mutations, 90% of which occur in DS patients¹⁴. Approximately two-thirds of these mutations give rise to truncations while the remaining third are missense mutations that are predicted to severely impair channel function⁶. In addition, intragenic and whole gene deletions of *SCN1A* as well as deletions within the 5' promoter sequence have also been identified in DS patients that are otherwise *SCN1A*-mutation-negative^{9, 10, 11, 12, 13}. Most *SCN1A* mutations in DS patients arise *de novo*, although approximately 5% of cases involve inheritance of familial *SCN1A* mutations from a mildly affected parent^{15, 16, 17, 18}. In familial cases of DS, the phenotype and severity of epilepsy can be clinically variable among family members carrying the same *SCN1A* mutation. This heterogeneity is proposed to be due to variable familial expression of *SCN1A* mutations, mediated either by *SCN1A* mosaicisms or by the genetic and environmental background^{19, 20, 21, 22}. Candidate modifier genes currently include *SCN9A* (encoding the pore-forming subunit of the Na_v1.7 voltage-gated sodium channel) and *CACNB4* (encoding the β4 auxiliary subunit of high-voltage activated calcium channels), variants of which have been found in DS patients with *SCN1A* mutations^{23, 24}. Mouse models in which *SCN1A* is either mutated or knocked out have demonstrated that the α1 subunit is critical for the excitability and *in vivo* function of inhibitory hippocampal and cortical interneurons^{25, 26}. Reduced firing of these inhibitory interneurons would compromise network inhibition and cause a hyperexcitable gain-of-function effect that may underlie the severe epilepsy seen in DS. Moreover, *SCN1A* mutant mice reproduce the characteristic temperature- and age-dependent seizures and EEG paroxysms observed in DS, although the phenotypic variability of DS patients with *SCN1A* mutations remains unexplained²⁷.

More than 20% of patients with DS have no detectable mutations in *SCN1A* and it is possible that many of these patients harbor mutations in regulatory elements located outside coding regions. Familial and *de novo* mutations of *PCDH19* (encoding protocadherin 19) have been reported in a subset of *SCN1A*-mutation-negative DS patients and it is estimated that *PCDH19* mutations could account for 5% of all DS cases^{28, 29}. Additional genes in which mutations cause DS include *GABRG2* (encoding the γ2 subunit of γ-aminobutyric acid -A receptors), *SCN1B* (encoding the β1 auxiliary subunit of voltage-gated sodium channels) and *SCN2A* (encoding the pore-forming subunit of the Na_v1.2 voltage-gated sodium channel), although very few cases have been reported^{30, 31, 32}.

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531 DS is one of the most pharmaco-resistant forms of epilepsy, with all seizure types
532 extremely refractory to conventional antiepileptic drugs (AEDs), especially during the
533 first several years. Sodium valproate is often used to prevent the initial recurrent
534 convulsive febrile seizures and benzodiazepines (e.g., diazepam, midazolam,
535 clonazepam or clobazam) are frequently co-administered to limit the duration of long-
536 lasting seizures. In most cases however, the relief provided by these agents is
537 insufficient^{33, 34}. Certain AEDs can paradoxically worsen seizures in DS patients,
538 namely lamotrigine, carbamazepine and vigabatrin, and the use of certain barbiturates
539 at high doses is associated with a poor outcome^{35, 36, 37}. Potassium bromide can be
540 effective at controlling convulsive status epilepticus and was found to be the most
541 efficacious AED in a Japanese cohort of DS patients³⁸. A study of DS patients treated
542 with potassium bromide as adjunctive therapy showed a reduction in seizures in 81%
543 of patients in the first three months, with 30% becoming seizure-free³⁹. However,
544 this compound has no effect on focal and tonic seizures and any initial efficacy is
545 often not maintained long-term^{34, 39}.

546 To date, the only AED that has proved efficacious in the majority of DS patients in
547 placebo-controlled, double-blind trials is stiripentol^{40, 41, 42}. In these studies,
548 stiripentol was administered as adjunctive therapy to sodium valproate and clobazam.
549 At least two thirds of patients experienced a >50% reduction in seizure frequency in
550 the stiripentol arms of these studies versus <10% of patients in the placebo arms^{40, 41}.
551 A subsequent meta-analysis of these studies showed that stiripentol reduced the
552 overall seizure rate by 70%⁴². Both the frequency and duration of seizures remained
553 significantly reduced at a median of 2.9 years follow-up, with the greatest efficacy
554 observed in infants³⁶. Both short-term and long-term benefits of stiripentol as
555 adjunctive therapy have also been demonstrated in an open-label study of Japanese
556 DS patients, with responder rates of 61% and 48% at six weeks and six months,
557 respectively⁴³. Stiripentol is generally well tolerated and can improve seizure control
558 in DS patients receiving pharmacotherapy other than valproate and/or clobazam^{43, 44}.

559 Topiramate and levetiracetam are two further AEDs that have undergone preliminary
560 trials as adjunctive therapy in DS patients. In three open-label studies, more than half
561 of patients receiving topiramate as add-on therapy achieved >50% reduction in
562 seizure frequency, with 17% becoming seizure-free for at least four months in all
563 cases^{45, 46, 47}. Similar results were demonstrated in a single open-label trial of
564 levetiracetam, with 64% of patients experiencing >50% reduction in tonic-clonic
565 seizures at 12 weeks⁴⁸. Although these new AEDs appear promising, larger

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randomized placebo-controlled studies are required to accurately assess their efficacy in the treatment of DS. Non-pharmacological treatments of DS that have demonstrated benefit as adjunctive therapy to AEDs include vagus nerve stimulation (VNS)^{49, 50} and the introduction of a ketogenic diet^{51, 52, 53, 54}. Despite the therapies listed above, DS remains one of the most pharmaco-resistant epilepsy syndromes. Consequently, there is a clear need for new, efficacious, pharmaceutical treatments.

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3.2 GWP42003-P Background

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The cannabis plant (*Cannabis sativa* L.) produce trichomes that synthesize a large number of pharmacologically active compounds called phytocannabinoids. The most abundant of these are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), although the amounts and proportions of the various phytocannabinoids in each plant vary by strain and can be adjusted by breeding.

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The Investigational Medicinal Product (IMP), GWP42003-P, is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (>95%) CBD that typically contains less than 0.5% (w/w) THC. The pure CBD is subsequently dissolved in excipients with added sweetener and flavoring.

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The pharmacological effects of phytocannabinoids are thought to be mediated primarily via their interaction with the endocannabinoid system, which consists of cannabinoid receptors, endogenous ligands (endocannabinoids) and enzymes for endocannabinoid synthesis and degradation. Two G-protein-coupled receptors for cannabinoids have so far been identified, designated cannabinoid CB₁ and CB₂ receptors. CBD does not bind to either of these receptors with any great affinity but does modulate the metabolizing enzymes of the endocannabinoid system. CBD also affects conduction of ion channels and acts on other G-protein-coupled receptors such as the transient receptor potential channel TRPV1⁵⁵ and the orphan receptor GPR55⁵⁶. Importantly, CBD lacks detectable psychoactivity as found with THC. Further to this, CBD has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant and anti-inflammatory activity⁵⁷. Very little data concerning adverse events (AEs) of CBD in humans exists to date. However, doses of up to 1500 mg CBD per day are reported to be well tolerated in humans⁵⁸.

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3.3 Rationale

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Given the limitations of current synthetic AEDs, it has been hypothesized that CBD can be tested for efficacy in children with pharmacoresistant epilepsy⁵⁹. A recent parent survey has reported that 84% of children with treatment-resistant epilepsy experienced a reduction in seizures while taking CBD-enriched cannabis, with over half of those reporting >80% reduction in seizure frequency⁶⁰. The majority of children had been diagnosed with DS, two thirds of which experienced $\geq 50\%$ reduction in seizure frequency with one patient (8.3%) achieving complete seizure freedom. The CBD-enriched cannabis was behaviorally well tolerated and children often experienced improved sleep, increased alertness, and better mood.

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The primary objective of this study is to evaluate the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the maintenance period of the study in convulsive seizure frequency, in children and young adults with DS. The dose response effect between two GWP42003-P Dose Levels and placebo will also be explored. Additional objectives include evaluating changes from baseline in non-convulsive seizure frequency, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, cognitive function, quality of life and adaptive behaviors in patients taking GWP42003-P in combination with AEDs compared with placebo. These endpoints are among those recommended by the European Medicines Agency guideline on clinical investigation of medicinal products in the treatment of epileptic disorders⁶¹.

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3.3.1 Selection of Study Dose

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Doses up to 800 mg CBD per day for up to eight weeks have been well tolerated in adults in GW Research Ltd (GW) clinical study GWMD09112⁶², which, assuming an average weight of 70 kg, equates to 11.4 mg/kg. In the literature, doses of CBD have been given up to 1500 mg CBD per day for four weeks in adults⁵⁸, which, in a 70 kg human, equates to a daily dose of 21.4 mg/kg CBD.

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GWP42003-P is currently being used by physicians for treatment of patients with intractable epilepsy resulting from a variety of etiologies in two open Individual Expanded Access Investigational New Drug (IND) studies and five open Intermediate Expanded Access IND studies. In the ongoing Individual Expanded Access IND studies, the initial dosing has been cautious (100 mg [morning] + 150 mg [afternoon/evening]), progressively increasing to 400 mg CBD/day; doses up to

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22 mg/kg per day have been well tolerated in an individual pediatric patient. The Sponsor is not aware of any safety issues arising from the dosing used in the Individual Expanded Access INDs. Treatment is expected to begin imminently in the Intermediate Expanded Access INDs. Based on the above, a daily maximum dose of 20 mg/kg CBD (given as two divided doses) was selected for the phase two/three study in patients with DS (GWEP1332). At the end of Part A of the GWEP1332 study a Data Safety Monitoring Committee (DSMC) will recommend the target dose and titration schedule for all subsequent studies, including this study (GWEP1424). The maximum dose patients can receive during the maintenance phase will be 20 mg/kg/day. During the maintenance phase, investigators may decrease the dose if a patient experiences intolerance. Patients whose dose has been decreased can have their dose increased again, if the tolerability improves.

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3.4 Clinical Hypothesis

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Pre-clinical studies have shown CBD to have anti-seizure and antiepileptic activity in a range of models. Anecdotal evidence and some literature reports⁶⁰ suggest that CBD is an effective AED in children with DS as discussed in [Section 3.3](#). The hypothesis underlying this study is that CBD has a positive risk/benefit outcome in the adjunctive treatment of DS.

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4 EXPERIMENTAL PLAN

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4.1 Study Design

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This study is a 1:1:1 randomized, double-blind, 14-week comparison of two Dose Levels of GWP42003-P versus placebo (40 patients per treatment group). The treatment period will consist of a two-week titration period followed by a 12-week maintenance period. The treatment period will be followed by a 10-day taper period and a four-week follow-up period. The study will aim to determine the efficacy, safety and tolerability of two Dose Levels of GWP42003-P compared with placebo. The High Dose Level will be as recommended by the DSMC after assessment of safety and pharmacokinetic data from Part A of study GWEP1332. The Low Dose Level will be defined as 50% of the High Dose Level. Patients in the placebo group will be split into two equivalent cohorts; half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes. The first patient will not enroll into this study until the DSMC has reviewed the safety data from Part A of study GWEP1332.

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Following study completion, all patients will be invited to continue to receive GWP42003-P in an open label extension (OLE) study (under a separate protocol).

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A study schema (Figure 1-1), presented at the end of [Section 1](#), depicts the overall study design. More detailed information on treatment and study procedures is provided in [Section 8](#) and [Section 9](#), respectively.

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4.1.1 Primary Endpoint

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The primary endpoint is the mean percentage change from baseline in convulsive seizure frequency during the maintenance period (Day 15 to the end of the evaluable period) in patients taking GWP42003-P compared with placebo.

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4.1.2 Secondary Endpoint(s)

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The following endpoints will be compared between the three treatment groups over the 12-week, double-blind maintenance period:

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- Number of patients experiencing a >25% worsening, -25 to +25% no change, 25–50% improvement, 50–75% improvement or >75% improvement in convulsive seizures from baseline.
- Number of patients who are convulsive seizure free.
- Percentage changes from baseline in non-convulsive seizure frequency.

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- 725 • Change in types of seizures.
- 726 • Changes from baseline in usage of rescue medication.
- 727 • Changes from baseline in number of inpatient hospitalizations due to epilepsy.
- 728 • Changes from baseline in Sleep Disruption 0–10 Numerical Rating Scale (0–
- 729 10 NRS) score.
- 730 • Changes from baseline in Epworth Daytime Sleepiness Scale (EDSS) score.
- 731 • Changes from baseline in the Quality of Life in Childhood Epilepsy (QOLCE)
- 732 score.
- 733 • Change in cognitive function as measured with a cognitive assessment battery.
- 734 • Changes from baseline in the Vineland Adaptive Behavior Scales, Second
- 735 Edition (Vineland-II) score.
- 736 • Caregiver Global Impression of Change (CGIC).

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The safety profile of GWP42003-P compared with placebo will also be the assessed at each Dose Level by measuring:

- 740 • AEs.
- 741 • Vital signs.
- 742 • Physical examination parameters.
- 743 • 12-lead Electrocardiogram (ECG).
- 744 • Laboratory parameters.
- 745 • Columbia-Suicide Severity Rating Scale (C-SSRS) score.
- 746 • Cannabis Withdrawal Scale (CWS) score.
- 747 • Abuse liability.

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749 **4.2 Number of Centers**

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Approximately 30 centers are expected to participate in this study.

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754 **4.3 Number of Patients**

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If patients fail screening they will be replaced until the target numbers of patients are achieved.

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A total of 120 patients will be enrolled. The 120 patients will be randomly allocated to receive one of two Dose Levels of active IMP or placebo on a 1:1:1 basis (40 patients per treatment group).

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The sample size calculation is explained fully in [Section 13.1](#).

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5 INVESTIGATIONAL MEDICINAL PRODUCT

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

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5.1 GWP42003-P Oral Solution

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

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Table 5.1-1 Formulation of GWP42003-P Oral Solution	
Material	Quantity
CBD	100 mg/mL
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

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5.2 Placebo Oral Solution

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Placebo oral solution contains the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring (Table 5.2-1).

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Table 5.2-1 Formulation of Placebo Oral Solution	
Material	Quantity
Anhydrous ethanol	79 mg/mL
Sucralose	0.5 mg/mL
Strawberry flavoring	0.2 mg/mL
Sesame oil	make up to 1 mL

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5.3 Packaging, Storage and Drug Accountability

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5.3.1 Packaging and Labelling

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The IMP will be manufactured and packaged by GW Pharma Ltd (GWP). It will be distributed by GWP or delegated contractors. The IMP will be presented in 100 mL amber glass bottles with child-resistant caps and packed in cartons. Sufficient IMP will be dispensed at each relevant visit considering the dose group and weight of each patient. A unique pack identification number will be used to identify each box and the medication it contains. The pack numbers will cross check with the batch numbers held at GWP and the IMP information held on the Interactive Voice Response System (IVRS). GWP will ensure that all IMP provided is fully labelled

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803 and packaged. Label text will comply with European Union (EU) guidance on Good
804 Manufacturing Practice, Annex 13 Labelling. In addition, any local country
805 requirements in accordance with local Drug Law or Regulatory Requirement will be
806 included in the final label text.

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

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811 **5.3.2 Storage**

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

815 The IMP must be stored in compliance with the local regulations for a controlled drug
816 (if applicable to country). The sponsor must approve storage location and facilities.

817 Should storage conditions deviate from these specified requirements, the GW study
818 monitor should be contacted immediately to confirm if the IMP remains suitable for
819 use. IMP should be placed under quarantine until confirmation is received that IMP is
820 suitable for use.

821 Temperature records of the storage location must be maintained on a daily basis (a
822 minimum of Monday–Friday, excluding public holidays) from date of receipt of first
823 shipment until end of study dispensing period at each site. These records must
824 contain at least the minimum and maximum daily temperatures and should be made
825 available to the appropriate GW personnel for review throughout the study.

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827 **5.3.3 Supply and Return of Investigational Medicinal Product**

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829 Once a site has been activated via the IVRS at study initiation, IMP will be shipped to
830 a responsible person, such as the pharmacist, at the investigator's center, who will
831 check the amount received (against the IVRS Shipment Request) and the condition of
832 the drug. Details of the IMP received will be recorded in the IMP accountability
833 record (see [Section 5.3.4](#)). The site will acknowledge IMP receipt via the IVRS and
834 will complete any receipt forms required. IMP will be dispensed and returned as
835 detailed in [Section 8.4](#) with further IMP shipments to be initiated by the IVRS. As
836 directed, all supplies, including unused, partially used, or empty containers, will be
837 returned to GWP or destroyed at the center if agreed in writing by the study monitor.

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5.3.4 Investigational Medicinal Product Accountability

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

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- The dates and quantities of IMP received from GWP.
- Patient's identification.
- Date and quantity of IMP dispensed.
- The initials of the dispenser.
- Date and quantity of IMP returned to the investigator/pharmacy.

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A record of returned IMP must be completed and included in the shipment of used and unused IMP to GWP. At the end of the study a record/statement of reconciliation must be completed and provided to GWP.

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These inventories must be made available for inspection by an authorized GW or GWP representative and local officials or regulatory agency inspectors.

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

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6 PATIENT ELIGIBILITY

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869 Investigators will be required to maintain a log that includes limited information about
870 all screened patients (initials, age, gender; as allowed per local regulations) and
871 outcome of screening.

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6.1 Inclusion Criteria

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

876 **6.1.1** Patient and/or parent(s)/legal representative must be willing and able to
877 give informed assent/consent for participation in the study (see
878 [Section 15.2](#)).

879 **6.1.2** Patient and their caregiver must be willing and able (in the
880 investigator's opinion) to comply with all study requirements.

881 **6.1.3** Patient must be male or female aged between two and 18 years
882 (inclusive).

883 **6.1.4** Patient must have a documented history of DS which is not completely
884 controlled by current AEDs.

885 **6.1.5** Patient must be experiencing **four or more** convulsive seizures (i.e.,
886 tonic-clonic, tonic, clonic, atonic seizures) during the 28-day baseline
887 observation period.

888 **6.1.6** Patient must be taking one or more AEDs at a dose which has/have been
889 stable for at least four weeks.

890 **6.1.7** All medications or interventions for epilepsy (including ketogenic diet
891 and VNS) must have been stable for four weeks prior to screening and
892 patient and caregiver are willing to maintain a stable regimen
893 throughout the study.

894 **6.1.8** Patient and/or parent(s)/legal representative is willing to allow his or her
895 primary care practitioner and consultant to be notified of participation in
896 the study.

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6.2 Exclusion Criteria

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

901 **6.2.1** Patient has clinically significant unstable medical conditions other than
902 epilepsy.

903 **6.2.2** Patient has had clinically relevant symptoms or a clinically significant
904 illness in the four weeks prior to screening or randomization, other than
905 epilepsy.

906 **6.2.3** Patient has clinically significant abnormal laboratory values, in the
907 investigator's opinion, at screening or randomization.

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- 914 **6.2.4** Patient has clinically relevant abnormalities in the ECG measured at
915 screening or randomization.
- 916 **6.2.5** Patient has any concurrent cardiovascular conditions which will, in the
917 investigator's opinion, interfere with the ability to assess their ECGs.
- 918 **6.2.6** Patient has a history or presence of alcohol or substance abuse within
919 the last two years prior to the study or daily consumption of five or more
920 alcohol-containing beverages.
- 921 **6.2.7** Patient is currently using, or has in the past used, recreational or
922 medicinal cannabis, or synthetic cannabinoid-based medications
923 (including Sativex[®]) within the three months prior to study entry and is
924 unwilling to abstain for the duration of the study.
- 925 **6.2.8** Patient has a history of symptoms (e.g., dizziness, light-headedness,
926 blurred vision, palpitations, weakness, syncope) related to a drop in
927 blood pressure due to postural changes.
- 928 **6.2.9** Patient has ingested alcohol in the 24-hour period prior to the first study
929 visit and/or is unwilling to abstain from drinking alcohol throughout the
930 treatment period.
- 931 **6.2.10** Patient has any known or suspected hypersensitivity to cannabinoids or
932 any of the excipients of the IMPs (e.g., sesame oil).
- 933 **6.2.11** Female patient is of child bearing potential or male patient's partner is
934 of child bearing potential; unless willing to ensure that they or their
935 partner use effective contraception, for example oral contraception,
936 double barrier, intra-uterine device, during the study and for three
937 months thereafter (however a male condom should not be used in
938 conjunction with a female condom).
- 939 **6.2.12** Female patient is pregnant, lactating or planning pregnancy during the
940 course of the study and for three months thereafter.
- 941 **6.2.13** Patient has been part of a clinical trial involving another IMP in the
942 previous six months.
- 943 **6.2.14** Any other significant disease or disorder which, in the opinion of the
944 investigator, may either put the patient at risk because of participation in
945 the study, may influence the result of the study, or affect the patient's
946 ability to participate in the study.
- 947 **6.2.15** Patient has significantly impaired hepatic function at screening (Visit 1)
948 or randomization (Visit 2) (Alanine aminotransferase [ALT] $>5 \times$ upper
949 limit of normal [ULN] or total bilirubin [TBL] $>2 \times$ ULN) OR the ALT
950 or Aspartate aminotransferase (AST) $>3 \times$ ULN **and** (TBL $>2 \times$ ULN
951 **or** international normalized ratio [INR] >1.5). *This criterion can only*
952 *be confirmed once the laboratory results are available; patients*
953 *randomized into the study who are later found not to meet this criterion*
954 *should be withdrawn from the study.*
- 955 **6.2.16** Following a physical examination the patient has any abnormalities that,
956 in the opinion of the investigator, would prevent the patient from safe
957 participation in the study.

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- 964 **6.2.17** Patient is unwilling to abstain from donation of blood during the study.
- 965 **6.2.18** There are plans for the patient to travel outside their country of
966 residence during the study.
- 967 **6.2.19** Patient has previously been randomized into this study.
- 968 **6.2.20** Any history of suicidal behavior or any suicidal ideation of type four or
969 five on the C-SSRS at screening.

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976 **7 PATIENT ENROLLMENT**

977 Before patients may be entered into the study, GW requires a copy of the relevant
978 center's Ethical Committee (EC) or Institutional Review Board (IRB) written
979 approval of the protocol, informed consent/assent forms and other patient information
980 material. Patients will be considered enrolled in the study from the time of providing
981 written informed consent/assent. All patients and/or parent(s)/legal representatives,
982 where appropriate, must personally sign and date the consent/assent form prior to any
983 procedures being performed (refer to [Section 9.1.1](#) and [Section 15.2](#)).

984

985 **7.1 Treatment Assignment**

986 At the start of Visit 1, a screening number will be assigned to each patient using an
987 IVRS. After completion of assessments and confirmation of eligibility at Visit 2,
988 patients will be assigned a unique patient number (to be used for the remaining
989 duration of the study) and randomly allocated to one of two Dose Levels of
990 GWP42003-P or placebo using the IVRS. GWP will provide all IMP in a packed and
991 labelled state and the IVRS will identify the pack number to be dispensed to the
992 patient at each visit, according to the treatment assigned in the randomization
993 schedule.

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995 **7.2 Randomization**

996 The allocation of IMP to treatment number will be done according to a randomization
997 schedule produced by an independent statistician. The randomization schedule will be
998 held centrally and not divulged to any other person involved in the study until the
1000 database has been locked and unblinding authorized by the relevant GW personnel.
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8 TREATMENT PROCEDURES

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8.1 Investigational Medicinal Product Dosage, Administration and Schedule

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The IMP will be presented as an oral solution containing either the active pharmaceutical ingredient and excipients (in the case of GWP42003-P) or only excipients (in the case of placebo). For details regarding IMP formulations, see [Section 5](#).

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The IMP will consist of two types of medication:

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- GWP42003-P Oral Solution containing 100 mg/mL CBD.
- Placebo Oral Solution containing excipients.

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Patients will be assigned one of two Dose Levels of active IMP or placebo on a 1:1:1 basis (40 patients per treatment group). Patients in the placebo group will be split into two cohorts (20 receiving Low Dose Level dosing volumes and 20 receiving High Dose Level dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy. The High Dose Level will be determined by the DSMC of Part A of study GWEP1332. The maximum dose considered will be 20 mg/kg/day. The Low Dose Level will be defined as 50% of the High Dose Level.

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8.1.1 Dose Administration

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

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8.1.2 Dose Escalation, Dose Adjustments and Down-Titration

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Titration regimens will be produced for the High Dose Level, Low Dose Level and placebo treatment groups. All patients will be weighed during Visit 2 and the daily volumes of IMP solution to be taken during the two-week titration period and for the remainder of the maintenance period will be calculated via the IVRS and the dosing regimen provided to the patient and/or caregiver. Further information on dispensing procedures will be provided in a separate Pharmacy Manual.

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Each patient will take their first dose of IMP at Visit 2 (Day 1) and their final maintenance dose of IMP at Visit 8 (Day 99). If an unacceptable AE develops at any time during the titration period, dosing should initially be suspended or amended, at the investigator's discretion, until the event has resolved. During the maintenance

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period, patients should continue on a stable dosing regimen at the target Dose Level. If that dose becomes poorly tolerated, the investigator may consider temporarily or permanently reducing the dosage for the remainder of the maintenance period. However, where possible, the patient should be encouraged to return to the target Dose Level.

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Patients who do not immediately enter the OLE study at Visit 8 or withdraw early will have their dose of IMP tapered gradually (10% each day) over a period of 10 days. However, the taper period may be interrupted if the patient wishes to enter the OLE study within seven days of Visit 8. Patients who require early termination prior to Visit 8 should also begin the taper period at the time the decision is made to discontinue (unless continued dosing is not possible due to an AE). Patients participating in the taper period will return used and unused IMP to the clinic at Visit 9.

1066 **8.2 Concomitant Therapy**

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It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including AEDs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant AEDs must have been stable for at least four weeks prior to screening and must remain stable throughout the study period. Further information on drug interactions can be found in the Investigator Brochure (IB)⁶³.

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

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

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1080 **8.3 Prohibited Therapy During Study Period**

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

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- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.
- Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.
- Any other IMP taken as part of a clinical trial within six months or during the study.

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8.4 Compliance in Investigational Medicinal Product Administration

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

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- Visit 2 (Day 1).
- Visit 4 (Day 29).
- Visit 6 (Day 57).
- Visit 8 (Day 99) (for patients not entering the OLE study on Day 99; if required).

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Patients or their caregivers will confirm the daily dose has been administered using the IVRS and record the total volume of IMP administered on each treatment day using the paper diary. Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 4, 6, 8 and 9). The site will check the returned IMP against the usage recorded using the IVRS report and diary. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

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

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

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Records of IMP accountability will be maintained according to [Section 5.3.4](#).

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8.5 Access to Blinded Treatment Assignment

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

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1139 The investigator is encouraged to contact GW to discuss the rationale for unblinding
1140 prior to doing so. However, to prevent delays to the investigator or medical personnel
1141 responding to a potentially emergent situation, unblinding of study medication will
1142 not be dependent upon the investigator receiving approval from GW (i.e., the
1143 investigator will be able to obtain the code break information independent of
1144 contacting GW).

1145 If the investigator does unblind they must contact GW within one working day of the
1146 event and must document the time, date and reason(s) for unblinding in the patient's
1147 CRF.

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1154 **9 STUDY PROCEDURES**

1155 A list of the required study procedures is provided in the subsections that follow, refer
1156 also to the Schedule of Assessments (APPENDIX 1). Assessments or tests that are
1157 not done and examinations that are not conducted must be reported as such on the
1158 CRFs.

1159 The location of the source data for the following procedures will be documented, per
1160 center, in a signed ‘Source Data Verification’ plan, for further details see
1161 [Section 16.2](#).

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1164 **9.1 Study Procedure Listing**

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1167 To be eligible for the study, the patient must have agreed that if they or their partner
1168 are of child bearing potential they are willing to use effective contraception for the
1169 duration of the study and for three months thereafter. A highly effective method of
1170 birth control is defined as those which result in a low failure rate (i.e., less than 1%
1171 per year) when used consistently and correctly such as implants, injectables,
1172 combined oral contraceptives, some IUDs, sexual abstinence or vasectomized partner
1173 (CPMP/ICH/286/95 mod)⁶⁴. Abstinence, as referenced above, is only acceptable as
1174 true abstinence: when this is in line with the preferred and usual lifestyle of the
1175 patient; periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation
1176 methods) and withdrawal are not acceptable methods of contraception.

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1177 **9.1.1 Informed Consent/Assent**

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1180 The parent(s)/legal representative of minor patients must personally sign and date the
1181 EC/IRB approved consent form before any study specific procedures are performed or
1182 any patient related data is recorded for the study. In addition, in cases where the
1183 patient possesses adequate understanding, assent will be taken along with
1184 parent(s)/legal representative consent, using EC/IRB approved assent forms. Assent
1185 is defined as the minor’s permission or affirmative agreement to participate in the
1186 study. The explicit wish of a minor, who is capable of forming an opinion and
1187 assessing the information provided, to refuse participation in, or to be withdrawn
1188 from, the clinical trial at any time must be considered by the investigator.

1188 Adult patients with an adequate level of understanding must personally sign and date
1189 the EC/IRB approved informed consent form before any study specific procedures are
1190 performed or any patient related data are recorded for the study. For adult patients

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with an insufficient level of understanding of what is proposed, only parent(s)/legal representative consent will be sought.

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

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

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9.1.2 Demographics

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The following information will be obtained for each patient: date of birth, gender and ethnic origin.

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9.1.3 Medical History

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Relevant, significant medical history (including seizure frequency over the last six months) will be obtained and is defined as any condition or disease that:

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

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The mutation status (positive or negative for mutation) of the *SCN1A* gene will be determined through the patient's medical records. If the mutation status of *SCN1A* is unknown, *SCN1A* analysis will be carried out during the study analysis (a blood sample can be taken at any clinic visit).

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9.1.4 Inpatient Epilepsy-Related Hospitalizations

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The number of inpatient hospitalizations that are, in the investigator's opinion, due to epilepsy will be recorded in the patient's CRF and through the Serious Adverse Events (SAE) reporting process.

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9.1.5 Concomitant Medication

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Details of all current and recent medication (i.e., taken within the previous 14 days), including AEDs, will be recorded at each study visit. AEDs used during the study should be maintained at a stable dose. Any changes in concomitant medication during

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the study must be recorded in the CRF at study visits. Patients should stop taking any prohibited therapy prior to the screening visit, as defined in [Section 8.3](#).

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1243 **9.1.6 Physical Examination**

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Physical examinations will include height and body weight measurements.

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1248 **9.1.7 Vital Signs**

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Vital sign measurements, taken in a sitting position at rest for five minutes, will be completed alongside the physical examination. Postural blood pressure should be measured after five minutes in supine position and, if possible, two minutes in standing position. Blood pressure must be recorded using the same arm throughout the study.

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1256 **9.1.8 12-Lead Electrocardiogram**

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An ECG will be performed, after five minutes in a supine position. A physician must review the ECG and any abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately in the CRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

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1263 **9.1.9 Clinical Laboratory Sampling**

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Laboratory tests will include hematology, biochemistry and urinalysis (provided urine can be obtained, with the exception of screening where a urine sample for THC screen must be obtained). Analysis of all clinical blood samples, pregnancy tests (using serum) and tests to detect the presence of THC will be conducted at a central clinical laboratory.

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

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The THC results will be reported back to the study site to permit confirmation of eligibility and to be used as a measure of study compliance (i.e., to confirm that the patient did not take cannabis during the course of the study).

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The investigator and study monitor will be provided with a list of the normal ranges used by the testing laboratory for all variables assayed during the study and a statement of accreditation (or similar) for the laboratory. Clinical laboratory sample parameters are detailed in Table 9.1-1.

Biochemistry (serum)	Hematology (whole blood)	Urinalysis (urine)	Pregnancy Test (serum)	THC screen (urine)
Alanine aminotransferase (ALT)	Hematocrit	Bilirubin		THC
Albumin	Hemoglobin	Blood		
Alkaline phosphatase	Mean cell volume	Glucose		
Aspartate aminotransferase (AST)	Mean corpuscular hemoglobin	Ketones		
Calcium	Platelets	Nitrites		
Creatinine	Red blood cell count	pH		
Estimates of glomerular filtration rate	White blood cell count with automated differential	Protein		
Gamma-glutamyl transferase		Specific gravity		
Glucose		Urobilinogen		
HDL-cholesterol				
Potassium				
Prolactin				
Prothrombin time (plasma)				
Sodium				
Total bilirubin (TBL)				
Total protein				
Urea				

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Investigators at study sites will be notified of safety laboratory test results. All laboratory results will be reviewed and the reports signed by an investigator. Any results considered to be of clinical significance must be addressed and followed up as clinically appropriate. See [Section 12.3.1](#) for guidance on evaluation of potential drug induced liver injury. All laboratory results considered to represent an AE must be documented on the CRF.

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

Sample volume requirements and processing procedures will be detailed in a separate laboratory manual. The patient/caregiver must be advised that it may not be safe for the patient to undertake further blood tests within one month of any study-related

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blood draws and to inform the investigator if they suffered any blood loss during the one-month period leading up to a planned blood draw.

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9.1.10 Interactive Voice Response System

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The IVRS will be used to collect patient reported diary data (refer to [Section 9.1.12](#)), to assign patients to treatment groups and to provide treatment allocation information in the event of patient unblinding. The IVRS will also be used to manage IMP supply.

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

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- Obtain a patient's screening number (Visit 1).
- Randomize a patient and obtain their patient number (Visit 2).
- Obtain dispensing information (Visits 2, 4, 6 and 8).
- Provide completion/taper/premature termination information (Visit 8 and 9).

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

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9.1.11 Questionnaires and Assessments Completed at Scheduled Visits

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The same caregiver should complete/answer the questionnaires/assessments in order to maintain consistency. The C-SSRS is to be administered by the investigator or his/her qualified designee at every visit as indicated in the time and events table. (Qualified designee is defined as physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant, who is licensed and has completed the C-SSRS training within the last 2 years). The survey should be administered by the same assessor, where possible, throughout the study.

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9.1.11.1 Sleep Disruption 0–10 Numerical Rating Scale

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The patient's caregiver will be asked:

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- “On a scale of ‘0 to 10’, please indicate the number that best describes your child's sleep disruption in the last week.”

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The markers range from 0 = slept extremely well, to 10 = unable to sleep at all.

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

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9.1.11.2 Epworth Daytime Sleepiness Scale

1356 The EDSS is a questionnaire that provides a measure of a person's general level of
1357 daytime sleepiness, or their average sleep propensity in daily life. The EDSS contains
1358 eight questions that are rated on a four-point numerical scale (0–3). The total EDSS
1359 score is the sum of the eight item-scores and can range between 0 and 24. Higher
1360 total scores represent greater levels of daytime sleepiness.

1361 The EDSS will be completed by the patient's caregiver.

1362 If the main caregiver is not available at the appropriate visit then this information can
1363 be captured over the telephone, ideally on the day of the visit or otherwise within
1364 three days.

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9.1.11.3 Caregiver Global Impression of Change

1366 The CGIC comprises the following question to be rated on a seven-point scale:

- 1368 • Since your child started treatment, please assess the status of your child's
1369 overall condition (comparing their condition now to their condition before
1370 treatment) using the scale below.

1371

1372 The markers are: Very Much Improved; Much Improved; Slightly Improved; No
1373 Change; Slightly Worse; Much Worse Very Much Worse.

1374 The caregiver will be asked to assess the status of the patient's overall condition at
1375 Visit 2 (i.e., prior to commencement of IMP) as a memory aid for subsequent visits.

1376 If the main caregiver is not available at the appropriate visit then this information can
1377 be captured over the telephone, ideally on the day of the visit or otherwise within
1378 three days.

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9.1.11.4 Quality of Life in Childhood Epilepsy

1381 The QOLCE questionnaire was designed specifically to measure quality of life in
1382 children with epilepsy and is composed of 16 subscales assessing seven domains of
1383 Health Related Quality of Life (physical function, social function, emotional well-
1384 being, cognition, behavior, general health and general quality of life). The QOLCE
1385 must be completed by a parent or caregiver who interacts with the child on a
1386 consistent, daily basis. It should take 20–30 minutes to complete.

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9.1.11.5 Cognitive Assessment Battery

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The cognitive assessment battery will be administered at Visit 2 before receiving study medication and repeated at Visit 8 or when the patient completes treatment. The items are age specific and the age of the patient at entry will be the age used when choosing the items to be given. Children and adults are to complete the battery as able. It is expected that a number of patients will only be able to complete part of the battery and some may not be able to complete it at all. Parent and/or caregivers are to complete certain items. The battery items are available in English, French, and Spanish (so will only be administered to a sub-group of countries: USA, UK, France and Spain) and need to be given by an experienced psychometrician. A summary of the battery is shown below in Table 9.1-2 and Table 9.1-3.

Function	Patient Measures	Age Range	Approximate Administration Time for Psychometrician
Intelligence IQ	WPPSI-4 Vocabulary, Matrix Reasoning	2;6 - 5;11 years	30 minutes
	WASI-2 Vocabulary, Matrix Reasoning (Including Wechsler: 'Digit Span' subtest from WISC-4 and WAIS-4; 'Coding' subtest from WISC-4 & WAIS-4; 'Bug Search' from WPPSI-4)	6 - adult	45 minutes
Attention/Exec Funct Trail Making	Trail Making Test D-KEFS	9 - adult	5 minutes
Language Naming Fluency	Expressive One-Word Picture Vocabulary Test-4 th Ed	2 - adult	5 minutes
	NEPSY-2 Word Generation	2 - 5 years	5 minutes
	F-A-S and Animals	6 - adult	5 minutes
Visual-Spatial VMI	Developmental Test of Visual Motor Integration-6	2 - adult	5 minutes
Fine Motor Speed Pegs	Purdue Pegboard	4 - adult	5 minutes

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Function	Parent Measures	Age Range	Approximate Administration Time for Parents
Executive	Behavior Rating Inventory of Executive Function (Parent and Teacher)	3 - 21 years	10 minutes
Attention	ADHD Checklist (Parent and Teacher)	All ages	5 minutes
Mood/Anxiety	BASC-2	3 - 21	20 minutes

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Table 9.1-3 Neuropsychological Protocol for Epilepsy Patients Treated with Cannabidiol - Parent Measures			
Function	Parent Measures	Age Range	Approximate Administration Time for Parents
	(Parent and Teacher)	years	
Free-form report	Report Form (Parent and Teacher)	All ages	5 minutes
SES	SES Scale	All ages	5 minutes (during first assessment only)

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9.1.11.6 Vineland Adaptive Behavior Scales (Second Edition)

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The Vineland-II is an individually administered instrument for assessing adaptive behaviors. Communication, Daily Living Skills, Socialization, and Motor Skills will be assessed by the caregiver using a rating scale.

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9.1.11.7 Columbia-Suicide Severity Rating Scale (Children's)

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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. At screening (Visit 1), questions will be in relation to lifetime experiences (Children's Baseline). Questioning at all subsequent visits will be in relation to the last assessment (Children's Since Last Visit).

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The C-SSRS is to be administered by the investigator or his/her qualified designee at every visit as indicated in the time and events table. (Qualified designee is defined as physician, osteopath, nurse practitioner, clinical psychologist or physician's assistant, who is licensed and has completed the C-SSRS training within the last 2 years). The survey should be administered by the same assessor, where possible, throughout the study. Assessments will be conducted only if patients are of an appropriate age (six years of age and older).

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9.1.11.8 Caregiver Impression of Investigational Medicinal Product Palatability

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The caregiver will be asked the following question to be rated on a five-point scale:

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- Overall, how acceptable did your child find the study medication?

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The markers are: Liked it a lot; Liked it; Neither liked nor disliked it, Didn't like it, Didn't like it at all.

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

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9.1.11.9 Cannabis Withdrawal Scale

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The CWS is a 19-item scale with each item (withdrawal symptom) measured on a 0–10 NRS (0 = Not at all; 5 = Moderately; 10 = Extremely). The patient or their caregiver is asked to record the extent to which each withdrawal symptom was experienced in the last 24 hours and also to rate the negative impact on normal daily activities (i.e., two separate scores are recorded for each item using the same 0–10 NRS). Scores are summed over the 19 items for each measure. Assessments will be conducted only if patients are of an appropriate age (six years of age and older).

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9.1.12 Patient Diary

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Seizure information and IMP dose administration data will be collected through an IVRS telephone diary completed daily throughout the study. The patient or their caregiver will also complete a paper diary daily to record daily IMP dosing volumes, usage of rescue medication, concomitant AEDs and AEs throughout the study.

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The number and type of convulsive and non-convulsive seizures as well as information on usage of rescue medication, concomitant AEDs and AEs will be collected each day from screening (Visit 1) until completion of dosing (Visit 8/9) or withdrawal. Information on IMP intake will also be recorded each day from randomization (Visit 2) until completion of dosing (Visit 8/9) or withdrawal.

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9.1.13 Investigational Medicinal Product Accountability

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IMP will be dispensed at each of the following visits:

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- Visit 2 (Day 1).
- Visit 4 (Day 29).
- Visit 6 (Day 57).
- Visit 8 (Day 99) (for patients not entering the OLE study on Day 99; if required).

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Patients will be asked to return all IMP (used and unused) to each relevant visit (Visits 4, 6, 8 and 9). The site will check the returned IMP against the usage recorded

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using the IVRS report and diary. Any discrepancies will be discussed with the patient/caregiver and documented accordingly within the patient's source documents.

1491 Refer to [Section 9.1.15.2.1](#) for the list of 'Triggering Drug Accountability
1492 Discrepancies' associated with monitoring of drug abuse liability.

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1494 **9.1.14 Adverse Events**

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1496 Any adverse changes in the patient's medical condition, following completion of the
1497 consent/assent form by the patient, will be recorded on the CRF as AEs, questioning
1498 the patient further if necessary. All AEs occurring during the study, whether or not
1499 attributed to the IMP, observed by the investigator or reported by the patient will be
1500 recorded in the CRF.

1501 SAEs must be reported to GW Pharmacovigilance Department (PVD) within 24 hours
1502 of discovery or notification of the event, and recorded in the CRF.

1503 Refer to [Section 12](#) for definitions, procedures and further information.

1504 The number of inpatient hospitalizations that are, in the investigator's opinion, due to
1505 epilepsy will be recorded in the patient's CRF and through the SAE reporting process.

1506 Refer to [Section 9.1.15.1.1](#) for the list of 'Triggering AEs of Interest' associated with
1507 monitoring of drug abuse liability.

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1509 **9.1.15 Monitoring of Drug Abuse Liability (for Patients 12 Years of 1510 Age and Older)**

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1512 There are two triggers that will require the investigator or study coordinator to discuss
1513 abuse potential signals with the patient or their caregiver. These are either AEs of
1514 interest that may be reported by the patient/caregiver, or drug accountability issues
1515 regarding overuse of the IMP or missing bottles. Different questionnaires will be
1516 completed by the site depending upon which trigger occurs (see Figure 9-1).

1517 Irrespective of the above, all patients/caregivers will be interviewed at their final
1518 dosing visit (Visit 8/9) or withdrawal visit and a Study Medication Use and Behavior
1519 Survey will be completed by the investigator or study coordinator. Investigators and
1520 study coordinators will be provided with training on how to complete and perform the
1521 processes outlined in this section. This training must be completed and documented
1522 by the relevant site staff prior to implementation at site.

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9.1.15.1 Monitoring of Adverse Events

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AE information will be collected according to [Section 9.1.14](#).

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9.1.15.1.1 List of ‘Triggering Adverse Events of Interest’

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During the collection of AEs, if the patient reports an AE consistent with any of the following categories, then the investigator or study coordinator is required to complete an additional Supplemental Adverse Event Form and a Site Classification Form (investigator only) following further discussion of the event(s) with the patient or their caregiver. The categories are:

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- Euphoria or inappropriate elation.
- Inappropriate laughter or exhilaration.
- Mood changes.
- Drunk, high or intoxicated.
- Hallucinations (visual or auditory), dissociations, disorientation, agitation.
- Disturbance in cognition, memory, or attention.
- Drug abuse.
- Drug withdrawal or drug withdrawal syndrome.
- Addiction.
- Overdose.
- Misuse of IMP.
- Thoughts of suicide, attempted suicide or suicide.

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An AE that is consistent with the above categories will be known as a ‘triggering AE of interest’ for the purposes of this study.

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9.1.15.1.2 Supplemental Adverse Event Form

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This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an interview with the patient/caregiver when a triggering AE of interest is reported. It is important that this is completed by a trained investigator or study coordinator with the patient/caregiver present. The answers on the Supplemental Adverse Event Form will then be transcribed into the patient’s CRF for the study. If the Supplemental Adverse Event Form cannot be completed at the time the triggering AE of interest is reported, then the site should contact the patient/caregiver to obtain the required answers as soon as possible.

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9.1.15.2 Monitoring Drug Accountability Discrepancies

1571 Any time after enrollment until final collection of study data, drug accountability
1572 discrepancies are monitored as follows:

- 1573 • At routine Drug Accountability collection times (i.e., Visits 2, 4, 6 and 8):
1574 the site personnel will collect the IMP clinical supplies and make sure the
1575 usage is in line with the expectations reported within the IVRS report and
1576 paper diary.
 - 1577 • At any time that the site is informed by either the IVRS or by the
1578 patient/caregiver about any overuse of IMP, suspected misuse, abuse, or
1579 diversion.
- 1580

9.1.15.2.1 List of 'Triggering Drug Accountability Discrepancies'

1581 If there are any discrepancies in drug accountability as outlined by the criteria below,
1582 known as 'triggering drug accountability discrepancies', then the trained investigator
1583 or study coordinator will complete a Supplemental Drug Accountability Form and
1584 Site Classification Form (investigator only) following further discussion of the
1585 event(s) with the patient/caregiver. The triggering drug accountability discrepancies
1586 are as follows:
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- 1588 • Missing bottle(s).
 - 1589 • Compliance issues where one or more bottles are used compared to what was
1590 the expected use, according to the IVRS report and paper diary.
 - 1591 • Returned IMP supply with evidence of tampering.
 - 1592 • Greater than the target daily dose as recorded in the IVRS report and paper
1593 diary.
- 1594

9.1.15.2.2 Supplemental Drug Accountability Form

1595 This form consists of eight questions regarding various aspects of drug accountability
1596 and patient usage. It is completed as part of an interview with the patient/caregiver
1597 when a triggering drug accountability discrepancy is identified. It is important that
1598 this is completed by a trained investigator or study coordinator with the
1599 patient/caregiver present. The answers on the Supplemental Drug Accountability
1600 Form will then be transcribed into the patient's CRF for the study. The accountability
1601 reporting procedures will still occur. If the Supplemental Drug Accountability Form
1602 cannot be completed at the time the triggering drug accountability discrepancy is
1603 identified, then the site should contact the patient/caregiver by telephone to obtain the
1604 required answers as soon as possible. (Note: IMP refers to GWP42003-P or placebo,
1605 not other concomitant medications).
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9.1.15.3 Site Classification Form

1616 The investigator should review the applicable Supplemental Adverse Event Form or
1617 Supplemental Drug Accountability Form, and then complete the Site Classification
1618 Form. For each Supplemental Adverse Event Form or Supplemental Drug
1619 Accountability Form completed, there should be an associated Site Classification
1620 Form.

1621 The Site Classification Form requires the investigator to assign the finding to an
1622 appropriate classification and then to also assign the possible relationship to the IMP.
1623 The investigator is also required to indicate the level of the certainty of the
1624 classification. The answers from the Site Classification Form will then be transcribed
1625 into the patient's CRF for the study.

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9.1.15.4 Study Medication Use and Behavior Survey

1627 This form consists of 18 questions regarding the use of the IMP. The trained
1628 investigator or study coordinator will complete this survey as an interview with the
1629 patient/caregiver at the final dosing visit (Visit 8/9) or withdrawal visit. The answers
1630 on the Study Medication Use and Behavior Survey will then be transcribed into the
1631 patient's CRF for the study.

1632 The Study Medication Use and Behavior Survey will be completed for all patients 12
1633 years of age and older in the study and not only those that have reported a triggering
1634 AE or drug accountability discrepancy.

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

1637 Any triggering AE or triggering drug accountability must be notified to the GW PVD
1638 using the same fax number for SAE reporting within 24 hours of becoming aware of
1639 the event.

1640 A formal Adjudication Committee will be appointed and assigned to this initiative to
1641 classify triggered cases. The Adjudication Committee will meet on a periodic basis to
1642 review and assess all of the information collected on triggered cases. Only data from
1643 patients who have completed the study will be assessed.

1644 A detailed charter will be agreed, which will describe the roles, responsibilities and
1645 duties of the members of Adjudication Committee. The Committee will review all of
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1654 the information collected in the process and in the assessment of the abuse potential of
1655 GWP42003-P, such as:

- 1656 • All triggering AE information.
- 1657 • Supplemental Adverse Event Form (if applicable).
- 1658 • All triggering drug accountability discrepancies.
- 1659 • Supplemental Drug Accountability Form (if applicable).
- 1660 • Site Classification Form.
- 1661 • Study Medication Use and Behavioral Survey.
- 1662 • Additional information from site(s) as requested by the Committee.

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1664 The Adjudication Committee will assess all of the information. It will form a position
1665 on the classification of each event and will write a study-related report, detailing the
1666 conclusions and recommendations.

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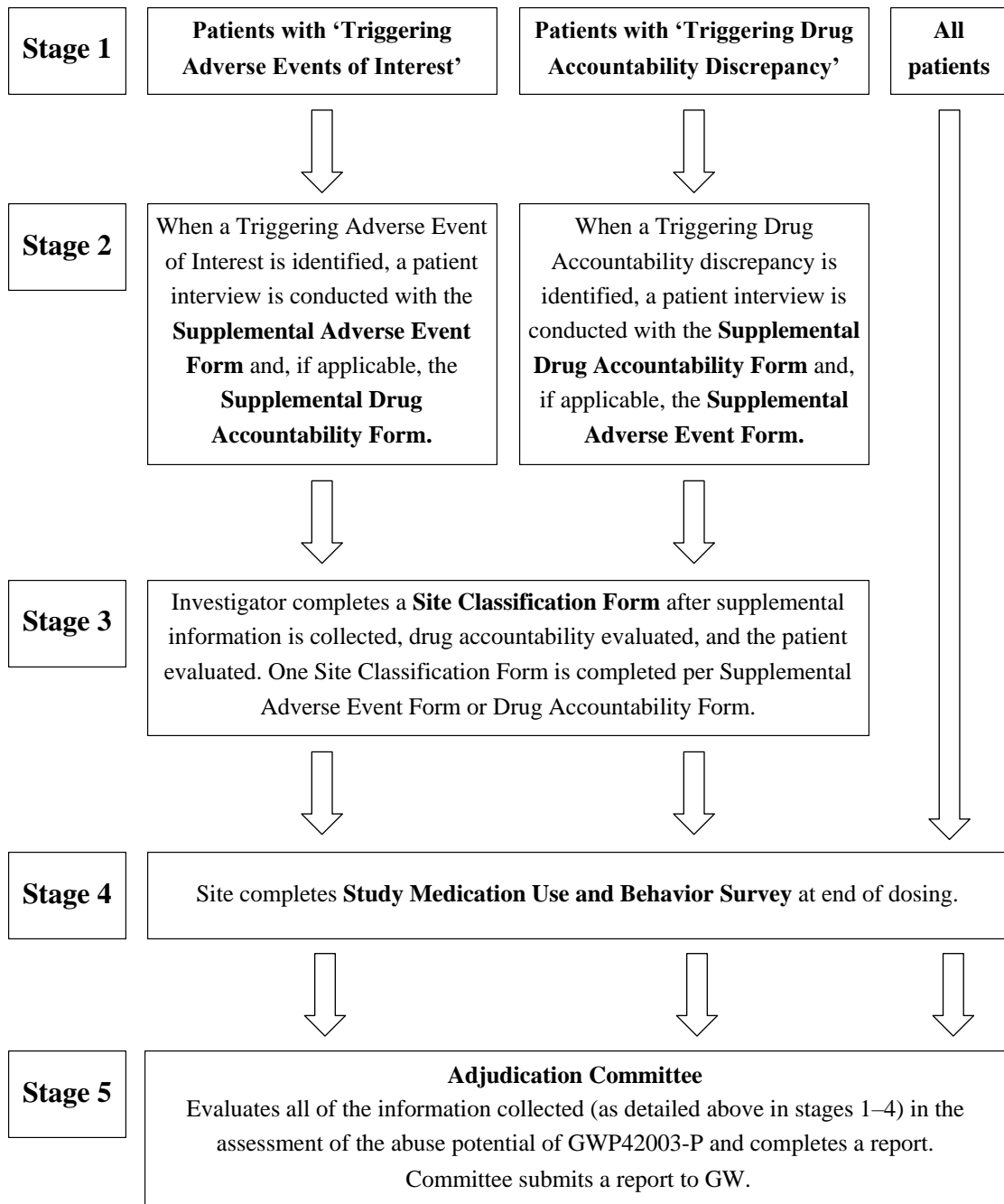
The overall process is summarized in Figure 9-1.

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Figure 9-1 **Flow Diagram for Identifying and Evaluating Clinical Trial Adverse Event Data Through Systematic Categorization, Tabulation and Analysis which can Illuminate an Abuse Potential Signal (for Patients 12 Years of Age and Older)**

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9.2 Study Procedures by Visit

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Patients and their parent(s)/legal representative will be invited to participate in the study and will be issued with the patient information and informed assent or the patient/parent(s)/legal representative information and informed consent (as applicable). Following adequate time to discuss the study with the investigator, nurse, relatives or caregiver, patients/parent(s)/legal representatives who provide written informed consent/assent at Visit 1 will be enrolled into the study.

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9.2.1 Visit 1 (Day -28, Screening)

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The following assessments will be made at Visit 1: demographics, medical history (including seizure frequency over the last six months and *SCN1A* mutation status), vital signs, postural blood pressure, physical examination (including height and body weight), ECG, C-SSRS (Children's Baseline) and visit procedure-related AEs. If the mutation status of *SCN1A* is unknown, a blood sample will be taken for *SCN1A* analysis (this can be taken at any visit during the study). Clinical laboratory samples (urine and blood) will be taken for hematology, biochemistry, urinalysis (where possible), a urine THC screen (required) and a pregnancy test (using a serum sample, as appropriate). Patients or their caregivers will also be asked for information regarding concomitant medications and/or changes to medication (including AEDs). Patients who satisfy all inclusion and none of the exclusion criteria specified in [Section 6](#) will then begin the 28-day baseline observation period.

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The IVRS must be contacted by the site to register the screening visit and issue the screening number. If this does not occur, the patient will not be able to call into the telephone diary.

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Patients or their caregivers will be issued with the IVRS details and will be instructed on how to use it to record daily seizure information. Patients or their caregivers will also be given a paper diary to record usage of rescue medication, concomitant AEDs and AEs and will be instructed on how to do so.

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The investigator should review the laboratory results as soon as these become available. If the results show a patient is ineligible, the patient must be withdrawn from the study.

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9.2.2 Visit 2 (Day 1, Randomization)

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This visit will occur 28 days after Visit 1. A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

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The following assessments will be made at Visit 2: vital signs, postural blood pressure, physical examination (including height and body weight) and ECG. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen and a pregnancy test (using a serum sample, as appropriate). The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).

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The investigator must assess the patient's daily number of convulsive seizures from the patient's IVRS data. Patients who have experienced four or more convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the baseline period and who meet all of the other inclusion and none of the exclusion criteria specified in [Section 6](#) will be eligible to continue in the study. If a patient does not meet the eligibility criteria within this period, consideration will be given to rescreen at a later date.

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Eligible patients will then be randomized to receive one of two Dose Levels of GWP42003-P or placebo using the IVRS (see [Section 7.1](#)). Patients in the placebo group will be split into two equivalent cohorts: half receiving Low Dose Level dosing volumes and half receiving High Dose Level dosing volumes.

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Following randomization, patients will remain at the clinic where the following assessments will be performed prior to the administration of study medication: EDSS, Sleep Disruption 0–10 NRS, QOLCE, C-SSRS (Children's Since Last Visit), cognitive assessment battery, CWS and the Vineland-II. Caregivers will be asked to write a brief description of the patient's overall condition as a memory aid for the CGIC at subsequent visits or withdrawal. Patients will then receive sufficient IMP and a dosing regimen as assigned by the IVRS for the following four weeks. Each patient will take their first dose of IMP at the clinic and will titrate to their target Dose Level during the following two weeks. Patients or their caregivers will be instructed on using the IVRS's daily dosing record, as well as how to record IMP dosing information in the paper diary.

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The investigator should review the laboratory results as soon as these become available. If the results show a patient is ineligible, the patient must be withdrawn from the study.

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9.2.3 Visit 3 (Day 15)

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This visit will occur 14 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

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The following assessments will be made at Visit 3: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC, C-SSRS (Children’s Since Last Visit) and the Vineland-II. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. The patient’s IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the titration regimen.

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9.2.4 Visit 4 (Day 29)

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

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The following assessments will be made at Visit 4: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC, C-SSRS (Children’s Since Last Visit) and the Vineland-II. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. The patient’s IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen.

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All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The IVRS will be contacted for treatment pack assignment. Patients will receive sufficient IMP as assigned by the IVRS for the following four weeks.

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9.2.5 Visit 5 (Day 43, Safety Telephone Call)

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This visit will occur 42 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

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Visit 5 will be completed by telephone. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).

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9.2.6 Visit 6 (Day 57)

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This visit will occur 56 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

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The following assessments will be made at Visit 6: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC, C-SSRS (Children's Since Last Visit) and the Vineland-II. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry and urinalysis. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen.

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All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The IVRS will be contacted for treatment pack assignment. Patients will receive sufficient IMP as assigned by the IVRS for the following six weeks.

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9.2.7 Visit 7 (Day 71, Safety Telephone Call)

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This visit will occur 70 days after randomization (Visit 2). A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

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Visit 7 will be completed by telephone. Patients or their caregivers will be asked for information on AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).

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9.2.8 Visit 8 (Day 99, End of Treatment)

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This visit will occur 98 days after randomization (Visit 2) or earlier if the patient withdraws from the study. A visit window of ± 3 days from the scheduled visit date is permitted, but it is preferred that the visit is performed on the scheduled visit day where possible.

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The following assessments will be made at Visit 8: vital signs, physical examination (including height and body weight), ECG, EDSS, Sleep Disruption 0–10 NRS, CGIC, QOLCE, C-SSRS (Children’s Since Last Visit), cognitive assessment battery and the Vineland-II. The Caregiver Impression of IMP Palatability will also be assessed. Clinical laboratory samples (blood and urine [where possible]) will be taken for hematology, biochemistry, urinalysis, a urine THC screen (required) and a pregnancy test (using a serum sample, as appropriate). The patient’s IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the dosing regimen.

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All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. For patients who withdraw early, the IVRS will be contacted to confirm withdrawal from the study.

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Patients who have completed all of the scheduled study visits will be offered the option of entering an OLE study. Entry is to be on the same day as Visit 8 (Day 99) or within seven days of Visit 8.

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For patients who enter the OLE study on Day 99, the IVRS will be contacted to confirm the patient’s completion of this study and the paper diaries will be collected. For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

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For patients not entering the OLE study on Day 99, the IVRS will be contacted to confirm start of the 10-day taper period and for additional treatment pack assignment (if required). The IVRS will generate the patient’s daily IMP dosing volumes for the 10-day taper period, during which time IVRS and diary information will continue to be recorded. The taper period may be interrupted if the patient wishes to enter the OLE study within the seven-day timeframe.

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9.2.9 Visit 9 (Day 100–106 or Day 109, End of Taper Period)

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This visit is required only for those patients who do not enter the OLE study on the day of Visit 8 (i.e., Day 99±3) or for those who withdraw early. For patients who do not enter the OLE study, Visit 9 should occur 10 (+3) days after Visit 8 (i.e., on Day 109). For patients who delay entry into the OLE study, Visit 9 should occur on the day the patient enters the OLE study and within seven days of Visit 8 (i.e., up to Day 106) to allow the patient to enter the OLE study within this timeframe.

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The following assessments will be made at Visit 9: vital signs, physical examination (including height and body weight) and C-SSRS (Children's Since Last Visit). The CWS will also be assessed. The patient's IVRS report and paper diary will be reviewed and the information recorded along with information regarding AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs). The investigator must assess adherence to the down-titration regimen.

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All IMP (used and unused) will be collected and a check of the returned IMP against usage should be made. The IVRS will be contacted to confirm the patient's completion of the study and the paper diaries will be collected. For patients 12 years of age and older, the trained investigator or study coordinator will complete the Study Medication Use and Behavior Survey as an interview with the patient/caregiver.

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9.2.10 Visit 10 (Day 137, Safety Follow-Up)

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This visit is required for patients who do not enter the OLE study or who withdraw from the study early. This visit should occur four weeks after Visit 9 (±3 days), or withdrawal from treatment, and can be conducted by telephone.

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The purpose of the follow-up is to ascertain the status of AEs continuing after Visit 9 or any new AEs commencing after Visit 9. Epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs) must also be recorded.

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

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9.2.11 Safety Telephone Calls

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For patients not entering the OLE study, or who withdraw from the study early, safety telephone calls will be made weekly (± 3 days) from Visit 9 until Visit 10. Patients or their caregivers will be asked for information on ongoing and new AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication (including AEDs).

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10 WITHDRAWAL

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In accordance with the Declaration of Helsinki⁶⁵, the FDA regulations relating to good clinical practice (GCP) and clinical trials^{66, 67, 68}, the EU Clinical Trials Directive (2001/20/EC)⁶⁹ and/or other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

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

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- Administrative decision by the investigator, GW, or a Regulatory Authority.
- Pregnancy.
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- Withdrawal of patient consent/assent.
- Withdrawal of parent(s)/legal representative consent.
- Lost to follow-up.

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

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- Patient non-compliance.
- AE which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- ALT or AST $>8 \times$ ULN.
- ALT or AST $>5 \times$ ULN for more than two weeks.
- ALT or AST $>3 \times$ ULN **and** (TBL $>2 \times$ ULN **or** INR >1.5).
- Any evidence of drug abuse or diversion.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

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Should a patient request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients who withdraw should have their dose of IMP tapered gradually (10% each day) over a period of 10 days, beginning at the time the decision is made to discontinue. In some cases, tapering the dose of IMP may be inadvisable (e.g., continued dosing is not possible due to an AE). The decision on whether or not to taper IMP will be left to the investigator's clinical judgment. All assessments required at Visit 8 should be conducted if possible. If the tapered dose is

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administered, patients should return for Visit 9 if possible. Patients withdrawing due to an AE should be followed up according to [Section 12.7](#) safety follow-up visit. All information should be reported on the applicable CRF pages (refer to [Section 9.1](#)). Wherever possible, the safety follow-up visit should be conducted 28 days from the date of the last dose of IMP (refer to [Section 9.2.10](#)).

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11 URGENT SAFETY MEASURES

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The sponsor and investigator may take appropriate urgent safety measures in order to protect the patients of a clinical trial against any immediate hazard to their health or

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safety. If such measures are taken by the investigator they must notify GW

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immediately or at least within 24 hours of awareness. GW will report urgent safety

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measures to Competent Authorities by telephone within 24 hours of awareness,

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wherever possible, and will provided a written report to the Competent Authorities

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and IRB/EC within three days.

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12 ADVERSE EVENT REPORTING

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12.1 Definitions

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12.1.1 Adverse Event

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

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Any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which is present following screening (Visit 1) and the post treatment, safety follow-up visit (Visit 10), which may or may not be considered to be related to the IMP. Any event that is the result of a study procedure must be recorded as an AE.

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

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

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12.1.2 Investigator

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

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12.2 Serious Adverse Events

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

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

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- Results in death.
- Is life-threatening.*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

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- Is a congenital anomaly/birth defect.
 - Is medically significant.**
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2091 * The term “life-threatening” in the definition of “serious” refers to an event in which
2092 the patient was at risk of death at the time of the event; it does not refer to an event,
2093 which hypothetically might have caused death if it were more severe.

2094 ** Medical and scientific judgment should be exercised in deciding whether SAE
2095 reporting is appropriate in other situations. Important medical events may not be
2096 immediately life threatening or result in death or hospitalization but may jeopardize
2097 the patient or may require intervention to prevent one of the other outcomes listed in
2098 the definition above. These should also usually be considered serious. Examples of
2099 such events are intensive treatment in an emergency room or at home for allergic
2100 bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or
2101 development of drug dependency or drug abuse.

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2103 **12.3 Reporting Procedures for Serious Adverse Events**

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2105 All SAEs occurring during the study must be reported to GW with any other
2106 supporting information and recorded in the AE section of the CRF. Any on-going
2107 SAEs should be followed up until resolution wherever possible. For all deaths, the
2108 working diagnosis or cause of death as stated on a death certificate, available autopsy
2109 reports and relevant medical reports should be sent to GW promptly.

2110 **All SAEs must be reported directly to GW PVD within 24 hours of discovery or**
2111 **notification of the event.** All SAE information must be recorded on the SAE forms
2112 provided in the site files and faxed to GW PVD. Additional information received for
2113 a case (follow-up or corrections to the original case) need to be detailed on a new
2114 SAE form, signed/dated and faxed to the GW PVD and the AE section of the CRF
2115 must be updated.

2116 The investigator should continue to document all AEs which occur up to the last
2117 formal follow-up observational period (Visit 10). If the investigator subsequently
2118 becomes aware of a new IMP-related SAE after the last formal follow-up period of
2119 the study, these should still be reported to the GW PVD.

2120 Any other problem discovered outside these time limits which is deemed to be an
2121 unexpected safety issue and is likely to have an impact on patients who have
2122 participated in the study, then these should be treated as an SAE and reported to GW
2123 PVD. Such post study SAEs do not need to be recorded on the patient’s CRF if
2124 editing rights to the CRF have been removed.

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Contact details for the GW PVD are provided at the front of the site files for all study centers, and upon the GW SAE Report form.

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12.3.1 Potential Cases of Drug-Induced Liver Injury

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Abnormal values in AST and/or ALT concurrent with abnormal elevations in TBL that meet the criteria outlined below are considered potential cases of drug-induced liver injury and will be considered as protocol defined criteria for withdrawal and important medical events.

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

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The investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment, detailed history and physical examination. Patients should be followed until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

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12.4 Pregnancy

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Any patient, or patient's partner, who has become pregnant whilst receiving IMP, or within 90 days of last dose of IMP, must be reported to the GW PVD within 24 hours of first awareness. Please use the GW Pregnancy Monitoring Forms provided. Where possible the investigator should provide the outcome of the pregnancy.

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The investigator is not obliged to actively monitor for any pregnancies that commence more than 90 days after the final dose of IMP. However, if the investigator becomes aware of a new pregnancy outside this time limit then they should report it as above. GW PVD will follow-up for all pregnancy outcomes.

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12.5 Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the IMP must be reported as such. The expression

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“reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

2177 The following question which must be answered by the investigator for all AEs is
2178 used to capture the reasonable causal relationship of an event to the IMP:

2179 “In your opinion is there a plausible relationship to the IMP?” The answer is “yes”,
2180 or “no”.

2181 Events that start before the first dose of IMP (pre-treatment) should be considered as
2182 not causally related. Where a pre-treatment event worsens in severity following the
2183 first dose of IMP a new event record should be entered into the CRF.

2184 Considering the explanation given above, investigators are strongly encouraged to
2185 express their opinion on what the cause of an AE might be. For individual patients,
2186 the investigator is usually in the best position to assess the underlying suspected cause
2187 of an AE. For all AEs and especially SAEs, it is important that the investigator assess
2188 not only the possible role of the IMP but also competing etiological factors as the
2189 underlying cause. Factors for consideration may include:

- 2190 • Medical history.
 - 2191 • Lack of efficacy/worsening of treated condition.
 - 2192 • Concomitant or previous treatment.
 - 2193 • Withdrawal of IMP.
 - 2194 • Protocol-related procedure.
- 2195

2196 **12.6 Reporting Procedures for All Adverse Events**

2197 All AEs (including SAEs) occurring during the study will be reported on the running
2198 logs in the AE section of the CRF. This includes all events from the time following
2199 screening (Visit 1) to post study follow-up (Visit 10), whether or not attributed to IMP
2200 and observed by the investigator or patient.

2202 The following information will need to be provided for all AEs:

2203 **A) Adverse event (diagnosis or syndrome if known, or signs and symptoms)**

2204 Where the investigator cannot determine a diagnosis, signs or symptoms should be
2205 recorded on the AE section of the CRF. Once a diagnosis has been determined the
2206 AE section of CRF must be updated to reflect the diagnosis in replacement of the
2207 original symptoms. In circumstances where only a provisional diagnosis is possible
2208 (working diagnosis), the CRF must be updated to reflect the provisional diagnosis in
2209 replacement of the original symptoms. In some circumstances it may be relevant for
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the investigator to include the symptoms alongside the diagnosis in the verbatim event description. However, the diagnosis (full or provisional) should be clearly stated e.g., fever and malaise due to a respiratory tract infection.

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B) Adverse Event Start date and Stop date

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

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C) Outcome

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

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

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D) Severity

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

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If the severity of an AE fluctuates day-to-day, for example, a headache or constipation, the change in severity should not be recorded each time, instead only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration regardless of severity.

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A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore it should not be classed as serious.

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E) Causality

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See [Section 12.5](#) above.

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F) Action taken with Study Medication

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2259 This question refers to the action taken with the IMP due to an AE. The action with
2260 the IMP must be classed as:

- 2261
- None.
 - Dose reduced temporarily.
 - Dose reduced.
 - Study medication interrupted.
 - Study medication stopped.
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12.7 Follow-up Procedures for Adverse Events

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2268 The investigator may be asked to provide follow-up information to the GW PVD for
2269 any AEs reported.
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2271 AEs considered related to the IMP by the investigator or the sponsor should be
2272 followed up until resolution or the event is considered stable.

2273 It will be left to the investigator's clinical judgment whether or not an AE is of
2274 sufficient severity to require the patient's removal from treatment. A patient may also
2275 voluntarily withdraw from treatment due to what he or she perceives as an intolerable
2276 AE; further details of withdrawal are presented in [Section 10](#). If either of these
2277 occurs, the patient must undergo an end of treatment assessment and be given
2278 appropriate care under medical supervision until symptoms cease or the condition
2279 becomes stable.
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12.8 Reporting Clinically Significant Laboratory Results

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2282 All investigational sites are required to submit to the GW PVD the laboratory results
2283 for any patient after randomization that meet the criteria for the selected laboratory
2284 parameters as follows:
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- ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting,
2287 right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
2288 ($>5\%$).
 - ALT or AST $>8 \times$ ULN.
 - ALT or AST $>5 \times$ ULN for more than two weeks.
 - ALT or AST $>3 \times$ ULN **and** (TBL $>2 \times$ ULN **or** INR >1.5).
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2298 These reports must be sent to the GW PVD using the same fax number for SAE
2299 reporting within 24 hours of becoming aware of the results. In addition, please send a
2300 copy of the patient's baseline laboratory results with all reports to GW PVD.
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12.9 Notification of Safety Information to Investigators, Regulatory Authorities and Ethics Committees

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In accordance with the EU Clinical Trials Directive⁶⁹, relevant parts of the FDA Code of Federal Regulations⁷⁰ and any national regulations, GW will inform investigators, regulatory authorities and relevant IRB/ECs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Reactions (SUSARs).

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This information will be provided through three sources:

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- 1) IB⁶³: a compilation of the clinical and non-clinical safety data available on the IMP that is relevant to the study on the IMP in human patients. The IB is updated annually.
- 2) Development Core Safety Information: this document actually forms the Safety Section of the IB⁶³, or is updated as an appendix of the IB⁶³. This document is revised if necessary, when new important safety information becomes available (potentially up to a few times a year).
- 3) Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to GW. They provide information on individual case reports and are sent to all the regulatory authorities, the relevant central IRB/ECs which have approved the study and investigators. As required, the investigator should notify their regional ethical committees of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from GW, in accordance with local procedures.

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In the USA, investigators are normally required to promptly report to their IRBs all unanticipated problems involving risks to human patients, or others, including AEs that should be considered unanticipated problems. Based on current FDA guidance⁶⁶ the following clarification is provided in determining what constitutes an unanticipated problem:

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In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human patients, and reported to the IRB, *only* if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring

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requirement, informed consent/assent, or IB). An individual AE occurrence *ordinarily* does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

2346 The FDA guidance⁷⁰ states that, accordingly, to satisfy the investigator's obligation to
2347 notify the IRB of unanticipated problems, any investigators participating in a
2348 multicenter study may rely on the sponsor's assessment and provide to the IRB a
2349 report of the unanticipated problem prepared by the sponsor.

2350 GW will inform investigators (regulatory authorities and applicable IRB/ECs) of any
2351 safety issues or case reports that are considered to be unanticipated and provide such
2352 reports as mentioned above. It should be noted that a single SUSAR report notified to
2353 investigators in the study does not necessarily constitute an unanticipated problem
2354 unless identified by GW in the submission cover letter.

2355 As a minimum, the recipient will be sent all of the above and relevant updates
2356 between the period from ethical approval and final database lock.

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13 STATISTICAL CONSIDERATIONS

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A statistical analysis plan (SAP) will be produced prior to unblinding of the study.

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Any deviations from the original SAP will be described in the final clinical study

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13.1 Sample Size, Power and Significance Levels

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A total of 120 patients will be enrolled. The 120 patients will be randomly allocated on a 1:1:1 basis to the three treatment groups (40 patients per group). Patients in the placebo group will be split into two cohorts (20 receiving Low Dose Level dosing volumes and 20 receiving High Dose Level dosing volumes), but it is assumed that these two cohorts can be pooled for the analyses of efficacy.

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If it is assumed that patients in the placebo group will experience a mean reduction in convulsive seizure frequency of 10% (from baseline), this sample size of 40 patients per group will be sufficient to detect a difference of 40% between treatments (i.e., patients receiving GWP42003-P will experience at least a 50% reduction in convulsive seizures). This is based on a standard deviation of 63%, using a two-tailed 5% significance level and 80% power.

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13.2 Interim Analysis

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No interim analysis is planned for this study.

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13.3 Analysis Sets

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There will be up to three analysis sets:

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Intention to Treat (ITT)

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- All patients who are randomized and receive IMP in the study will be included and analyzed according to their randomized treatment group.

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- The ITT analysis set is the primary analysis set for all efficacy endpoints.

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Per Protocol (PP)

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

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- All patients who complete the study with no protocol deviations deemed to compromise the assessment of efficacy will be included and analyzed

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according to the treatment group they were randomized. The rules determining the PP analysis set will be fully defined prior to unblinding of the database.

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Safety

2411 All patients who received at least one dose of IMP in the study will be included and
2412 analyzed according to the treatment received. Only patients for whom it has been
2413 confirmed that they did not take any IMP will be excluded from this safety analysis
2414 set.

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13.3.1 Protocol Deviations

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2418 Protocol deviations will be listed and reasons for exclusion from the analysis
2419 populations will be summarized.

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13.4 General Considerations

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2423 Unless stated otherwise, continuous variables will be summarized showing the
2424 number of non-missing values (n), mean, standard deviation, median, minimum and
2425 maximum and categorical variables will be summarized showing the number and
2426 percentage of patients falling in each category.

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13.5 Accountability and Background Characteristics

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13.5.1 Enrollment and Disposition

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2432 All patients (screened, randomized, prematurely terminated IMP) will be accounted
2433 for in the enrollment and disposition summary tables.

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13.5.2 Baseline and Demographic Characteristics

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2437 Age, sex, race and any other demographic or baseline characteristics will be
2438 summarized by randomized treatment group, using appropriate summary statistics.

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13.5.3 Medical History

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2442 Previous and current medical conditions will be summarized by system organ class,
2443 including details of the duration of epilepsy and the types of seizures currently
2444 experienced by the patients.

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13.5.4 Concomitant Medication

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

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13.6 Endpoints and Statistical Methods

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Statistical hypothesis testing will be performed on the primary endpoint and other endpoints as appropriate. Since there is a single primary analysis endpoint, no formal adjustment of statistical significance for multiple testing on multiple endpoints is required, although such multiplicity should be allowed for when interpreting the results for secondary endpoints. However, there are three treatments, so multiple significance testing will occur when making comparisons between the treatments; the major comparisons of interest are those between each of the GWP42003-P Dose Levels and placebo and, in particular, the High Dose Level and placebo. The dose response effect between the two GWP42003-P Dose Levels and placebo will also be explored. No formal adjustment will be made for the comparisons between multiple treatment groups.

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A Mixed-Effect Model Repeated Measures (MMRM) approach will be used for the analysis of continuous variables and logistic regression for categorical variables: the overall test from these procedures will determine whether there are any statistically significant differences between the treatment groups. Comparisons between individual treatments should be interpreted in the light of the result of the overall test, e.g., if the overall test is not statistically significant (indicating that there is little evidence of any difference between the treatments) then an individual comparison that does appear to be significant should be treated with caution.

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13.6.1 Evaluable Period

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

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

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- (i) Day 99 of treatment for the IVRS reported efficacy data and the day of Visit 8 for the CRF-based efficacy data;

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

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13.6.2 Primary Endpoint(s)

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The primary endpoint is the mean percentage change from baseline in convulsive seizure frequency during the maintenance period of the study (Day 15 to the end of the evaluable period) in patients taking GWP42003-P compared with placebo.

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If the data are found to be normally distributed, they will be analyzed using a MMRM approach. The model will include baseline as a covariate and treatment group as fixed factor. The time variable will be the assessment time-point (nominal visit number, corresponding to each 28 days of the maintenance period) treated as a categorical repeated factor. Assessments will be assigned to the nominal visit number using visit windows such that each assessment will be assigned to the earliest scheduled visit that occurs either within three days before the actual visit date or on or after the date of the actual visit. The baseline-by-time and treatment-by-time interactions will also be included. The model will have a separate unstructured covariance matrix in each treatment group.

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The fitted model will then be used to produce a final time-point comparison, which implicitly adjusts for missing observations under the assumption of missing at random; there will be no imputations for missing values at individual time-points.

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The time course of the treatment effect will also be examined by estimating treatment differences, together with their 95% confidence intervals (CIs), for each nominal visit during the randomized treatment period.

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However, due to the nature of seizure data, if a normal distribution cannot be assumed, the data will be analyzed using appropriate non-parametric methods (e.g., Kruskal-Wallis and Wilcoxon Signed Rank tests).

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13.6.3 Secondary Endpoint(s)

The following endpoints will be compared between the three treatment groups over the 12-week, double-blind maintenance period:

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- 2534 • Number of patients experiencing a >25% worsening, -25 to +25% no change,
- 2535 25–50% improvement, 50–75% improvement or >75% improvement in
- 2536 convulsive seizures from baseline.
- 2537 • Number of patients who are convulsive seizure free.
- 2538 • Percentage changes from baseline in non-convulsive seizure frequency.
- 2539 • Change in types of seizures.
- 2540 • Changes from baseline in usage of rescue medication.
- 2541 • Changes from baseline in number of inpatient hospitalizations due to epilepsy.
- 2542 • Changes from baseline in Sleep Disruption 0–10 NRS score.
- 2543 • Changes from baseline in EDSS score.
- 2544 • Changes from baseline in the QOLCE score.
- 2545 • Change in cognitive function as measured with the cognitive assessment
- 2546 battery.
- 2547 • Changes from baseline in the Vineland-II score.
- 2548 • CGIC.

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The number of patients experiencing at least a 25%, 50% and 75% reduction in convulsive seizures and the number of patients seizure free will be summarized and analyzed using the difference in proportions and the odds ratios comparing the treatment groups will be presented together with 95% CIs.

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For changes in non-convulsive seizure frequency, number of convulsive seizure free days, changes in frequency of other seizure type, usage of rescue medication, number of hospitalizations due to epilepsy, sleep disruption, daytime sleepiness, QOLCE, cognitive function and behavior assessments, the data will summarized at baseline and at each time point (or 28-day period, as appropriate) during the treatment period. Changes from baseline to the end of study will be analyzed using MMRM, as with the primary endpoint (or appropriate non-parametric methods if data are found to be not normally distributed).

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The CGIC will be summarized at all time-points and the final assessments recorded at the end of treatment will be analyzed with ordinal logistic regression using the proportional odds model.

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13.6.4 Handling of Missing Data

The primary efficacy analysis uses the ITT analysis set over the evaluable period. MMRM analysis will be used to handle missing values under the Missing at Random assumption.

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If any patients have data censored then a sensitivity analysis will be done using all available data, including the data censored from the primary analyses, to assess the impact of censoring the data.

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Analysis of covariance of the final time-point, using the Last Observation Carried Forward (LOCF) approach, will also be performed as sensitivity analyses for the primary and key secondary endpoints.

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In order to explore the robustness of the primary analysis, further sensitivity analysis may be specified in the SAP.

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Similar approaches, using the LOCF, will be applied if the data are analyzed using non-parametric methods.

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13.6.5 Safety

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In the presentation of safety data, data from the two cohorts of placebo patients (Low Dose Level and High Dose Level) will be presented separately and pooled together.

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This will allow the possibility to explore any effects of the volume of IMP on safety endpoints.

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13.6.5.1 Treatment Compliance and Extent of Treatment Exposure

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Treatment compliance and exposure to treatment will be summarized.

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13.6.5.2 Adverse Events

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

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

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

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The following summaries will be produced:

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- All-causality AEs.

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- Treatment related AEs.

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- All-causality AEs by severity.

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- All-causality serious AEs.

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- 2618 • Treatment related serious AEs.
- 2619 • AEs reported as leading to permanent cessation of study treatment.
- 2620 • Fatal AEs.

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2622 **13.6.5.3 Clinical Laboratory Data**

2623 Clinical laboratory data at screening, during and at the end of treatment and the
2624 change from baseline to end of treatment will be summarized for the safety analysis
2625 set using appropriate summary statistics. Categorical shift tables will also be
2626 presented, showing the numbers of patients with values outside of the normal range.

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2628 **13.6.5.4 Vital Signs, 12-lead Electrocardiogram, Physical** 2629 **Examination, Columbia-Suicide Severity Rating Scale and** 2630 **Other Safety Data**

2631 Vital signs, ECG, physical examination and C-SSRS data will be summarized for the
2632 safety analysis set, at screening, baseline and at each time point during the treatment
2633 period using appropriate summary statistics. Changes in the vital signs from baseline
2634 to end of treatment will also be summarized. CWS and Study Medication Use and
2635 Behavior Survey data will be summarized for the safety analysis set using appropriate
2636 summary statistics.

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14 DATA SAFETY MONITORING COMMITTEE

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An independent DSMC will monitor the DS diagnosis of screened patients on an ongoing basis in order to ascertain the correct study population is randomized.

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Investigators will submit a documented history of DS, directly to the DSMC, for confirmation of diagnosis by the DSMC. The DSMC will provide written documentation of the confirmation of diagnosis directly to the investigator, for inclusion in the patient file.

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

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15 REGULATORY AND ETHICAL OBLIGATIONS

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15.1 Declaration of Helsinki

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The investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki⁶⁵, EU Clinical Trials Directive⁶⁹ and the clinical trial regulations adopting European Commission Directives into national legislation^{71, 72, 73}.

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15.2 Informed Consent/Assent

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Initial master informed consent and assent forms will be provided to the investigator to prepare the informed consent/assent documents to be used at his or her center. The GW Clinical Manager will communicate updates to the templates by letter. The written informed consent/assent documents should be prepared in the language(s) of the potential patient population.

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Before a patient's participation in the trial, the investigator is responsible for obtaining written informed consent/assent from the patient and/or parent(s)/legal representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol specific screening procedures or any IMPs are administered. The patient and parent(s)/legal representative should have ample time for review to consider the information provided before giving written consent/assent; more specific definitions of ample time may be in force if required by ECs/IRBs or local regulations.

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The acquisition of informed consent/assent should be documented in the patient's medical records and the informed consent/assent forms should be signed and personally dated by the patient and/or parent(s)/legal representative (as applicable) and by the person who conducted the informed consent/assent discussion. GW also requires a physician to be present for consent/assent and to sign the consent/assent forms as well. The original signed informed consent/assent forms should be retained and a copy provided to the patient and/or parent(s)/legal representative. Please note that in certain countries there is a requirement for the patient's family doctor to be informed of the patient's participation in the clinical study.

15.3 Institutional Review Board/Ethics Committee

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A copy of the protocol, proposed informed consent/assent forms, other patient information material, any proposed advertising material and any further

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documentation requested must be submitted to the IRB/EC for written approval. GW must receive a copy of the written approval of the protocol and informed consent/assent forms before enrollment of patients into the study and shipment of IMP.

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

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The investigator will be responsible for obtaining on-going IRB/EC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/EC continuance of approval must be sent to GW.

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15.4 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to GW for review before allowing any patients to consent/assent for entry into the study:

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- Signed and dated protocol signature page.
- Copy of approved informed consent/assent forms and other patient information material.
- Copy of the IRB/EC approval of the protocol, informed consent/assent forms and other patient information material.
- Up to date curriculum vitae and medical licenses (as per local regulations) of the PI and all sub-investigators.
- The IRB/EC composition and/or written statement of the IRB/EC in compliance with the FDA regulations relating to GCP and clinical trials^{66, 67, 68, 74}, the EU Clinical Trials Directive⁶⁹, or International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP)⁷⁵ where the EU Clinical Trials Directive does not apply.
- Signed laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by GW.
- Signed clinical trial agreement (including patient/investigator indemnity insurance and financial agreement).
- FDA 1572 form.
- Completed financial disclosure statements for the PI and all sub-investigators if relevant.

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15.5 Patient Confidentiality

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The investigator must ensure that the patient's anonymity is maintained. On the CRFs and within the databases used to collect the trial data or other documents submitted to GW, patients should be identified by their initials (if allowed per local regulations) and a patient study number only. Documents that are not for submission to GW, e.g., signed informed consent/assent forms, should be kept in strict confidence by the investigator.

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In compliance with the FDA regulations relating to GCP and clinical trials^{66, 67, 68, 74}, and the EU Clinical Trials Directive⁶⁹/ICH GCP Guidelines⁷⁵, it is required that the investigator and institution permit authorized representatives of the company, the regulatory agencies and the IRB/EC direct access to review the patient's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the patient that his/her study related records will be reviewed by the above named representatives without violating the confidentiality of the patient.

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All information concerning the IMP and operations of GW such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the company and not previously published is considered confidential by the company and shall remain the sole property of the company. The investigator will agree to use this information only in accomplishing the study and will not use it for any other purposes without the written consent of the company.

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2773 **16 ADMINISTRATIVE AND LEGAL OBLIGATIONS**

2774 **16.1 Protocol Amendments and End of Study or Termination**

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2776 Protocol amendments must be made only with the prior approval of GW. Agreement
2777 from the investigator must be obtained for all protocol amendments and amendments
2778 to the informed consent/assent documents. The IRB/EC must be informed of all
2779 amendments and give approval for any substantial amendments. Amendments for
2780 administrative changes can be submitted to the IRB/EC for information only. The
2781 investigator must send a copy of the approval letter from the IRB/EC to GW.

2782 Both GW and the investigator reserve the right to terminate the study, according to
2783 the clinical trial agreement. The investigator should notify the IRB/EC in writing of
2784 the study's completion or early termination and send a copy of the notification to GW.
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2786 **16.2 Study Documentation and Storage**

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2788 The investigator should maintain a list of appropriately qualified persons to whom
2789 he/she has delegated study duties. All persons authorized to make entries and/or
2790 corrections on CRFs will be included on the GW delegation of authority and signature
2791 form.

2792 Source documents are original documents, data and records from which the patient's
2793 CRF data are obtained. These include, but are not limited to, hospital records, clinical
2794 and office charts, laboratory and pharmacy records, diaries, electronic data captured
2795 by IVRS, microfiches, radiographs and correspondence. CRF entries may be
2796 considered source data if the CRF is the site of the original recording, that is, there is
2797 no other written or electronic record of data. In the rare situations of this happening,
2798 then the source data from the CRF should be transcribed in the patient's notes with
2799 appropriate signature and date to provide a full audit trail. A source data verification
2800 plan, identifying the source for each data point at each center, will be agreed with
2801 each center prior to patient recruitment.

2802 The investigator and study staff are responsible for maintaining a comprehensive and
2803 centralized filing system of all study related, essential documentation (as outlined in
2804 ICH E6 Section 8.2⁷⁵), suitable for inspection at any time by representatives from GW
2805 and/or applicable regulatory authorities. Elements should include:

- 2806 • Patient files containing completed CRFs, informed consent/assent forms and
2807 supporting copies of source documentation.

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- 2814 • Study files containing the protocol with all amendments, IB, copies of pre-
2815 study documentation (see [Section 15.4](#)) and all correspondence to and from
2816 the IRB/EC and GW.
- 2817 • Proof of receipt, IMP accountability record, return of IMP for destruction,
2818 final IMP reconciliation statement and all drug related correspondence.

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In addition, all original source documents supporting entries on the CRFs, diary data and electronic data captured by IVRS must be maintained and be readily available.

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Following completion or termination of a clinical study GW will initiate proper archive of clinical study related documentation and electronic records generated by the investigator and/or GW. All clinical trial related documents and electronic records will be retained within an archiving system for a period dependent upon need and for a minimum of 20 years. Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by GW (EU Directive 2005/28/EC Chapter 4 Trial Master File and Archiving Article 16⁷⁶).

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

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16.3 Study Monitoring and Data Collection

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

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The GW study monitor, or designee, is responsible for inspecting the CRFs and available IVRS/diary data at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. The study monitor should have access to patient medical records and other study related records needed to verify the entries on the CRFs.

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The investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

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The investigator is responsible for ensuring the data recorded in the CRFs are accurate and complete. The CRF should be completed within five working days after the patient's visit and before review by the study monitor. Queries generated by GW or its representative are to be answered within a similar period of time. Shorter periods of time may apply during specific situations such as interim analysis or final database cleaning.

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All handwritten medical records should be filled out with a black or blue ball-point pen and must be legible. Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator. No correction fluid or tape may be used. The PI will sign and date the indicated places on the CRF. These signatures will indicate that the PI inspected or reviewed the data on the CRF, the data queries and the site notifications and agrees with the content.

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To ensure the quality of clinical data across all patients and centers, a clinical data management review will be performed on patient data received at GW or a contract research organization (CRO). During this review, patient data will be checked for consistency, omissions and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and FDA regulations^{66, 67, 68, 74}, the ICH GCP Guideline⁷⁵, and all other applicable regulatory requirements; to resolve any questions arising from the clinical data management review process, data queries and/or center notifications will be sent to the center for completion and then returned to GW or the CRO, as applicable.

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GW's or the CRO's Clinical Data Management Department will correct the following issues in CRFs without any notification to site staff:

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- Misspellings that do not change the meaning of the word, excluding AEs and medications.
- Date errors that occur at the end of the year and into the New Year.
- Temperature unit errors (Fahrenheit vs Centigrade).
- Weight unit errors (pounds vs kilograms) if a baseline weight has been established.
- Administrative data for example, event names for unscheduled visits or retests.
- Clarifying "other, specify" if data are provided for example, race, physical exam.

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- If a YES or NO question for example, ‘Were there any AEs?’ is left blank yet AEs are listed on the CRF, YES will be entered in the blank.
- Correct CRF page numbers.

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16.4 Electronic Data collected by Interactive Voice Response System

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Source data for the assessments collected via the IVRS will be managed by the service provider in accordance with GCP and in adherence to a quality management system. All data will be stored in a secure (for example, redundant hardware, password control, limited physical access to servers), fully audit trailed environment with appropriate industry standard back-up and off-site storage practices.

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Access for patients providing assessments and investigators will be authenticated and meet industry standards and comply with FDA 21 CFR part 11 (subpart B – Electronic Records) requirements⁷⁴.

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After database lock all investigators will receive a certified copy of all the IVRS assessment data. This data will be in an agreed, read-only format with a covering letter explaining the content of the data, a quality statement from the IVRS provider and the investigator’s responsibilities.

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Regulatory and sponsor auditors will have the ability to review but not modify the IVRS data via an agreed means of access.

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16.5 Quality Assurance

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In accordance with the FDA regulations, EU Clinical Trials Directive/ICH GCP and the sponsor’s audit plans, representatives from GW’s Clinical Quality Assurance Department may select this study for audit. Inspection of site facilities for example, pharmacy, drug storage areas, laboratories and review of study related records will occur to evaluate the study conduct and compliance with the protocol, as per the EU Clinical Trials Directive/ICH GCP and applicable regulatory requirements.

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16.6 Compensation

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GW will indemnify the investigator and the study site in the event of any claim in respect of personal injury arising due to a patient’s participation in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the IMP or any clinical intervention or procedure provided for or required by the protocol to which the clinical study

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patient would not otherwise have been exposed providing there is no evidence of negligence on behalf of the investigator or their team. GW will not be liable for any claims arising from negligence on the part of the investigator or their team.

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2946 **16.7 Publication Policy**

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GW recognizes that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will co-ordinate this dissemination and may solicit input and assistance from the chief/PIs. A summary of the results of this study will be made available on <http://www.ClinicalTrials.gov>, as required by U.S. Law.

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The raw data from this study may be obtained by the PIs or by their steering committee representatives on request. Should they wish, PIs are allowed to conduct their own analysis and are permitted to present such information along with methods and results of the clinical study at symposia, national or regional professional meetings, and to publish it in theses or dissertations.

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All publications e.g., manuscripts, abstracts, oral/slide presentations or book chapters based on this study, must be submitted to GW Medical Writing Department and, as applicable, GW Publication Committee for review before release. To ensure adequate time for GW to make comments and suggestions where pertinent, all such material should be submitted to them at least 60 days prior to the date for submission for publication, public dissemination, or review by a publication committee. The PIs must then incorporate all reasonable comments made by GW into the publication.

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GW also reserve the right to delay the submission of such information by a period of up to six months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

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2969 **16.8 Intellectual Property Rights**

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

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16.9 Confidential Information

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

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Visit Number	1	2	3	4	5 (Tel.)	6	7 (Tel.)	8	9*	10** (Tel.)
Day Number (Visit window)	-28	1 (±3)	15 (±3)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	99 (±3)	100-106 or 109 (+3)	137 (±3)
Informed consent/assent	X									
Eligibility Criteria	X	X								
Randomization		X								
Demographics	X									
Medical history	X									
Blood sample for SCNIA analysis [†]	X									
Vital signs	X	X	X	X		X		X	X	
Postural blood pressure	X	X								
Physical examination (including height and body weight)	X	X	X	X		X		X	X	
ECG	X	X	X	X		X		X		
Clinical laboratory blood sampling	X	X	X	X		X		X		
Clinical laboratory urine sampling (dipstick urinalysis) [§]	X	X	X	X		X		X		
Urine THC screen	X	X						X		
Serum pregnancy test (if appropriate)	X	X						X		
AEs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Inpatient epilepsy-related hospitalizations		X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X		X		X	X	
Sleep Disruption 0-10 NRS		X	X	X		X		X		
EDSS		X	X	X		X		X		
Vineland-II		X	X	X		X		X		
CGIC [¶]			X	X		X		X		
QOLCE		X						X		
Cognitive assessment battery		X						X		
Caregiver Impression of IMP Palatability								X		
CWS		X							X	
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)		X	X	X		X		X	X	
IVRS Caregiver Training	X									
IMP dispensing		X		X		X		X		
Collection of IMP				X		X		X	X	
IMP compliance review			X	X		X		X	X	
Study Medication Use and Behavior Survey [#]									X	

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3245 * Only required for those patients who delay entry into or do not participate in the OLE study or for
3246 those who withdraw from the study early. Visit 9 should be within seven days of Visit 8 for
3247 patients delaying entry to the OLE study. For patients who do not participate in the OLE study,
3248 Visit 9 should be 10 days after Visit 8. Patients who opt not to enter the OLE study must have
3249 weekly (± 3 days) safety telephone calls until Visit 10.
3250 ** For patients who do not enter the OLE study or who withdraw from the study early.
3251 § Urine sample taken if possible.
3252 † Sample can be taken at any clinic visit during the study.
3253 ¶ Caregivers are to compare to the memory aid from Visit 2.
3254 # To be performed at final dosing visit (Visit 8 or 9, as applicable) for patients 12 years of age and
3255 older.
3256 Tel. Visit can be conducted by telephone.

APPENDIX 2. STUDY PERSONNEL

Appendix 2.1 Investigator Details

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

Appendix 2.2 Sponsor Contact Details

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1.1 Changes in the Conduct of the Trial or Planned Analysis

1.1.1 Changes in the Conduct of the Trial

A summary of amendments to the protocol is provided in Table 1.1.1-1. The protocol amendments provide the rationale for each modification to the protocol.

Amendment Number	Date	Amendment Type	Action
1	23 Oct 2014	Substantial	<p>This amendment to Protocol Version 1 (creating Protocol Version 2) incorporated additional requirements identified by GW. Key changes included:</p> <ul style="list-style-type: none"> • Adding a secondary objective/endpoint to evaluate change in duration of subtypes of seizures as assessed by the CGICSD. • Clarifying of the exclusion criteria addressing previous and current use of cannabinoids. • Adding collection of a full record of epilepsy-specific genetic testing and prior AEDs taken as part of the patient's medical history for safety assessment and to aid/confirm diagnosis of DS. • Clarifying that IMP usage was to be recorded via the paper diary to reduce the IVRS call time. • Clarifying that the baseline period must be a minimum of 28 days to capture sufficient baseline data. • Clarifying that the safety follow-up period must be a minimum of 28 days after end of treatment to capture sufficient safety data. • Clarifying the subtypes of seizures and definition of "countable partial seizures" to aid identification of seizure types. • Clarifying that the Cognitive Assessment Battery would only be performed at sites that had expertise to conduct the test. • Clarifying that the pre-randomization pregnancy test was to be performed using urine rather than serum to provide an immediate result for assessment of inclusion/exclusion criteria. • Adding the PCWS for children 4–17 years of age. • Correcting minor spelling/formatting/consistency issues.
2	20 Nov 2014	Substantial	<p>This amendment to Protocol Version 2 (creating Protocol Version 3) incorporated additional requirements identified by the Medicines and Healthcare products Regulatory Agency (MHRA) as follows:</p> <ul style="list-style-type: none"> • Clarifying that patients randomized into the trial who were later found to meet criteria for DILI must be withdrawn from the trial.
3	20 Mar 2015	Substantial	<p>This amendment to Protocol Version 3 (creating Protocol Version 4) incorporated additional requirements identified by the FDA and GW. Key changes included:</p> <ul style="list-style-type: none"> • Specifying that patients would be stratified by age across treatment arms. • Adding assessment of growth and development through measurement of height, body weight, serum IGF-1 levels, and Tanner staging. • Adding measurement of effects of menstruation. • Amending the statistical methods for analysis of the primary and secondary endpoints.

Amendment Number	Date	Amendment Type	Action
			<ul style="list-style-type: none"> • Adding blood sampling for PK analyses of CBD and its major metabolites. • Adding measurement of serum triglycerides in clinical laboratory assessments. • Clarifying that Visit 8 ('End of Treatment' visit) would also be labeled as the Withdrawal visit. • Adding ECG and clinical laboratory assessments at the 'End of Taper' visit for patients who withdrew early and tapered IMP and for patients who opted not to enter the OLE trial. • Updating contact details in line with a change in GW's business address. • Increasing the number of patients per treatment group from 40 to 50 (a total increase from 120 to 150 patients) and amending the assumption that patients in the placebo group would experience a mean reduction in convulsive seizure frequency of 10% to 18%. • Clarifying the eligibility criterion regarding contraception requirements in line with recommendations related to contraception and pregnancy testing in clinical trials. • Adding an eligibility criterion excluding patients taking felbamate for < 1 year. Felbamate was also listed as a prohibited therapy if taken for < 1 year. • Clarifying the use of the ESC to verify each patient's seizure subtypes and diagnosis of DS. • Amending wording to allow patients who suspended IMP dosing due to an AE to resume dosing prior to complete recovery, provided that the AE was well tolerated. • Adding secondary endpoints to align the protocol with the OLE trial and editing the primary and secondary endpoints to clarify that the total number of convulsive and non-convulsive seizures would be measured. • Clarifying when the Cognitive Assessment Battery should be administered. • Clarifying that even though patients may achieve their target dose before the end of the 2-week titration period, the titration period was 2-weeks to ensure that all patients achieved stable dosing. • Assimilating text from Section 12.3.1 to Section 12.8 to avoid repetition. • Clarifying text for improved readability. • Correcting minor spelling/formatting/consistency issues.
4	29 May 2015	Not submitted	This amendment to Protocol Version 4 (creating Protocol Version 5) incorporated additional requirements identified by the FDA and GW. However, due to subsequent recommendations received from the FDA, Protocol Amendment 4 and corresponding Protocol Version 5 were not submitted to any competent authority or IRB/IEC and hence Protocol Version 5 was never implemented at any trial sites.
5	29 Jun 2015	Substantial	<p>This amendment to Protocol Version 4 (creating Protocol Version 6) incorporated additional requirements identified by the FDA and GW. Key changes included:</p> <ul style="list-style-type: none"> • Updating statistical analyses of the primary and secondary endpoints to include the full treatment period (titration plus maintenance period). • Including further details of statistical methods.

Table 1.1.1-1 Protocol Amendments and Administrative Changes			
Amendment Number	Date	Amendment Type	Action
			<ul style="list-style-type: none"> • Updating the lower age limit for Tanner Staging to include adolescent patients aged 10–17 (inclusive) or earlier if clinically indicated by the onset of menarche or other signs of precocious puberty. • Clarifying that during the follow-up of patients with potential cases of DILI, levels of ALT, AST, TBL and ALP should be monitored until levels normalize (in the investigators opinion) or return to normal. • Removing references to “High Dose Level” and “Low Dose Level” and replaced with “20 mg/kg/day” and “10/mg/kg/day” respectively in line with the DSMC recommendation from trial GWEP1332 Part A. • Replacing wording of concomitant AED blood sampling in the event of an AE with a secondary objective/endpoint requesting the investigator monitor plasma concomitant AED levels and discuss results with the GW medical monitor. Samples were only to be taken if the risk/benefit outcome was favorable, in the investigator’s opinion. • Reclassifying effects on menstruation as a safety measure. • Amending responder and sensitivity analyses to state the average number of seizures per 28 days rather than per week. • Clarifying the convulsive seizure inclusion criterion to state that only the first 28 days of the baseline period counted towards a patient’s eligibility. • Removing the Socioeconomic Scale test item (parent measure) from the Cognitive Assessment Battery as it was not possible to standardize this endpoint across different countries. • Clarifying liver function testing regarding follow-up of elevated liver enzyme levels that do not meet the criteria for DILI. • Clarifying eligibility criteria for impaired hepatic function in line with the criteria for DILI. • Adding a compliance statement, setting out a minimum number of days a patient needed to complete the IVRS diary during baseline to be eligible for the trial. • Clarifying blood sampling for PK was only to be taken from patients weighing ≥ 20 kg. Sampling times and windows were also clarified. • Updating references to ‘baseline observation period’ as ‘baseline period’. • Clarifying the age restriction for C-SSRS suitability to include consideration of developmental delays as well as age. • Adding paper diary entry of seizure counts over 99. • Amending ‘Ethnic origin’ to ‘race’. for consistency within the protocol.
6	23 Feb 2017	Substantial	<p>This amendment to Protocol Version 6 (creating Protocol Version 7) incorporated additional requirements identified by GW. Key changes included:</p> <ul style="list-style-type: none"> • Increasing the number of patients per treatment group from 50 to 62 (a total increase from 150 to 186 patients). • Changing the statistical analyses of seizure data to use nonparametric rather than parametric methods.

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Amendment Number	Date	Amendment Type	Action
			<ul style="list-style-type: none"> • Adding assessments of plasma and urine concentrations of THC and its major metabolites, and urine concentrations of CBD and its major metabolites. • Amending the PK parameters to allow for accurate determination of the defined parameters. • Adding instructions for patients to record the time of meals the day before and the day of PK sampling. • Clarifying that any clinical symptoms of concern resulting from possible drug-drug interactions should be discussed with the GW medical monitor and if required, adjustments to AEDs will be permitted. • Broadening the mode of IMP administration to encompass patients who have difficulty swallowing.
7	06 Sep 2018	Non-substantial	<p>This amendment to Protocol Version 7 (creating Protocol Version 8) incorporated additional requirements identified by GW. Key changes included:</p> <ul style="list-style-type: none"> • Updating the primary analysis method from the Wilcoxon rank-sum test to a negative binomial regression analysis. • Removing the words “percentage change” from the primary endpoint wording and for percentage change in other seizure types under secondary endpoints throughout the protocol. • Adding the replaced Wilcoxon rank-sum test primary analysis as a sensitivity analysis. • Updating other sensitivity analyses from Wilcoxon rank-sum tests to negative binomial regression analyses. • Amending the treatment allocation ratio to clarify that patients were allocated to one of 4 treatment groups (GWP42003-P 10 mg/kg/day, GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo 20 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio, and that the 2 placebo groups will be pooled for the analyses of efficacy. The planned sample size was not changed.

3331 Source: [Appendix 1.1](#), Protocol amendments.3332 **1.1.2 Changes in the Planned Analyses**

3333

- 3334
- The identification of 3 key secondary endpoints and the hierarchical testing procedure were not defined in the protocol but were included in the SAP prior to unblinding.
- 3335
- Upon blinded review of IVRS data for the number of convulsive seizures greater than 30 minutes in duration and the number of non-convulsive seizures greater than 30 minutes in duration, it was determined that there were insufficient numbers of patients reporting these seizures to perform the analyses planned in the protocol.
- 3336
- Upon blinded review of the number of patients with inpatient epilepsy-related hospitalizations, it was determined that there were insufficient numbers of patients to perform the analyses planned in the protocol.
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- The protocol included change from baseline in usage of rescue medication as an efficacy endpoint. However, due to inconsistencies in the collection of these data, no analyses were performed.
- The endpoint planned in the protocol of number of patients experiencing a > 25% worsening, - 25 to + 25% no change, 25 – 50% improvement, 50 – 75% improvement or > 75% improvement in convulsive seizures from baseline was updated in the SAP to the following:
 - Number of patients experiencing a > 25% increase, ≥ 0 to $\leq 25\%$ increase, > 0 to < 25% reduction, ≥ 25 to < 50% reduction, ≥ 50 to < 75% reduction, or $\geq 75\%$ reduction from baseline in convulsive seizure frequency.
- The protocol included determination of THC, CBD, and their major metabolites in urine after multiple doses of GWP42003-P. However, none of the consented patients were able to provide a urine sample so no analyses were performed.
- The IVRS system was designed to allow caregivers to report a maximum of 99 seizures per day for any individual seizure type since this was considered adequate during the trial design process. However, during the trial some caregivers reported that for some individual seizure types the patient was experiencing more than 99 per day. As described in Section 5.5.2 of the SAP ([Appendix 1.9](#)) a '> 99 seizure log' was introduced into to the CRF. If a caregiver's patient experienced > 99 of any individual seizure type, they were instructed to enter '99' into the IVRS and then record the actual number into the paper diary so it could be added to the CRF at the next clinic visit. This process was followed at some sites; however, for many sites the actual number of seizures was not provided by the caregiver. It was agreed that for any entries of '99' within the IVRS where the actual number was not provided by the caregiver the seizure count would remain as 99.

The data showed that only 1 patient, randomized to placebo, recorded 99 for a convulsive seizure type (1 instance of 99 tonic-clonic seizures reported on Day 37). When reviewing the ePRO data profile for this patient it appears the entry should have been 9 and not 99, however this cannot be confirmed so 99 has been reported ([Appendix 2; Listing 8.1.1](#)). It has been concluded that this process did not change the interpretation of the primary endpoint.

3378

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3379

Study Code: GWEP1424

3380

3381 **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO**
3382 **INVESTIGATE THE EFFICACY AND SAFETY OF CANNABIDIOL**
3383 **(GWP42003-P) IN CHILDREN AND YOUNG ADULTS WITH DRAVET**
3384 **SYNDROME**

3385

Statistical Analysis Plan

3386

05 October 2018

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3456

ABBREVIATION

ADHD	-	Attention Deficit Hyperactivity Disorder
AEDs	-	Antiepileptic Drugs
AEs	-	Adverse Events
ALQ	-	Above Limit of Quantification
ALT	-	Alanine Aminotransferase
ANCOVA	-	Analysis of Covariance
AST	-	Aspartate Aminotransferase
ATC	-	Anatomical Therapeutic Chemical
BASC-2	-	Behavior Assessment System for Children – Second Edition
BDRM	-	Blinded Data Review Meeting
BLQ	-	Below Limit of Quantification
BSA	-	Body Surface Area
CGIC	-	Caregiver Global Impression of Change
CGICSD	-	Caregiver Global Impression of Change in Seizure Duration
CI	-	Confidence Interval
CMH	-	Cochran–Mantel–Haenszel
CRF	-	Case Report Form
C-SSRS	-	Columbia-Suicide Severity Rating Scale
CWS	-	Cannabis Withdrawal Scale
D-KEFS	-	Delis–Kaplan Executive Function System
DS	-	Dravet Syndrome
ECG	-	Electrocardiogram
EDSS	-	Epworth Daytime Sleepiness Scale
EEG	-	Electroencephalography
eGFR	-	Estimated Glomerular Filtration Rate
IGF-1	-	Insulin-like Growth Factor-1
IMP	-	Investigational Medicinal Product
INR	-	Prothrombin International Normalized Ratio
ITT	-	Intention to Treat
IVRS	-	Interactive Voice Response System
LOCF	-	Last Observation Carried Forward
MAR	-	Missing at Random
MedDRA	-	Medical Dictionary for Regulatory Activities
MI	-	Multiple Imputation
MNAR	-	Missing Not at Random
NOCB	-	Next Observation Carried Backward
NRS	-	Numerical Rating Scale
OLE	-	Open Label Extension

PCWS	-	Pediatric Cannabinoid Withdrawal Scale
PK	-	Pharmacokinetics
PP	-	Per Protocol
QOLCE	-	Quality of Life in Childhood Epilepsy
SAP	-	Statistical Analysis Plan
SOC	-	System Organ Class
TEAE	-	Treatment Emergent Adverse Event
ULN	-	Upper Limit of Normal
Vineland-II	-	Vineland Adaptive Behavior Scales, Second Edition
WAIS-4	-	Wechsler Adult Intelligence Scale - Fourth Edition
WASI-2	-	Wechsler Abbreviated Scale of Intelligence – Second Edition
WISC-4	-	Wechsler Intelligence Scale for Children – Fourth Edition
WPPSI-4	-	Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition

3458 1. Introduction

3459 This statistical analysis plan (SAP) documents the statistical reporting to be performed for Study
3460 GWEP1424. Details of the analysis and reporting of pharmacokinetics (PK) of CBD and its major
3461 metabolites are not included as part of this SAP.

3462 This SAP has been prepared based on the following study documents:

- 3463 • Protocol GWEP1424 (Version 8, dated 06 September 2018).
- 3464 • Case Report Form (CRF) GWEP1424, Version 1 (dated 08 April 2015).

3465 1.1 Rationale

3466 Dravet syndrome (DS), also known as severe myoclonic epilepsy in infancy, is a rare form of severe
3467 epilepsy with onset in early childhood.

3468 DS is characterized by a variety of treatment-resistant seizures (febrile and afebrile, generalized and
3469 unilateral, clonic or tonic–clonic) that occur in the first year of life and has a poor cognitive
3470 prognosis.

3471 DS is one of the most pharmacoresistant forms of epilepsy, with all seizure types extremely
3472 refractory to conventional antiepileptic drugs (AEDs), especially during the first several years.

3473 In this study the active Investigational Medicinal Product (IMP) is GWP42003-P oral solution.

3474 2. Study Objectives

3475 The protocol defined the study objectives as:

3476 2.1 Primary

3477 To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with
3478 placebo, with respect to the change during the treatment period of the study compared to baseline in
3479 convulsive seizure frequency. The dose response effect between 2 GWP42003-P Dose Levels (10
3480 mg/kg/day and 20 mg/kg/day) and placebo will also be explored. Convulsive seizures are defined
3481 as tonic–clonic, tonic, clonic or atonic and non-convulsive seizures as myoclonic, partial or absence.

3482 2.2 Secondary

- 3483 • To assess changes from baseline in non-convulsive seizure frequency, duration, usage of rescue
3484 medication, number of inpatient hospitalizations due to epilepsy, sleep disruption, daytime sleepiness,
3485 quality of life, growth and development, and conduct behavioral and cognitive assessments in patients
3486 taking GWP42003-P as an adjunctive treatment, when compared with placebo.
- 3487 • To determine the PK of CBD and its major metabolites following single and multiple doses of
3488 GWP42003-P and to assess the presence of Δ^9 -tetrahydrocannabinol (THC) and its major metabolites
3489 in plasma and the presence of THC, CBD and their major metabolites in urine after multiple doses of
3490 GWP42003-P.
- 3491 • To determine effects of GWP42003-P on plasma concentrations of concomitant AEDs, where
3492 available.
- 3493 • To assess the safety of both GWP42003-P doses when compared with placebo.

3494 3. Investigational Plan

3495 3.1 Study Design

3496 This study is a randomized, double-blind, 14-week comparison of 2 Dose Levels of GWP42003-P
3497 (10 mg/kg/day and 20 mg/kg/day) versus placebo. The treatment period will consist of a 2-week

3498 titration period followed by a 12-week maintenance period. The treatment period will be followed
3499 by a 10-day taper period and a 4-week follow-up period. The study will aim to determine the
3500 efficacy, safety and tolerability of 2 Dose Levels of GWP42003-P compared with placebo.
3501 Following study completion, all patients will be invited to continue to receive GWP42003-P in an
3502 open label extension (OLE) study (under a separate protocol).

3503 **3.2 Definition of Sample Size**

3504 A total of 186 patients will be randomized to one of 4 treatment groups (GWP42003-P 10 mg/kg/day,
3505 GWP42003-P 20 mg/kg/day, placebo 10 mg/kg/day dose volume equivalent, or placebo
3506 20 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio. The randomization will be stratified by age
3507 group (2–5 years, 6–12 years and 13–18 years). The placebo groups will be pooled for the analyses
3508 of efficacy.

3509 For a Wilcoxon–Mann–Whitney test comparing 2 distributions with a 2-sided significance level of
3510 0.05, a sample size of 62 per group is required to obtain a power of at least 80%. This is based on a
3511 gamma distribution for the GWP42003-P groups with scale parameter of 65.614 and shape parameter
3512 of 1.0886, and a gamma distribution for the placebo group with scale parameter of 40.887 and shape
3513 parameter of 2.3059.

3514 Maximum likelihood estimates using the Newton–Raphson approximation were computed for the
3515 scale and shape parameters using data from study GWEP1332 Part B.

3516 3.3 Efficacy and Safety Endpoints

3517 3.3.1 Primary Efficacy Endpoint

3518 The primary endpoint is the change in total convulsive seizure frequency during the treatment period
3519 (Day 1 to the end of the evaluable period) compared to baseline in patients taking GWP42003-P
3520 compared with placebo.

3521 3.3.2 Secondary Efficacy Endpoints

3522 The secondary endpoints will be tested hierarchically, based on the order given in Section 5.5.1,
3523 Table 3. No multiplicity adjustments will be made for all other secondary endpoints.

3524 3.3.2.1 Key Secondary Efficacy Endpoints

- 3525 1. Change in total seizure frequency.
- 3526 2. Number of patients considered treatment responders, defined as those with a $\geq 50\%$ reduction
3527 in convulsive seizures from baseline.
- 3528 3. Caregiver Global Impression of Change (CGIC) score.

3529 3.3.2.2 Other Secondary Efficacy Endpoints

3530 The following endpoints will be compared between treatment groups over the 14-week, double-blind
3531 treatment period:

- 3532 • Number of patients experiencing a $>25\%$ increase, ≥ 0 to $\leq 25\%$ increase, >0 to $<25\%$
3533 reduction, ≥ 25 to $<50\%$ reduction, ≥ 50 to $<75\%$ reduction or $\geq 75\%$ reduction in convulsive
3534 seizures from baseline.
- 3535 • Number of patients considered treatment responders, defined as those with a $\geq 25\%$ or $\geq 75\%$
3536 reduction in convulsive seizures from baseline (overall and 4-weekly).
- 3537 • Number of patients who are convulsive seizure free.
- 3538 • Change in non-convulsive seizure frequency.
- 3539 • Change in subtypes of seizures.
- 3540 • Changes from baseline in number of episodes of status epilepticus.
- 3541 • Changes from baseline in duration of seizure subtypes as assessed by the Caregiver Global
3542 Impression of Change in Seizure Duration (CGICSD).
- 3543 • Changes from baseline in usage of rescue medication.
- 3544 • Changes from baseline in number of inpatient hospitalizations due to epilepsy.
- 3545 • Changes from baseline in Sleep Disruption 0–10 Numerical Rating Scale (0-10 NRS) score.
- 3546 • Changes from baseline in Epworth Sleepiness Scale (ESS) score.
- 3547 • Changes from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score.
- 3548 • Change from baseline in cognitive function as measured with a cognitive assessment battery.
- 3549 • Changes from baseline in the Vineland Adaptive Behavior Scales, Second Edition (Vineland-
3550 II) score.
- 3551 • Change from baseline in growth and development by measurement of height, weight, insulin-
3552 like growth factor-1 (IGF-1) levels and Tanner Staging (for patients aged 10–17 [inclusive],
3553 or earlier if clinically indicated by onset of menarche or other signs of precocious puberty).

- 3554 PK:
- 3555 • The plasma concentrations of CBD and its major metabolites will be determined following
- 3556 single and multiple doses of GWP42003-P. The following PK parameters will be calculated
- 3557 from sparse sampling:
- 3558 ○ The concentration at each time interval (C_t) of CBD and its metabolites.
 - 3559 ○ Area under the plasma concentration curve (AUC_{0-t}) from time zero to the last
 - 3560 measurable concentration.
- 3561 • Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P,
 - 3562 where available.
 - 3563 • The plasma concentrations of THC and its major metabolites will be determined at a single
 - 3564 time point (Visit 8, 2–3 hours post-dose) following multiple doses of GWP42003-P.
 - 3565 • The concentrations of THC, CBD, and their major metabolites will be determined in urine
 - 3566 after multiple doses of GWP42003-P.

3567 3.3.3 Safety Variables

3568 The safety profile of GWP42003-P compared with placebo will also be assessed at each Dose Level

3569 by measuring:

- 3570 • Adverse events (AEs).
- 3571 • Vital signs.
- 3572 • Physical examination parameters.
- 3573 • 12-lead electrocardiogram (ECG).
- 3574 • Clinical laboratory parameters.
- 3575 • Columbia-Suicide Severity Rating Scale (C-SSRS) score.
- 3576 • Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale (PCWS)
- 3577 score, as appropriate.
- 3578 • Abuse liability.
- 3579 • Effects on menstruation cycles (in females).

3580 4. Blinded Data Review Meeting

3581 Prior to breaking the blind, it is anticipated that a Blinded Data Review Meeting (BDRM) will take

3582 place. The objectives of the meeting will include:

- 3583 • Assessment of any study entry violations and protocol deviations.
- 3584 • Assessment of the use of concomitant medications (including rescue medication) to identify
- 3585 changes which could affect the primary assessment of efficacy.
- 3586 • Review of any protocol deviations and any potential effect on the study results. Assess the
- 3587 need for additional analyses using a per protocol (PP) population.
- 3588 • Review of missing data and any potential effect on the study results.
- 3589 • Safety reporting approach for any patients who potentially received the incorrect IMP during
- 3590 the double-blind phase.
- 3591 • Assessment of any changes in concomitant AEDs for medical reasons.

3592 The meeting will have access to the following blinded summary tables and listings:

- 3593 • All pre-randomization patient data.

- 3594 • All patient efficacy data.
- 3595 • All concomitant medication data.
- 3596 • All patient safety data.
- 3597 • Patient protocol deviation logs.

3598 This SAP documents the currently planned analyses for this study that will be approved prior to
 3599 breaking the blind for the study. Changes to the analyses planned within any previously approved
 3600 versions of the SAP will be summarized in Section 5.8 and integrated into the text of the SAP. The
 3601 minutes of the BDRM will be documented separately.

3602 5. Statistical Methods

3603 5.1 General Considerations

3604 In all tables, listings and figures, the treatment arms will be referred to and labelled as per Table 1.

3605 **Table 1 Study Treatments**

Endpoint	Actual Treatment	Treatment Label
Efficacy	Pooled Placebo	Placebo
Safety	10 mg/kg/day Placebo	Placebo 10 mg/kg
	20 mg/kg/day Placebo	Placebo 20 mg/kg
All	10 mg/kg/day GWP42003-P	10 mg/kg
All	20 mg/kg/day GWP42003-P	20 mg/kg

3608 For safety tables where placebo is split by dosing volume, an additional Pooled Placebo column will
 3609 be included.
 3610

3611 In all tables, listings and figures, the study visits will be referred to and labelled as per Table 2.

3612 **Table 2 Study Visits**

Actual Visit	Visit Label
Visit 1: Screening	Screening
Visit 2: Day 1, baseline visit	Day 1
Visit 3: Day 15	Day 15
Visit 4: Day 29	Day 29
Visit 5: Day 43	Day 43
Visit 6: Day 57	Day 57
Visit 7: Day 71	Day 71
Visit 8: Day 99	End of Treatment
Visit 9: Day 109	End of Taper
Visit 10: Day 137	Safety Follow-Up

3613 Unless stated otherwise, continuous variables will be summarized showing the number of
 3614 non-missing values (n), mean, standard deviation, median, minimum and maximum and
 3615 categorical variables will be summarized showing the number and percentage of patients
 3616 falling into each category. For continuous summaries of seizure frequency, the lower and
 3617 upper quartiles will also be presented.
 3618 Minimum and maximum values will be presented to the same decimal precision as the raw
 3619 data. Mean and median will be presented to 1 more decimal place than the raw data, and
 3620 standard deviation to 2 more decimal places than the raw data. Percentages will be presented
 3621 to 1 decimal place.
 3622 All analyses and summaries will be produced using SAS Version 9.3 or higher.
 3623

3624 **5.1.1 Missing Data**

3625 **5.1.1.1 Handling of Missing Data for the Primary Efficacy Endpoint**

3626 If a patient withdraws during the treatment period, then the primary analysis variable will be
 3627 calculated from all the available data, during the treatment period, prior to the patient withdrawing.
 3628 Section 5.5.2.1 describes sensitivity analyses to account for missing data arising from unreported
 3629 days in the Interactive Voice Response System (IVRS), and missing data arising from patients
 3630 withdrawing during the treatment period.

3631 **5.1.1.2 Handling of Missing Data for the Secondary Efficacy Endpoints**

3632 **5.1.1.2.1 Epworth Sleepiness Scale**

3633 If the scores of fewer than 4 of the 8 individual questions are missing, the missing items will be
 3634 imputed as the mean of the remaining non-missing scores, for the calculation of the total score only.
 3635 If the scores of 4 or more of the individual questions are missing, the missing items will not be
 3636 imputed and the total score will be missing; hence, the patient will not be included in the summary or
 3637 analysis for that visit.

3638 **5.1.1.2.2 Quality of Life in Childhood Epilepsy**

3639 The calculations of subscale and overall scores for the QOLCE will treat responses of ‘Not
 3640 Applicable’ as missing values.
 3641 For each subscale, if less than 50% of the items within the subscale are missing (including ‘Not
 3642 Applicable’) then the subscale score will be calculated using the mean of the non-missing items. If
 3643 50% or more of the items within the subscale are missing then the subscale score will not be
 3644 calculated and will be missing.
 3645 For the overall quality of life score, if fewer than 8 of the 16 subscale scores are missing then the
 3646 overall quality of life score will be calculated using the mean of the non-missing subscale scores. If
 3647 8 or more of the subscale scores are missing then the overall quality of life score will not be
 3648 calculated and will be missing.

3649 **5.1.1.3 Adverse Events**

3650 Missing and/or incomplete dates/times for AEs will be imputed in a manner resulting in the earliest
 3651 onset or the longest duration during the treatment period, taking into account that the start date/time
 3652 should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing.
 3653 The imputation method will only be used to determine treatment emergence, and imputed dates/times
 3654 will not be presented in AE outputs.
 3655 A worst-case approach will be followed in the event of missing severity or causality data. If the
 3656 severity is missing, ‘Severe’ will be imputed. If causality data is missing, ‘Yes’ will be imputed for
 3657 the question ‘Plausible relationship to study medication’.

3658 **5.1.1.4 Concomitant Medication**

3659 Missing concomitant medication dates will be handled in a similar fashion as described for AEs in
 3660 Section 5.1.1.3.

3661 **5.1.2 Day Numbering**

3662 The first day of treatment (Day 1) will be the date of the Visit 2. However, if the first dose
 3663 of IMP was not administered on site (as indicated on the CRF) then the date of first dose will
 3664 be calculated using the information on the ‘IMP Missed Doses Log’ CRF page.

3665 Any days prior to Day 1 will be numbered relative to this day and calculated as:

3666 $\text{Date} - (\text{Date of Day 1})$

3667 to give Day -1, -2, -3 etc.

3668 Any days post Day 1 will be calculated as:
3669 $1 + \text{Date} - (\text{Date of Day 1})$

3670 **5.1.3 Definitions**

3671 **5.1.3.1 Baseline**

3672 For clinic visit based endpoints, baseline is defined as the last record or measure collected
3673 prior to the first dose of IMP.

3674 For IVRS based endpoints, baseline will include all available data prior to Day 1.

3675 **5.1.3.2 Last Visit**

3676 Last visit for endpoints assessed at clinic visits is defined as the last scheduled visit (not
3677 including the end of taper or safety follow-up visits) at which a patient's last evaluation is
3678 performed.

3679 **5.1.3.3 Treatment Period**

3680 The treatment period is defined as Day 1 to the earlier of:

- 3681 • Day 99.
- 3682 • The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF
3683 page.

3684 **5.1.3.4 Maintenance Period**

3685 The maintenance period is defined as Day 15 to the earlier of:

- 3686 • Day 99.
- 3687 • The date of last dose as recorded on the 'End of Treatment Study Outcome' CRF
3688 page.

3689 **5.1.3.5 Convulsive Seizures**

3690 Convulsive seizures are defined as tonic-clonic, tonic, clonic or atonic seizures.

3691 **5.1.3.6 Non-Convulsive Seizures**

3692 Non-convulsive seizures are defined as myoclonic, countable partial, other partial or absence
3693 seizures.

3694 **5.1.3.7 Total Seizures**

3695 Total seizures are defined as the combination of convulsive and non-convulsive seizures.

3696 **5.2 Analysis Sets and Protocol Deviations**

3697 There will be 3 analysis sets.

3698 **5.2.1 Safety Analysis Set**

3699 All randomized patients who received at least one dose of IMP will be included and
3700 analyzed according to the treatment received. Only patients for whom it has been confirmed
3701 that they did not take any IMP will be excluded from this safety analysis set.

3702 Upon blinded review of the data, it was identified that 1 patient was randomized in error, but
3703 did not receive IMP. This patient will be excluded from the safety analysis set.

3704 Upon blinded review of the data, it was identified that 4 patients randomized to receive the
3705 10 mg/kg/day dose (GWP42003-P or placebo) incorrectly received up to 20 mg/kg/day (up
3706 to 50 mg/kg/day for 1 patient) during the treatment period. For safety reporting, these
3707 patients will be assigned to the 20 mg/kg/day dose groups (GWP42003-P or placebo).

3708 **5.2.2 Intention to Treat Analysis Set**

3709 All randomized patients who received at least one dose of IMP and have post-baseline
3710 efficacy data will be included and analyzed according to the treatment group to which they
3711 were randomized.

3712 The intention to treat (ITT) analysis set is the primary analysis set for all efficacy endpoints.
3713 Upon blinded review of the data, it was identified that 1 patient was randomized in error, but
3714 did not receive IMP. This patient will be excluded from the ITT analysis set.

3715 **5.2.3 Per Protocol Analysis Set and Protocol Deviations**

3716 If there are a sufficient number of significant protocol deviations in the study, a PP analysis
3717 set may also be presented.

3718 All patients who complete the study, with no protocol deviations deemed to compromise the
3719 assessment of efficacy, will be included and analyzed according to the treatment group they
3720 were randomized to. The rules determining the PP analysis set will be fully defined prior to
3721 unblinding of the database.

3722 A listing will be produced of protocol deviations for the clinical study report. These protocol
3723 deviations will be imported from the protocol deviations log. Protocol deviations will be
3724 classed as minor, important or major, where major deviations are classed as important
3725 protocol deviations leading to exclusion from the PP analysis set.

3726 Protocol deviations were reviewed during the BDRM on 21st September 2018. In addition to
3727 patients in the ITT analysis set who withdrew from the study during the treatment phase, a
3728 number of patients were deemed to have protocol deviations that should lead to exclusion
3729 from the PP analysis set. These patients, together with their deviations, are detailed in a
3730 separate document finalized prior to unblinding.

3731 **5.3 Listings**

3732 All data will be listed and ordered by site, treatment, patient number and, where appropriate,
3733 chronological order of assessment. Listings will be created for each of the subsequent
3734 sections of the SAP.

3735 Visit date need not be included on all of the listings, but day numbers will be included,
3736 where appropriate.

3737 Other derived variables (e.g. changes from baseline values) that are calculated for analysis
3738 purposes or to aid interpretation of the data will be added to the listings as appropriate.

3739 **5.4 Demographic Data and Patient Characteristics**

3740 **5.4.1 Patient Disposition**

3741 Patient disposition, by site, by country and overall, will be summarized using standard
3742 summary statistics. The number screened, number of screen failures and number
3743 randomized will be included.

3744 A screen failure disposition table will be presented, including number of patients screened,
3745 number failing screening, number randomized and the reasons for failing screening.

3746 Patient disposition, including patients treated, patients completed the treatment phase and the

3747 taper phase, patients discontinued (including reason for discontinuation) from the treatment
 3748 and taper phases will be summarized by absolute counts (n) and percentages (%). A further
 3749 table split by site, and by country will be produced, showing number of patients randomized,
 3750 withdrawn and completed the treatment phase at each site or in each country.

3751 **5.4.2 Analysis Sets**

3752 Patients included in the safety, ITT and PP analysis sets, and patients excluded together with
 3753 reasons for exclusion, will be summarized by absolute counts (n) and percentages (%).

3754 **5.4.3 Demographic Data and Baseline Characteristics**

3755 The following demographic data will be summarized by treatment group and overall for the
 3756 safety, ITT and PP analysis sets:

- 3757 • Age (years);
- 3758 • Age group (2-5 years, 6-12 years and 13-18 years);
- 3759 • Sex;
- 3760 • Race;
- 3761 • Country;
- 3762 • Region (United States, Rest of the World);
- 3763 • Weight at baseline (kg);
- 3764 • Height at baseline (cm);
- 3765 • Body mass index at baseline (kg/m²).

3766 Age will be calculated as:

3767 (Date of screening – date of birth) ÷ 365.25.

3768 The following baseline characteristics will be summarized by treatment group and overall for
 3769 the safety, ITT and PP analysis sets:

- 3770 • Average number of convulsive seizures per 28 days.
- 3771 • Average number of non-convulsive seizures per 28 days.
- 3772 • Average number of total seizures per 28 days.
- 3773 • Number of patients with seizures during the baseline period, by seizure type.
- 3774 • Number of antiepileptic medications a patient has used, prior to the study.
- 3775 • Number of antiepileptic medications a patient is currently taking.
- 3776 • Total number of prior and current antiepileptic medications.
- 3777 • Number of patients taking clobazam (Yes, No, and if no, Prior).
- 3778 • Number of patients taking valproic acid (Yes, No, and if no, Prior).
- 3779 • Number of patients taking stiripentol (Yes, No, and if no, Prior).
- 3780 • Number of patients taking levetiracetam (Yes, No, and if no, Prior).
- 3781 • Number of patients taking topiramate (Yes, No, and if no, Prior).

3782 The number of prior antiepileptic medications a patient has used will be taken from the
 3783 'History of antiepileptic medications and therapies' CRF page. The number of antiepileptic

3784 medications a patient is currently taking is based on the ‘Concomitant antiepileptic
3785 medications’ CRF page. If a patient has a medication listed on both the ‘History of
3786 antiepileptic medications and therapies’ and ‘Concomitant antiepileptic medications’ CRF
3787 pages, then the medication is considered concomitant (see Section 5.7.1); this will not be
3788 included in the number of prior antiepileptic medications for that patient. Antiepileptic
3789 medications starting after the last dose of IMP during the treatment period will not be
3790 counted.

3791 Patients taking the same antiepileptic medication type, but where the medications were
3792 coded to different generic terms will be counted only once within the medication type. For
3793 example, valproate sodium, valproic acid, valproate semisodium and ergenyl chrono will all
3794 be counted as valproic acid and counted once under that term.

3795 The number of patients taking clobazam is defined as the number of patients taking
3796 clobazam at any point during baseline period or treatment period. The same definition will
3797 apply for the number of patients taking valproic acid, stiripentol, levetiracetam and
3798 topiramate.

3799 Previous cannabis use will be included within the baseline characteristics listing.

3800 **5.4.4 Epilepsy and Dravet Syndrome History**

3801 **5.4.4.1 Dravet Syndrome History**

3802 The following DS history data will be summarized by treatment group and overall for the
3803 safety analysis set:

- 3804 • Was development ever normal? (Yes, No, Unknown).
- 3805 • If developmental delay is present, age concerns first arose (years).
- 3806 • Is there intellectual disability, mental retardation or learning disability? (Yes, No).
 - 3807 ○ If yes, how severe is the intellectual disability, mental retardation or learning
 - 3808 disability? (Mild, Moderate, Severe, Profound, Other, Unknown).
- 3809 • Was there developmental regression? (Yes, No).
 - 3810 ○ If yes, at what age (years).
- 3811 • Is the patient verbal or nonverbal? (Verbal, Non-Verbal).
 - 3812 ○ If Verbal, extent of vocabulary (Single words, 2–3 word phrases, Long
 - 3813 sentences, Other).
- 3814 • Age patient started walking (years).
- 3815 • Has any medication increased seizure frequency? (Yes, No).
- 3816 • Has any medication reduced seizure frequency? (Yes, No).
- 3817 • Has there been a prolonged seizure free period greater than 6 months? (Yes, No).
 - 3818 ○ If yes, age at last occurrence (years).

3819 **5.4.4.2 History of Seizures No Longer Occurring and History of Current Seizures**

3820 Data will be summarized by treatment group and overall for the safety analysis set,
3821 separately, for history of seizures no longer occurring and history of current seizures.

3822 The following will be summarized by each seizure type:

- 3823 • Number of patients with the seizure type.

- 3824 • Age at onset (years).
- 3825 • Age of last occurrence (years). For history of seizures no longer occurring only.
- 3826 • Seizure duration (<2 minutes, 2–10 minutes, >10 minutes, Unknown). For history of
- 3827 current seizures only.

3828 Seizure frequency and trigger data will be listed only.

3829 For patients with more than 1 record for a particular seizure type, the earliest onset, most
3830 recent age of last occurrence and longest duration will be used for the summary table.

3831 **5.4.4.3 Electroencephalography History**

3832 The following electroencephalography (EEG) history data will be summarized by treatment
3833 group and overall for the safety analysis set:

- 3834 • Has the patient ever had a normal EEG? (Yes, No).
 - 3835 ○ If yes, how old was the patient when they last had a normal EEG? (Years).
- 3836 • Has the patient ever had an abnormal EEG? (Yes, No, Unknown).
- 3837 • If yes:
 - 3838 ○ EEG findings (Focal spikes, Generalized spike wave discharges,
 - 3839 Hypsarrhythmia, Electrographic seizures).
 - 3840 ○ Seizure type (Partial (focal) seizures, Generalized seizures, Other).
 - 3841 ▪ Generalized seizures type (Generalized spike & wave, Generalized
 - 3842 paroxysmal fast activity, Generalized electrodecrement at onset).
 - 3843 ○ Seizure features (Background slowing and/or disorganization, Focal slowing,
 - 3844 Other).

3845 **5.4.4.4 Neuroimaging History**

3846 Neuroimaging history data will be listed only.

3847 **5.4.5 Medical and Surgical History and Current Medical Conditions**

3848 All conditions and diagnoses on the ‘non-epilepsy medical history’ CRF page will be coded
3849 using Version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA v17.1).
3850 The number of patients with relevant or significant non-epilepsy medical or surgical history
3851 and medical history by system organ class, and preferred term, will be summarized by
3852 absolute counts (n) and percentages (%). Percentages will be calculated based on the
3853 number of patients in the specific treatment group. Two tables will be produced, one
3854 including any events classified as resolved at screening, and the other including all current
3855 conditions.

3856 **5.5 Efficacy Analysis**

3857 **5.5.1 General Approach**

3858 The primary analyses will use the ITT analysis set. Further analyses using the PP analysis
3859 set will also be performed for the primary endpoint and secondary endpoints where specified
3860 in the sections below.

3861 The primary null hypothesis is:

- 3862 • Following 14 weeks of treatment there is no difference in effect between the
- 3863 20 mg/kg/day GWP42003-P treatment group and the placebo treatment group in
- 3864 terms of the change in convulsive seizure frequency during the treatment period
- 3865 compared to baseline.

3866 The null hypothesis will be rejected if there is statistical evidence of a difference between the

3867 treatment groups at the α -level of 0.05 for the primary endpoint.

3868 Statistical hypothesis testing will be performed on the primary endpoint and other endpoints

3869 as appropriate. Each endpoint, including the primary will have 2 comparisons against

3870 placebo (20 mg/kg/day GWP42003-P and 10 mg/kg/day GWP42003-P vs. placebo). Also,

3871 3 key secondary endpoints have been defined.

3872 The primary and key secondary endpoints will be tested with their Type I error controlled by

3873 use of a hierarchical gate-keeping procedure, in the sequence given in Table 3. One must

3874 reject the null hypothesis of an endpoint at the level of 0.05 (2-sided) to test the hypothesis

3875 of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis

3876 is not rejected then testing will stop and all subsequent analyses will be declared not

3877 statistically significant.

3878 **Table 3 Hierarchy for Analysis**

Test	Endpoint	Treatment Comparison
1	Primary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
2	Primary endpoint	10 mg/kg/day GWP42003-P vs. Placebo
3	1 st key secondary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
4	1 st key secondary endpoint	10 mg/kg/day GWP42003-P vs. Placebo
5	2 nd key secondary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
6	2 nd key secondary endpoint	10 mg/kg/day GWP42003-P vs. Placebo
7	3 rd key secondary endpoint	20 mg/kg/day GWP42003-P vs. Placebo
8	3 rd key secondary endpoint	10 mg/kg/day GWP42003-P vs. Placebo

3879

3880 All statistical tests will be 2-sided and use the 5% significance level.

3881 The assumptions of normality and homogeneity of variance, for endpoints analyzed using

3882 parametric tests, will be checked where appropriate via examination of residual plots as well

3883 as computation of summary statistics for normality using the Shapiro–Wilk statistical test. If

3884 assumptions are violated then alternative non-parametric techniques will be used. In this

3885 instance the original parametric tests will be presented as a sensitivity analysis.

3886 5.5.2 Primary Efficacy Endpoint

3887 The primary endpoint is the change in convulsive seizure frequency during the treatment

3888 period (see Section 5.1.3.3) of the study compared to baseline (see Section 5.1.3.1) in

3889 patients taking GWP42003-P compared with placebo.

3890 The primary endpoint will be analyzed using negative binomial regression on the sum of the

3891 convulsive seizure counts during the treatment period. However, convulsive seizure

3892 frequency (28-day average) and percentage change in seizure frequency will be presented

3893 using summary statistics. Percentage change from baseline in convulsive seizure frequency

3894 will be calculated as:

$$3895 \quad \left[\frac{\text{Frequency during the treatment period} - \text{Frequency during baseline}}{\text{Frequency during}} \right. \\ 3896 \quad \left. \text{baseline} \right] \times 100$$

3897 The frequency during each period will be based on 28-day averages and calculated as:

$$3898 \quad \left(\frac{\text{Number of seizures in the period}}{\text{Number of reported days in IVRS in the period}} \right) \times 28$$

3899 For convulsive seizure endpoints only, if patients are randomized with no convulsive

3900 seizures during the baseline period then the percentage change from baseline will be
3901 calculated as:

$$3902 \quad (\text{Frequency during the treatment period} + 1) \times 100$$

3903 A mixed effect model with repeated measures will be performed modelling the observed
3904 number of convulsive seizures in the baseline period and treatment period implemented
3905 within the framework of general linear models using the negative binomial response
3906 distribution. The model will include stratified age group (2–5 years, 6–12 years and
3907 13–18 years), time, treatment arm and treatment arm by time interaction as fixed effects and
3908 patient as a random effect. The log transformed number of days in which seizures were
3909 reported will be included as an offset. The time variable corresponds to an indicator for the
3910 baseline period and treatment period.

3911 The GLIMMIX procedure in SAS will be utilized to perform the analysis with the option
3912 maxopt=300 applied. If the model fails to converge, then the statement ‘nloptions
3913 tech=nr ridge;’ will be added. If convergence is still not achieved then ‘method=laplace’ will
3914 be utilized. However, if convergence is still not possible, then the model will be changed to
3915 utilize the log normal response distribution (log rate model). If the log rate model is required
3916 and there are patients with a seizure frequency during the baseline or treatment period of 0
3917 then all patients will have their baseline and treatment period seizure frequency adjusted by
3918 adding a value of 1.

3919 The estimated ratio of least squares means for treatment period to baseline period and 95%
3920 confidence intervals (CIs) will be presented for each treatment arm. In addition, the
3921 estimated ratio of each GWP42003-P group to placebo and 95% CIs will be presented along
3922 with the p-value testing the null hypothesis that this ratio is 1.

3923 For each ratio and upper and lower bound of the 95% CI, the percentage reduction will also
3924 be presented, calculated as:

$$3925 \quad [1 - (X \div Y)] \times 100\%$$

3926 Where X corresponds to the treatment period estimate, or GWP42003-P ratio, and Y
3927 corresponds to the baseline period estimate, or placebo arm ratio.

3928 Primary efficacy analysis will be performed using ITT analysis set.

3929 For a period of time, the limit for the number of daily seizures for each seizure type recorded
3930 in IVRS was 99. A >99 seizure log was added to the CRF to allow the capture of the exact
3931 number of seizures where the count on a particular day was >99. When deriving the seizure
3932 frequencies, the count >99 provided on the CRF will replace the recorded 99 seizures in
3933 IVRS for the corresponding seizure type. This will only be done when the corresponding
3934 IVRS record was exactly 99.

3935 **5.5.2.1 Sensitivity Analyses for the Primary Efficacy Endpoint**

3936 The following sensitivity analyses will be conducted for the primary endpoint:

- 3937 • Primary endpoint analysis repeated using the PP analysis set.
- 3938 • Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure
3939 frequency during the treatment period. An estimate of the median differences
3940 between each GWP42003-P group and placebo, together with approximate 95% CIs,
3941 will be calculated using the Hodges–Lehmann approach.
- 3942 • A rank analysis of covariance (ANCOVA) on percentage change from baseline in
3943 convulsive seizure frequency during the treatment period.

3944 The ranks of the percentage change from baseline and the baseline convulsive seizure
3945 frequency will be calculated. The rank of the percentage change from baseline will
3946 then be analyzed using an ANCOVA model with the rank of the baseline convulsive

3947 seizure frequency and age group (2–5 years, 6–12 years and 13–18 years) as
 3948 covariates and treatment group as a fixed factor. The estimated least squares means,
 3949 treatment differences, together with the 95% CIs and p-values will be presented.

- 3950 • ANCOVA of log transformed convulsive seizure frequency during the treatment
 3951 period.

3952 The convulsive seizure frequency during the treatment period and the baseline
 3953 convulsive seizure frequency will be log transformed prior to analysis. The log
 3954 transformed convulsive seizure frequency during the treatment period will then be
 3955 analyzed using an ANCOVA model with the log transformed baseline convulsive
 3956 seizure frequency and age group as covariates and treatment group as a fixed factor.
 3957 The back transformed estimated treatment ratios, together with the 95% CIs and p-
 3958 values will be presented.

3959 If there are any patients with no seizures during the baseline or treatment periods,
 3960 then 1 will be added to the convulsive seizure frequency for all patients prior to log
 3961 transformation.

- 3962 • ANCOVA on percentage change from baseline in convulsive seizure frequency
 3963 during the treatment period including baseline and age group as covariates and
 3964 treatment group as a fixed factor. The estimated least squares means, treatment
 3965 differences, together with the 95% CIs and p-values will be presented.

- 3966 • Primary endpoint analysis repeated using the maintenance period (see Section
 3967 5.1.3.4) rather than the treatment period.

3968 This analysis will include only patients who have at least 7 days of seizure data
 3969 within the maintenance period.

- 3970 • Primary endpoint analysis repeated using each 4 weeks of the maintenance period
 3971 (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period).

3972 This analysis will include only patients who have at least 7 days of seizure data
 3973 within each corresponding 4-week period rather than the treatment period.

- 3974 • Primary endpoint analysis repeated using the worst case of last observation carried
 3975 forward (LOCF), next observation carried backward (NOCB) and the daily mean
 3976 from the non-missing data for each patient (rounded up to the nearest integer) to
 3977 impute missing data arising from unreported days in IVRS during the treatment
 3978 period only (not the baseline period).

3979 Any intermittent missing data for the number of convulsive seizures arising from
 3980 unreported days in IVRS will be imputed using the worst (highest number of
 3981 seizures) of the following for each patient: LOCF, NOCB and the mean daily number
 3982 of seizures during the treatment period (rounded up to the nearest integer) based on
 3983 using non-missing data:

$$\text{Number of seizures} \div \text{Number of reported days in IVRS}$$

- 3984 • Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure
 3985 frequency during the treatment period, using multiple imputation (MI) to impute data
 3986 under the Missing Not at Random (MNAR) assumption (see Section 5.5.2.1.1).
 3987
- 3988 • Primary endpoint analysis repeated using the safety analysis set.

3989 **5.5.2.1.1 Sensitivity Analysis of Missing Data**

3990 Missing data in this trial could potentially arise from the mechanism of MNAR. In order to
 3991 understand the impact on the trial findings from missing data under the MNAR assumption,
 3992 sensitivity analyses of the primary endpoint will be carried out for the ITT analysis set by

3993 multiple imputations on convulsive seizure frequency, based on time-points corresponding to
 3994 each 14 days of the treatment period. The final period will consist of 15 days to include Day
 3995 99, if applicable.

3996 For each 14 calendar days of the treatment period (15 days for the final period), the
 3997 convulsive seizure frequency will be calculated as:

3998
$$\left[\frac{\text{Number of convulsive seizures in the period}}{\text{Total number of reported days in IVRS for}} \right. \\
 3999 \quad \left. \text{all combined periods (maximum of 99 days)} \right] \times 28$$

4000 For patients with any periods with no reported days in IVRS, the total number of reported
 4001 days in IVRS will include an additional 14 days for each missing period. For example, if a
 4002 patient withdraws with 80 reported days in IVRS from 6 of the 7 14-calendar-day periods,
 4003 then the total number of reported days in IVRS for the above calculation will be the sum of
 4004 80 and 14, i.e. 94 days.

4005 Intermittent missing values for intermediate nominal visits before the last nominal visit will
 4006 be imputed using the MCMC method in PROC MI with an IMPUTE=MONOTONE
 4007 statement for 100 times for each treatment group separately. The resulting 100 partially
 4008 imputed datasets will have a monotone missing pattern and will be further imputed under an
 4009 MNAR assumption that the imputed value for the missing efficacy data of GWP42003-P
 4010 patients (discontinued for certain reasons) are similar to, worse than, or better than those of
 4011 placebo patients for the following 2 scenarios:

4012 (1) MNAR assumed for missing values resulting from discontinuation due to AEs in the
 4013 GWP42003-P groups and Missing at Random (MAR) for others, including other patients
 4014 discontinued in the GWP42003-P groups and patients in placebo group;

4015 (2) MNAR assumed for missing values resulting from discontinuation due to any reason or
 4016 any other monotone missing data in the GWP42003-P groups and MAR for others, including
 4017 patients in placebo group.

4018 For each of the 2 scenarios above, imputation will be carried out once on each of the 100
 4019 imputed datasets using the SAS MI procedure (with the 100 imputed datasets included in the
 4020 'BY' statement of the MI procedure) as follows:

4021 • Step 1: Monotone missing data under the MAR assumption at treatment period
 4022 time-point t will be imputed by means and covariance from the observed convulsive
 4023 seizure frequency at baseline and at each treatment period time-point up to time-point
 4024 t (in chronological order) in their corresponding treatment groups (i.e., patients in the
 4025 GWP42003-P groups whose missing data are assumed to be MAR and all patients in
 4026 the placebo group). The imputation will be realized using the MI procedure with the
 4027 'MONOTONE REG' option, for each treatment group separately. The imputation
 4028 model will include baseline convulsive seizure frequency and each treatment period
 4029 time-point up to time-point t (in chronological order).

4030 • Step 2: With the data imputed from Step 1, monotone missing data of patients in the
 4031 GWP42003-P groups under the MNAR assumption will be imputed. At each
 4032 treatment period time-point t , the input dataset for the MI procedure will include all
 4033 placebo patients and those patients from each GWP42003-P group that have values
 4034 missing under MNAR at that time-point. The imputation model will include
 4035 convulsive seizure frequency at baseline and each treatment period time-point up to
 4036 time-point t (in chronological order). After the sequential imputation is completed
 4037 for all time-points, the imputed values at time-point t plus, a sensitivity parameter, k
 4038 \times standard error of the observed convulsive seizure frequency in the placebo group at
 4039 the corresponding time-point (calculated using the denominator of the total number
 4040 of reported days in IVRS for all combined periods, as given above) will then form the
 4041 final imputed values. The sensitivity parameter k (where, for example, $k = 0, \pm 0.5, \pm$
 4042 $1.0, \pm 1.5$, etc.) will be used to explore the robustness of the estimated treatment

4043 difference to the degree of decrease or increase (positive values of k represent
4044 decrease and negative values represent increase) in MNAR efficacy from the placebo
4045 patients.

4046 After missing values at all the time-points are imputed, the overall percentage change from
4047 baseline in convulsive seizure frequency will be calculated as:

4048
$$[(\text{The sum of the frequencies of each 14 days of the treatment period} - \text{Frequency during}$$

4049
$$\text{baseline}) \div \text{Frequency during baseline}] \times 100$$

4050 If the sum of the frequencies of each 14 days of the treatment period becomes less than zero,
4051 as a result of imputation, then the percentage change from baseline in convulsive seizure
4052 frequency will be set to -100% .

4053 The data will then be analyzed using a Wilcoxon rank-sum test.

4054 The results of the Wilcoxon rank-sum test on the 100 imputed datasets will be combined to
4055 derive an overall p-value. The test statistic will be based on the method provided by Rubin¹
4056 and a modified macro from Mogg².

4057 For each analysis, the increment in the positive value of k will stop once the overall p-value
4058 is greater than 0.05. The decrease in the negative values of k will continue until the overall
4059 p-value becomes smaller than the p-value from the primary efficacy analysis, for the
4060 corresponding Dose Level.

4061 **5.5.3 Secondary Efficacy Endpoints**

4062 **5.5.3.1 Key Secondary Efficacy Endpoints**

4063 **5.5.3.1.1 1st Key Secondary Endpoint: Total Seizures**

4064 Summaries and analyses of total seizures (see Section 5.1.3.7) will be performed as per the primary
4065 endpoint (Section 5.5.2).

4066 The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

4067 Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using
4068 data for only the maintenance period, and during each 4 weeks of the maintenance period (Week 1–4,
4069 Week 5–8 and Week 9–12 of the 12-week maintenance period).

4070 Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only
4071 patients who have at least 7 days of seizure data within each corresponding period.

4072

4073 **5.5.3.1.2 2nd Key Secondary Endpoint: Convulsive Seizure Treatment Responders** 4074 **($\geq 50\%$ Reduction in Convulsive Seizure Frequency)**

4075 The proportion of patients considered treatment responders, defined as those with a $\geq 50\%$ reduction
4076 in convulsive seizure frequency from baseline, during the treatment period, will be summarized by
4077 treatment group and analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group.
4078 The proportion of patients who are considered treatment responders, the difference in proportions
4079 along with the 95% CI for the difference, the estimated odds ratios (GWP42003-P groups vs.
4080 placebo), 95% CI for the odds ratios, and the p-values from the CMH test will be presented. If no
4081 patients in a particular treatment group are considered responders then the odds ratio and 95% CI for
4082 the odds ratio will not be calculated.

4083 The analysis will be performed on the ITT analysis set and repeated on the PP analysis set.

4084 Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using
4085 data for the maintenance period only, and during each 4 weeks of the maintenance period (Week 1–4,
4086 Week 5–8 and Week 9–12 of the 12-week maintenance period).

4087 Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only
4088 patients who have at least 7 days of seizure data within each period.

4089 **5.5.3.1.3 3rd Key Secondary Endpoint: Caregiver Global Impression of Change**

4090 The CGIC will be assessed at Visits 3, 4, 6 and 8 (end of treatment). The CGIC comprises
4091 the following question to be rated on a 7-point scale:

- 4092 • Since your child started treatment, please assess the status of your child's overall
4093 condition (comparing their condition now to their condition before treatment) using
4094 the scale below.

4095 The possible responses are: Very Much Improved; Much Improved; Slightly Improved; No
4096 Change; Slightly Worse; Much Worse; Very Much Worse.

4097 The responses above are based on comparison with a brief description of the patient's overall
4098 condition used as a memory aid from Visit 2.

4099 Each response will be coded with a score from 1 to 7, where 1 = Very Much Improved, and
4100 7 = Very Much Worse.

4101 The CGIC response/score, recorded at each visit, will be summarized, on both a categorical and
4102 continuous scale, by treatment group.

4103 The score at the end of treatment visit and last visit (if different to the end of treatment) will
4104 be analyzed using ordinal logistic regression. Proportional odds modelling will be carried
4105 out by including treatment group as a factor. The estimated odds ratios (GWP42003-P arms
4106 vs. placebo), 95% CI for the odds ratios, and the p-value testing the null hypothesis that the
4107 odds ratio is equal to 1, will be presented. Analysis performed at the last visit will be
4108 considered the main analysis for this endpoint, with the analysis at the end of treatment visit
4109 considered a sensitivity analysis.

4110 Should the proportional odds assumption not hold, i.e. if the p-value for the score test for
4111 proportional odds assumption is <0.05, then, as a sensitivity analysis, the scores will also be
4112 analyzed using a Cochran-Armitage trend test. This will be presented together with the
4113 results of the ordinal logistic regression.

4114 **5.5.3.2 Other Secondary Efficacy Endpoints**

4115 **5.5.3.2.1 Convulsive Seizure Treatment Responders and Convulsive Seizure 4116 Freedom**

4117 The number of patients experiencing >25% increase, ≥ 0 to $\leq 25\%$ increase, >0 to <25% reduction,
4118 ≥ 25 to <50% reduction, ≥ 50 to <75% reduction or $\geq 75\%$ reduction in convulsive seizure frequency
4119 from baseline during the treatment period will be summarized by treatment group.

4120 In addition to the key secondary endpoint, the proportion of patients considered treatment responders,
4121 defined as those with a $\geq 25\%$ or $\geq 75\%$ reduction in convulsive seizure frequency from baseline and
4122 the proportion of patients who are convulsive seizure free, defined as those with a 100% reduction in
4123 convulsive seizure frequency from baseline, during the treatment period, will be summarized by
4124 treatment group and analyzed using a CMH test stratified by age as described in Section 5.5.3.1.2.

4125 Additionally, the proportion of patients responding will be presented graphically, by treatment arm,
4126 by plotting the percent reduction against the cumulative proportion of patients achieving that level of
4127 reduction. The x-axis will be the percent reduction from baseline and the y-axis will be the
4128 proportion of patients with at least that amount of reduction, i.e. $y = \Pr(X \geq x)$.

4129 Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using
4130 data for the maintenance period only, and during each 4 weeks of the maintenance period (Week 1–4,
4131 Week 5–8 and Week 9–12 of the 12-week maintenance period).

4132 Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only
4133 patients who have at least 7 days of seizure data within each corresponding period.

4134 **5.5.3.2.2 Status Epilepticus**

4135 The number of convulsive seizures greater than 30 minutes in duration and the number of non-

4136 convulsive seizures greater than 30 minutes in duration will be collected daily via IVRS.
 4137 The number of patients with convulsive and non-convulsive seizures greater than 30 minutes in
 4138 duration, will be presented for the baseline and treatment periods.
 4139 In addition, the number of patients with any episodes post-baseline and no episodes during the
 4140 baseline period, will be summarized by treatment group.

4141 **5.5.3.2.3 Non-Convulsive Seizures**

4142 Non-convulsive seizures will be summarized and analyzed as per the primary endpoint (Section
 4143 5.5.2). Patients with no non-convulsive seizures during the baseline period will be excluded from the
 4144 analysis.
 4145 Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using
 4146 data for only the maintenance period, and during each 4 weeks of the maintenance period (Week 1–4,
 4147 Week 5–8 and Week 9–12 of the 12-week maintenance period).
 4148 Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only
 4149 patients who have at least 7 days of seizure data within each corresponding period.
 4150 Non-convulsive seizure responders and freedom will also be summarized and analyzed using the
 4151 methods described in Section 5.5.3.2.1. Patients with no non-convulsive seizures during the baseline
 4152 period will be excluded from the analysis.

4153 **5.5.3.2.4 Individual Seizure Types**

4154 For each individual seizure type (tonic–clonic, tonic, clonic, atonic, myoclonic, countable partial,
 4155 other partial and absence seizures) summaries and analyses will be performed as per the primary
 4156 endpoint (Section 5.5.2). Patients with no seizures during the baseline period, for a particular seizure
 4157 type, will be excluded from the analysis of that seizure type.
 4158 Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis for tonic,
 4159 tonic–clonic, atonic and clonic seizures only, using data for only the maintenance period, and during
 4160 each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week
 4161 maintenance period).
 4162 Analyses on the maintenance period and by each 4 weeks of the maintenance period will include only
 4163 patients who have at least 7 days of seizure data within each corresponding period.
 4164 Individual seizure type responders and freedom will also be summarized and analyzed using the
 4165 methods described in Section 5.5.3.2.1. However, the summaries and analyses during the
 4166 maintenance period and during each 4 weeks of the maintenance period will be produced for tonic,
 4167 tonic–clonic, atonic and clonic seizures only. Patients with no corresponding seizures, for a
 4168 particular seizure type, during the baseline period will be excluded from the analysis for that seizure
 4169 type.
 4170 In addition, the number of patients with an occurrence of an individual seizure type not experienced
 4171 in the baseline period will be summarized by treatment group.
 4172 An occurrence of an individual seizure type not experienced in the baseline period is calculated as
 4173 seizure types with no seizures experienced during the baseline period and at least one seizure
 4174 experienced at any time post first dose of IMP.

4175 **5.5.3.2.5 Caregiver Global Impression of Change in Seizure Duration**

4176 The CGICSD comprises the following question to be rated on a 3-point scale for each seizure type:
 4177 • Since the patient started treatment, please assess the average duration of the patient’s seizures
 4178 (comparing their condition now to their condition before treatment) using the scale below.

4179 The 3 possible responses are:

- 4180 • Decrease in average duration.
- 4181 • No change in average duration.
- 4182 • Increase in average duration.

4183 The caregiver will be asked to assess the average duration of the patient’s seizures at Visit 2 (prior to

4184 commencement of IMP) as a memory aid for assessment at the end of treatment visit.
 4185 Each response will be coded with a score from 1 to 3, where 1 = Decrease in average
 4186 duration, and 3 = Increase in average duration.
 4187 For each seizure type, the CGICSD will be summarized by treatment group and analyzed using
 4188 ordinal logistic regression.
 4189 Proportional odds modelling will be carried out by including treatment group and age group as
 4190 factors. The estimated odds ratios (GWP42003-P groups vs. placebo), 95% CI for the odds ratios,
 4191 and the p-values testing the null hypothesis that the odds ratio is equal to 1, will be presented.

4192 **5.5.3.2.6 Inpatient Hospitalizations due to Epilepsy**

4193 The number of inpatient epilepsy-related hospitalizations since the previous visit are recorded at
 4194 every visit starting from Visit 2 (Day 1).
 4195 The number of patients with inpatient epilepsy-related hospitalizations will be presented for
 4196 the baseline and treatment periods.

4197 **5.5.3.2.7 Sleep Disruption 0-10 Numerical Rating Scale**

4198 The sleep disruption 0-10 NRS will be performed at Visits 2 (Day 1), 3, 4, 6 and 8 (end of
 4199 treatment). The patient's caregiver will be asked:

- 4200 • "On a scale of '0 to 10', please indicate the number that best describes your child's
 4201 sleep disruption in the last week."

4202 The markers range from 0 = slept extremely well, to 10 = unable to sleep at all.

4203 The sleep disruption 0-10 NRS score, recorded at each visit, will be summarized, on a
 4204 continuous scale, by treatment group. The change from baseline (Visit 2) will also be
 4205 included.

4206 The change from baseline to the end of treatment visit and last visit (if different to the end of
 4207 treatment) will be analyzed using ANCOVA. The model will include baseline and age
 4208 group as covariates and treatment group as fixed factor. Analysis performed at the last visit
 4209 will be considered the main analysis for this endpoint, with the analysis at the end of
 4210 treatment visit considered a sensitivity analysis.

4211 The estimated least squares means, treatment difference, together with the 95% CIs and
 4212 p-value will be presented.

4213 **5.5.3.2.8 Epworth Sleepiness Scale**

4214 The ESS is a questionnaire that provides a measure of a person's general level of daytime
 4215 sleepiness, or their average sleep propensity in daily life. The ESS contains 8 questions that
 4216 are rated on a 4-point numerical scale (0–3). The total ESS score is the sum of the 8 item-
 4217 scores and can range between 0 and 24. Higher total scores represent greater levels of
 4218 daytime sleepiness.

4219 The ESS questionnaire will be completed at Visits 2 (Day 1), 3, 4, 6 and 8 (end of treatment)
 4220 by the patient's caregiver.

4221 The total score, recorded at each visit, will be summarized, on a continuous scale, by
 4222 treatment group. The change from baseline (Visit 2) will also be included.

4223 The change from baseline in the total score to the end of treatment visit and last visit (if
 4224 different to the end of treatment) will be analyzed using the same ANCOVA approach as
 4225 specified in Section 5.5.3.2.7. Analysis performed at the last visit will be considered the
 4226 main analysis for this endpoint, with the analysis at the end of treatment visit considered a
 4227 sensitivity analysis.

4228 Missing data arising from missing individual questions will be handled according to
 4229 Section 5.1.1.2.1.

4230 **5.5.3.2.9 Quality of Life in Childhood Epilepsy**

4231 The QOLCE is a parent-reported questionnaire that evaluates health related quality of life in children
 4232 aged 4–18 years old. It contains 76 items with 16 subscales covering 7 domains of life function:
 4233 physical activities, social activities, cognition, emotional well-being, behavior, general health, and
 4234 general quality of life. The QOLCE will be completed by the parent or caregiver at Visits 2 (Day 1)
 4235 and 8 (end of treatment).

4236 All items in the questionnaire are rated on a 5-point or 6-point categorical scale. Based on the
 4237 responses to the items in each domain, scores for 16 subscales are derived. The subscales are
 4238 presented in Table 4.

4239 **Table 4 QOLCE Subscales**

Subscale	Item Domains	Items Used
Physical Restrictions	Physical Activities	3.1 (a to j)
Energy/Fatigue	Physical Activities	3.2 (a,b)
Attention/Concentration	Cognition	5.1 (a,d,e,f,g)
Memory	Cognition	5.1 (j,k,l,m,n,o)
Language	Cognition	5.1 (p,q,r,s,t,u,v,w)
Other Cognitive	Cognition	5.1 (b,c,h)
Depression	Emotional Well-Being	4.1 (a,d,e,l)
Anxiety	Emotional Well-Being	4.1 (b,g,j,n,o,p)
Control/Helplessness	Emotional Well-Being	4.1 (c,f,h,i)
Self-esteem	Emotional Well-Being	4.1 (k,m,q,r,s)
Social Interactions	Social Activities	6.1 (c,f,h)
Social Activities	Social Activities	6.1 (a,e) and 6.2
Stigma Item	Social Activities	6.1 (i)
Behavior	Behavior	7.1 (a,c,f,g,h,I,j,k,l,m,o,q,r,s,t)
General Health Item	General Health	8.1
Quality of Life Item	Quality of Life	9.1

4240
 4241 Items within each subscale will be coded and linearly transformed, according to the methods of
 4242 Sabaz et al.³, to a score of 0 to 100, where 0 represents the lowest or poorest category and 100
 4243 represents the highest level of functioning.

4244 A subscale score is calculated for each subscale by computing the mean of the items within the
 4245 subscale. An ‘Overall Quality of Life Score’ can be calculated by taking the mean of the subscale
 4246 scores.

4247 Individual items will be listed only. The subscale scores and the overall quality of life score,
 4248 recorded at each visit, will be summarized, on a continuous scale, by treatment group. The
 4249 change from baseline (Visit 2) will also be included.

4250 The change from baseline to the end of treatment visit, for the overall quality of life score,
 4251 and the attention/concentration, memory, language, other cognitive, social interactions and
 4252 behavior subscale scores only, will be analyzed using the same ANCOVA approach as
 4253 specified in Section 5.5.3.2.7. Exploratory analyses may also be performed on other
 4254 subscale scores.

4255 Missing data will be handled according to Section 5.1.1.2.2.

4256 **5.5.3.2.10 Vineland Adaptive Behavior Scales, Second Edition**

4257 The Vineland-II is an individually administered instrument for assessing adaptive behaviors.
 4258 The Vineland-II assessments will be made at Visits 2 (Day 1), 3, 4, 6 and 8 (end of
 4259 treatment).

4260 The Vineland-II consists of 44 adaptive behavior domains and a maladaptive behavior
 4261 domain. The details of each domain are presented in Table 5.

4262 **Table 5** Content Description of the Vineland-II

Domains and Subdomains	Number of Items	Age Range (Years)	Content
Adaptive Behavior Domains			
Communication Domain	99	≥ 0	
Receptive	20	≥ 0	How the individual listens and pays attention, and what he or she understands
Expressive	54	≥ 0	What the individual says, how he or she uses words and sentences to gather and provide information
Written	25	≥ 3	What the individual understands about how letters make words, and what he or she reads and writes
Daily Living Skills Domain	109	≥ 0	
Personal	41	≥ 0	How the individual eats, dresses and practices personal hygiene
Domestic	24	≥ 1	What household tasks the individual performs
Community	44	≥ 1	How the individual uses time, money, the telephone, the computer and job skills
Socialization Domain	99	≥ 0	
Interpersonal Relationships	38	≥ 0	How the individual interacts with others
Play and Leisure Time	31	≥ 0	How the individual plays and uses leisure time
Coping Skills	30	≥ 1	How the individual demonstrates responsibility and sensitivity to others
Motor Skills Domain	76	≥ 0 to <7	
Gross	40	≥ 0 to <7	How the individual uses arms and legs for movement and coordination
Fine	36	≥ 0 to <7	How the individual uses hands and fingers to manipulate objects
Maladaptive Behavior Domain			
Maladaptive Behavior Index	36	≥ 3	A composite of Internalizing, Externalizing, and Other types of undesirable behavior that may interfere with the individual's adaptive functioning
Internalizing (Section A)	11	≥ 3	
Externalizing (Section B)	10	≥ 3	
Other (Section C)	15	≥ 3	
Maladaptive Behavior Critical Items	14	≥ 3	More severe maladaptive behaviors that may provide clinically important information

4263

4264 For each subdomain, a raw score is calculated based on the responses to the individual items
 4265 within the subdomain. For the maladaptive behavior index, the raw score is the sum of the 3
 4266 subdomain raw scores. Using the raw score and the patients' age the following are obtained:

- 4267 • v-Scale Score: a type of standard score scale (standardized by age) to describe an
 4268 individual's relative level of functioning. Ranging from a score of 1 to 24.
- 4269 • 90% CI for the v-Scale Score: a range of scores that has a certain likelihood of
 4270 including the individual's true score.
- 4271 • Adaptive Level: a means to describe an individual's performance using terms that are
 4272 nearly universal (Low, Moderately Low, Adequate, Moderately High, High).
 - 4273 ○ For the maladaptive behavior index and maladaptive behavior subdomains the
 4274 adaptive levels are: Average, Elevated or Clinically Significant.

- 4275 • Age Equivalent: the age at which the raw score is average. Not applicable for the
4276 maladaptive behavior index and maladaptive behavior subdomains.
- 4277 For each adaptive behavior domain, the sum of the v-scale scores of the subdomains is used
4278 along with the patients' age to obtain the following:
- 4279 • Standard Score (standardized by age). Ranging from a score of 20 to 160.
- 4280 • 90% CI for the domain standard score.
- 4281 • Percentile Rank: the percentage of people whom the individual outperformed in his
4282 or her age group.
- 4283 • Adaptive Level (Low, Moderately Low, Adequate, Moderately High, High).
- 4284 • Stanine: whole number score ranging from 1 to 9 and representing a specific range of
4285 percentile ranks.

4286 An adaptive behavior composite can then be obtained using the sum of the adaptive behavior
4287 domain standard scores (excluding the motor skills domain for patients ≥ 7 years of age).
4288 The same derived information as the adaptive behavior domain is obtained for the adaptive
4289 behavior composite.

4290 For the maladaptive behavior index, all items within each section must be answered for a
4291 raw score to be calculated. If any of the items are missing then the maladaptive behavior
4292 index score will be missing.

4293 For the adaptive behavior subdomains, the derivation of the raw score allows for up to
4294 2 missing values or answers of "Don't Know" within the items used for scoring. If there are
4295 more than 2 missing values or answers of "Don't Know" then the raw score will not be
4296 calculated and the subdomain score, domain score and adaptive behavior composite score
4297 will be missing.

4298 The adaptive levels corresponding to the v-scale scores and standard scores are presented in
4299 Table 6.

4300 **Table 6 Adaptive Levels by v-Scale Scores and Standard Scores**

Adaptive Level	v-Scale Score for Subdomains and Maladaptive Behavior Index	Standard Score for Domains and Adaptive Behavior Composite
Adaptive Behavior Domains		
Low	1 to 9	20 to 70
Moderately Low	10 to 12	71 to 85
Adequate	13 to 17	86 to 114
Moderately High	18 to 20	115 to 129
High	21 to 24	130 to 160
Maladaptive Behavior Domain		
Clinically Significant	21 to 24	
Elevated	18 to 20	
Average	1 to 17	

4301

4302 The v-scale score from the 11 adaptive behavior subdomains, 3 maladaptive behavior
4303 subdomains and the maladaptive behavior index, and the standard score from the 4 adaptive
4304 behavior domains and the adaptive behavior composite, recorded at each visit, will be
4305 summarized, on a continuous scale, by treatment group. The change from baseline (Visit 2)
4306 will also be included.

4307 The change from baseline to the end of treatment visit and last visit (if different to the end of
4308 treatment), for the 4 adaptive behavior domains, the adaptive behavior composite and the

4309 maladaptive behavior index only, will be analyzed using the same ANCOVA approach as
4310 specified in Section 5.5.3.2.7. Analysis performed at the last visit will be considered the
4311 main analysis for this endpoint, with the analysis at the end of treatment visit considered a
4312 sensitivity analysis.

4313 The adaptive level from the 11 adaptive behavior subdomains, 4 adaptive behavior domains,
4314 the adaptive behavior composite, the 3 maladaptive behavior subdomains and the
4315 maladaptive behavior index, recorded at each visit, will be summarized, on a categorical
4316 scale, by treatment group.

4317 The adaptive level from the 4 adaptive behavior domains, the adaptive behavior composite and the
4318 maladaptive behavior index only will be analyzed using ordinal logistic regression. Factors for
4319 treatment and age group will be included along with the baseline adaptive level as a covariate. The
4320 estimated odds ratios (GWP42003-P groups vs. placebo), 95% CI for the odds ratios, and the p-
4321 values testing the null hypothesis that the odds ratio is equal to 1, will be presented.

4322 Each adaptive level for adaptive behavior will be coded with a score from 1 to 5, where
4323 1 = Low, and 5 = High. Each adaptive level for the maladaptive behavior index will be
4324 coded with a score from 1 to 3, where 1 = Clinically Significant, and 3 = Average.

4325 The individual responses within each domain will not be listed, only the derived information
4326 for each subdomain and domain will be listed.

4327 **5.5.3.2.11 Cognitive Assessment Battery**

4328 The cognitive assessment battery will be administered at Visit 2 (baseline) and Visit 8 (end
4329 of treatment). The items are age specific and the age of the patient at entry is the age used
4330 when choosing the items to be given. Children and adults are to complete the battery as
4331 able. It is expected that a number of patients will only be able to complete part of the battery
4332 and some may not be able to complete it at all. Parents and/or caregivers are to complete
4333 certain items.

4334 The battery items will only be administered to a sub-group of sites that have the expertise to
4335 conduct the test. Assessments are conducted by an experienced psychometrician.

4336 A summary of the patient and parent measures are given in Table 7.

4337
4338**Table 7 Neuropsychological Protocol for Epilepsy Patients Treated with Cannabidiol – Patient and Parent Measures**

Category	Function	Measures	Age Range
Patient	Intelligence IQ	Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-4) Vocabulary, Matrix Reasoning	2;6 - 5;11 years
		Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2) Vocabulary, Matrix Reasoning (Including Wechsler: ‘Digit Span’ subtest from Wechsler Intelligence Scale for Children – Fourth Edition (WISC-4) and Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-4); ‘Coding’ subtest from WISC-4 & WAIS-4; ‘Bug Search’ from WPPSI-4)	6 - adult
	Attention/Executive Trail Making	Trail Making Test Delis–Kaplan Executive Function System (D-KEFS)	9 - adult
	Language Naming Fluency	Expressive One-Word Picture Vocabulary Test-4th Edition	2 - adult
		NEPSY-2 Word Generation	2 - 5 years
		F-A-S and Animals	6 - adult
	Visual-Spatial VMI	Developmental Test of Visual Motor Integration-6	2 - adult
Fine Motor Speed Pegs	Purdue Pegboard	4 - adult	
Parent	Executive	Behavior Rating Inventory of Executive Function (Parent and Teacher)	3 - 21 years
	Attention	Attention deficit hyperactivity disorder (ADHD) Checklist (Parent and Teacher)	All ages
	Mood/Anxiety	Behavior Assessment System for Children – Second Edition (BASC-2) (Parent and Teacher)	3 - 21 years
	Free-form report	Behavior Report Form (Parent and Teacher)	All ages

4339 The following patient measures will be summarized, on a continuous scale, by treatment group at
4340 each visit and including the change from baseline using the score recorded on the CRF:

- 4341 • Intelligence:
- 4342 ○ WPPSI-4 T score:
- 4343 ▪ Receptive Vocabulary.
- 4344 ▪ Matrix Reasoning.
- 4345 ▪ Bug Search.
- 4346 ○ WASI-2 T score:
- 4347 ▪ Vocabulary.
- 4348 ▪ Matrix Reasoning.
- 4349 ○ WISC-4 and WAIS-4:
- 4350 ▪ Coding scaled score.
- 4351 ▪ Digit Span (Forward, Backward, Longest forward, Longest Backward).
- 4352 • Attention/Executive:
- 4353 ○ D-KEFS scaled scores.
- 4354 • Language:
- 4355 ○ Expressive One-Word Picture Vocabulary Test-4th Edition scaled score.

- 4356 ○ NEPSY-2 Word Generation scaled score.
- 4357 ● Visual-Spatial:
 - 4358 ○ Developmental Test of Visual Motor Integration-6 standard score.
- 4359 ● Fine Motor Speed:
 - 4360 ○ Dominant hand, non-dominant hand and both hands Z scores.

4361 The following parent measures will be summarized, on a continuous scale, by treatment group at
4362 each visit and including the change from baseline using the scored recorded on the CRF:

- 4363 ● Executive:
 - 4364 ○ Behavior Rating Inventory of Executive Function T scores for indexes and
4365 composite.
- 4366 ● Mood/Anxiety:
 - 4367 ○ BASC-2 T scores for composite scores.

4368 The behavior report form will be summarized, on a categorical scale, by treatment at each visit.
4369 The ADHD checklist consists of 18 questions, questions 1 to 9 relate to inattention and questions 10
4370 to 18 relate to hyperactivity. A derived Inattention and Hyperactivity score can be calculated by
4371 taking the sum of the corresponding question responses, where 0 = ‘Not at all’ and 3 = ‘Very much’
4372 and dividing by 9. A combined score can also be calculated by taking the sum of the responses from
4373 questions 1 to 18 and dividing by 18. The Inattention, Hyperactivity and combined scores will be
4374 summarized, on a continuous scale, at each visit and by treatment group. The change from baseline
4375 (Visit 2) will also be included.

4376 **5.5.4 Exploratory Efficacy Endpoints**

4377 **5.5.4.1 Time to Baseline Convulsive Seizure Frequency**

4378 Time to baseline convulsive seizure frequency is defined as the number of reported days in IVRS,
4379 from Day 1, that it takes for the cumulative number of convulsive seizures experienced to be greater
4380 than or equal to the number of seizures (per 28 days) experienced during the baseline period and will
4381 be calculated as:

4382 Date criterion was achieved – Date of Day 1 – Number of unreported days in IVRS between Day 1
4383 and date criterion was achieved + 1

4384 Patients who complete the study without experiencing greater than or equal to the number of seizures
4385 (per 28 days) experienced during the baseline period, or who withdraw from the study, will be
4386 censored at the earlier of:

- 4387 ● Day 99.
- 4388 ● The date of last dose as recorded on the ‘End of Treatment Study Outcome’ CRF page.

4389 The exact day used for censoring will be the day obtained from above minus the number of
4390 unreported days in IVRS between Day 1 and the day obtained from above.

4391 Time to baseline convulsive seizure frequency will be summarized on a continuous scale, by
4392 treatment group, for patients in the ITT analysis set. The lower and upper quartiles will also be
4393 presented. The Kaplan–Meier estimates for the median time to baseline convulsive seizure frequency
4394 will be presented along with 95% CIs for the median and p-values from log-rank tests comparing
4395 each GWP42003-P group with placebo. A Kaplan–Meier plot will also be produced.

4396 The above will be repeated using Day 15 instead of Day 1 as the start day for counting the
4397 cumulative number of convulsive seizures.

4398 **5.5.4.2 Number of Convulsive Seizure Free Days**

4399 The number of convulsive seizure free days during each period will be based on 28-day averages and

4400 calculated as:
 4401 $(\text{Number of seizure free days in the period} \div \text{Number of reported days in IVRS in the period}) \times 28$
 4402 The change from baseline in convulsive seizure free days per 28 days will be analyzed for
 4403 the treatment period using an ANCOVA approach. The model will include baseline and age
 4404 group as covariates and treatment group as fixed factor.
 4405 The estimated least squares means, treatment difference, together with the 95% CIs and p-value will
 4406 be presented.
 4407 The analysis will be repeated for the maintenance period. Analysis on the maintenance period will
 4408 include only patients who have at least 7 days of seizure data within the maintenance period.

4409 **5.5.5 Subgroup Analyses**

4410 To assess the degree of effect heterogeneity, effect modifier analyses are proposed, on the
 4411 ITT analysis set, for the primary efficacy endpoint and the key secondary efficacy endpoint
 4412 of $\geq 50\%$ reduction in convulsive seizure frequency.
 4413 For the primary efficacy endpoint, the effect modifier analysis will be performed using the
 4414 negative binomial regression analysis as described in Section 5.5.2. The model will be
 4415 updated to include covariates for each level of the effect being tested (excluding a reference
 4416 level), individually and with interactions with time, interactions with treatment arm and
 4417 interactions with time and treatment. A separate model will be used for testing each effect.
 4418 The treatment ratios (GWP42003-P vs. placebo), percent reduction and 95% confidence
 4419 intervals will be presented for each level of the effect. In addition, the effect by time by
 4420 treatment arm interaction p-value, testing the hypothesis that the effect level treatment ratios
 4421 are homogeneous, will be presented.
 4422 For the key secondary efficacy endpoint of $\geq 50\%$ reduction in convulsive seizure frequency,
 4423 patients with a $\geq 50\%$ reduction in seizure frequency will be modelled using logistic
 4424 regression, including stratified age group and treatment arm as covariates. The model will
 4425 also include covariates for each level of the effect being tested (excluding a reference level),
 4426 individually and with interactions with treatment arm. A separate model will be used for
 4427 testing each effect. The number and percent of responders, and odds ratios and 95%
 4428 confidence intervals will be presented for each level of the effect. In addition, the effect by
 4429 treatment arm interaction p-value, testing the hypothesis that the effect level odds ratios are
 4430 homogeneous, will be presented.
 4431 The following effects will be tested:

- 4432 • Age group (2-5 years, 6-12 years and 13-18 years). Note: stratified age group will be
 4433 removed as a covariate for this model.
- 4434 • Sex (Male, Female).
- 4435 • Region (US, Rest of the World).
- 4436 • Clobazam use (Yes, No).
- 4437 • Valproic acid use (Yes, No).
- 4438 • Stiripentol use (Yes, No).
- 4439 • Clobazam use and Stiripentol use (Yes/Yes, Yes/No, No/Yes, No/No).
- 4440 • Levetiracetam use (Yes, No).
- 4441 • Topiramate use (Yes, No).
- 4442 • Baseline average convulsive seizure frequency per 28 days (\leq observed Tertile 1, $>$
 4443 observed Tertile 1 to \leq observed Tertile 2, $>$ observed Tertile 2). The observed tertile
 4444 values will be rounded to the nearest whole number.

- 4445 • Number of concurrent AEDs (<3, ≥3).
- 4446 • Number of prior AEDs (<4, ≥4).
- 4447 • Number of prior and concurrent AEDs (<8, ≥8).

4448 **5.6 Safety Evaluation**

4449 **5.6.1 Exposure to IMP**

4450 Patients are required to take IMP twice daily (morning and evening). The first dose will be
 4451 taken in the clinic on Day 1. The date of final dose in the treatment phase will be recorded
 4452 on the CRF. The date of final dose, for patients who enter the taper period, will be recorded
 4453 on the CRF at the end of taper visit.

4454 The total number of dosing days in the treatment phase will be calculated as:

4455 $(\text{Date of last dose in the treatment phase} - \text{Date of Day 1}) + 1$

4456 The date of last dose in the treatment phase will be obtained from the CRF at the end of
 4457 treatment visit.

4458 Any missed doses during treatment should be recorded on the 'IMP Missed Doses Log' CRF
 4459 page. The number of days with any missed doses and the number of days where IMP was
 4460 not taken in the AM nor PM will be summarized based on data in the treatment phase (Day 1
 4461 to end of treatment visit).

4462 In addition, the number of days in which IMP was taken at least once (AM or PM) will be
 4463 summarized and calculated as:

4464 Total number of dosing days – the number of days where IMP was not taken in the AM nor
 4465 PM

4466 The number of days in which IMP was taken both AM and PM will be summarized and
 4467 calculated as:

4468 Total number of dosing days – the number of days with any missed doses

4469 The above summaries will be presented for all patients and repeated for patients who
 4470 completed the treatment phase.

4471 In addition, the expected daily volume of IMP to be administered during the treatment phase,
 4472 once a patient has titrated to target dose, will be summarized by treatment.

4473 The expected daily volume of IMP will be calculated as:

4474 $2 \times [\text{Weight (kg) at Day 1} \div 10 \text{ and rounded to the nearest 0.1}]$

4475 for patients randomized to the 20 mg/kg/day dose level and:

4476 $2 \times [\text{Weight (kg) at Day 1} \div 20 \text{ and rounded to the nearest 0.1}]$

4477 for patients randomized to the 10 mg/kg/day dose level.

4478 Finally, IMP compliance will be summarized by treatment and calculated as:

4479 $100 \times (\text{Number of days IMP taken at least once} + \text{number of days IMP taken both AM and}$
 4480 $\text{PM}) \div (2 \times \text{day of completion or withdrawal during the treatment period})$

4481 **5.6.2 Adverse Events**

4482 All reported AEs will be classified by system organ class (SOC), preferred term and lower
 4483 level term using Version 17.1 of MedDRA.

4484 Summaries will be presented by treatment group as well as SOC and preferred term.

4485 A treatment emergent AE (TEAE) is defined as an AE with a start date on or after the first
 4486 dose of IMP. If an AE has a partial start date and it is unclear from the partial date (or the
 4487 stop date) whether the AE started prior to or post first dose of IMP then the AE will be
 4488 considered treatment emergent. If the start date of the AE is the same as the date of first
 4489 dose of IMP and the plausible relationship to IMP is marked on the CRF as "Prior to study

4490 medication” then the AE will not be considered treatment emergent.

4491 An AE will be considered treatment-related if the plausibility relationship to IMP is recorded
4492 on the CRF as ‘yes’. If the data on plausibility relationship to IMP is missing then the AE
4493 will be considered treatment-related.

4494 An AE will be considered leading to permanent discontinuation of IMP if the action taken
4495 with IMP is recorded on the CRF as ‘study medication stopped’ or the outcome is recorded
4496 on the CRF as ‘patient died’.

4497 An AE will be considered leading to IMP dose reduction excluding permanent
4498 discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’, ‘dose
4499 reduced temporarily’ or ‘study medication interrupted’.

4500 An AE will be considered leading to temporary IMP dose reduction if the action taken with
4501 IMP is recorded on the CRF as ‘dose reduced temporarily’.

4502 An AE will be considered leading to permanent IMP dose reduction excluding permanent
4503 discontinuation if the action taken with IMP is recorded on the CRF as ‘dose reduced’.

4504 An AE will be considered fatal if the outcome is recorded on the CRF as ‘patient died’.

4505 The following summaries will be generated (counts are by patient unless specified
4506 otherwise):

4507 • Overall summary of AEs, including number of patients reporting each of; TEAEs,
4508 treatment-related TEAEs, TEAEs leading to withdrawal, treatment-related TEAEs
4509 leading to withdrawal, serious TEAEs, treatment-related serious TEAEs.

4510 • Summary of TEAEs.

4511 • Summary of TEAEs by event.

4512 • Summary of treatment-related TEAEs.

4513 • Summary of treatment-related TEAEs by event

4514 • Summary of TEAEs by maximal severity.

4515 • Summary of TEAEs by sex.

4516 • Summary of serious TEAEs.

4517 • Summary of serious TEAEs by event.

4518 • Summary of non-serious TEAEs.

4519 • Summary of non-serious TEAEs by event.

4520 • Summary of treatment-related serious TEAEs.

4521 • Summary of treatment-related serious TEAEs by event.

4522 • Summary of TEAEs leading to permanent discontinuation of IMP.

4523 • Summary of treatment-related TEAEs leading to permanent discontinuation of IMP.

4524 • Summary of TEAEs leading to IMP dose reduction excluding permanent
4525 discontinuation (by resolution and overall).

4526 • Summary of treatment-related TEAEs leading to IMP dose reduction excluding
4527 permanent discontinuation (by resolution and overall).

4528 • Summary of TEAEs leading to temporary IMP dose reduction (by resolution and
4529 overall).

- 4530 • Summary of treatment-related TEAEs leading to temporary IMP dose reduction (by
4531 resolution and overall).
- 4532 • Summary of TEAEs leading to permanent IMP dose reduction excluding permanent
4533 discontinuation (by resolution and overall).
- 4534 • Summary of treatment-related TEAEs leading to permanent IMP dose reduction
4535 excluding permanent discontinuation (by resolution and overall).
- 4536 • Summary of fatal TEAEs.
- 4537 • Summary of TEAEs by time of first onset of AE.
- 4538 • Summary of TEAEs by time to AE resolution.
- 4539 • Summary of TEAEs reported in $\geq 2\%$ of patients (after rounding) in the
4540 GWP42003-P treatment groups and where the incidence is greater than the placebo
4541 treatment group.
- 4542 • List of patients experiencing TEAEs by SOC and preferred term.
- 4543 • Summary of pre-treatment AEs.
- 4544 For the summary of TEAEs by maximal severity, for each patient, the worst severity
4545 recorded by preferred term, SOC and overall will be used for summary purposes. If severity
4546 is missing, the worst case (severe) will be assumed.
- 4547 For summaries by resolution, AEs with an outcome of ‘recovered’ or ‘recovered with
4548 sequelae’ will be summarized as ‘Resolved’ and AEs with an outcome of ‘continuing’,
4549 ‘patient died’ or those with a missing outcome will be summarized as ‘Not resolved’.
- 4550 For the summary of TEAEs by time of first onset of AE, data will be summarized under the
4551 following categories:
- 4552 • Weeks 1–2 (Day 1–14).
- 4553 • Weeks 3–6 (Day 15–42).
- 4554 • Weeks 7–10 (Day 43–70).
- 4555 • Weeks 11–14 (Day 71–98).
- 4556 • >14 weeks (> Day 98).
- 4557 The time to first onset of AE will be calculated for TEAEs as:
4558 $\text{Start date of AE} - \text{Date of first dose of IMP} + 1$
- 4559 If patients have multiple occurrences of an AE then the AE will be counted once for the first
4560 occurrence only. Percentages will be based on the number of patients in the safety analysis
4561 set who have a visit or follow-up call within each time period above.
- 4562 For the summary of TEAEs by time to AE resolution, data will be summarized under the
4563 following categories:
- 4564 • 1 week (≤ 7 days).
- 4565 • 2 weeks (8–14 days).
- 4566 • 3 weeks (15–21 days).
- 4567 • 4 weeks (22–28 days).
- 4568 • >4 weeks (>28 days).
- 4569 • Ongoing (for AEs not resolved).

4570 The time to AE resolution will be calculated for TEAEs as:

4571
$$\text{Stop date of AE} - \text{Start date of AE} + 1$$

4572 If patients have multiple occurrences of an AE then the AE will be counted once for the
4573 occurrence with the longest time to AE resolution. However, if any of the AEs are not
4574 resolved then the AE will be counted once within the ‘Ongoing’ category.

4575 The start and stop day of the AE relative to the first dose of IMP (as recorded on the CRF)
4576 will be calculated as per Section 5.1.2. For partial dates, if it is clear from the partial date
4577 that the start/stop day was prior to the first dose of IMP, then ‘pre’ will be listed, similarly if
4578 it is clear that the event was post the first dose of IMP then ‘post’ will be listed as the
4579 start/stop day as appropriate.

4580 All AEs will be listed. Listings will include the start and stop day of the AE, a flag for
4581 treatment emergence, and limited demographic information about the patient (age, sex, race
4582 and weight at screening). A separate listing will be provided for pre-treatment AEs, serious
4583 AEs and events of special interest (see Appendix 1).

4584 **5.6.3 Clinical Laboratory Evaluation**

4585 **5.6.3.1 Hematology and Biochemistry**

4586 Hematology and biochemistry safety parameters are measured at Visit 1 (screening), Visit 2
4587 (Day 1), Visit 3, Visit 4, Visit 6, Visit 8 (end of treatment) and Visit 9 (end of taper).

4588 Summaries will be presented by treatment group for each laboratory parameter at each visit.
4589 Change from baseline to each post-baseline visit will also be presented.

4590 If values for any of the parameters are below or above the limit of quantification of the assay
4591 (BLQ or ALQ), then they will be included in the summary tables at the BLQ or ALQ
4592 thresholds. However, for estimated creatinine clearance, results >60 are reported only as
4593 ‘>60’. Hence, estimated glomerular filtration rate (eGFR) will be calculated as:

4594 For patients who are ≥ 18 years at screening, the Cockcroft-Gault equation will be used:

4595
$$\text{eGFR (mL/min)} = [(140 - \text{age}) \times \text{weight} \times k] / \text{serum creatinine}$$

4596 where age is measured in years, weight is measured in kg, $k = 1.23$ if male, $k = 1.04$ if
4597 female and serum creatinine is measured in $\mu\text{mol/L}$. eGFR will be indexed to body surface
4598 area (BSA) using the following formula:

4599
$$\text{eGFR (mL/min/1.73m}^2\text{)} = \text{eGFR (mL/min)} \times 1.73/\text{BSA}$$

4600 where BSA is based on the Du Bois and Du Bois formula:

4601
$$\text{weight}^{0.425} \times \text{height}^{0.725} \times 0.007184$$

4602 where weight is measured in kg and height is measured in cm.

4603 For patients who are <18 years at screening, the revised Schwartz estimate will be used:

4604
$$(36.2 \times \text{height}) / \text{serum creatinine}$$

4605 where height is measured in cm and serum creatinine is measured in $\mu\text{mol/L}$. When
4606 available, enzymatic serum creatinine will be used. Otherwise, the Jaffe serum creatinine
4607 will be used. If height or weight is missing at the collection date, then the closest value to
4608 the sample date will be used. If there is more than one height or weight value on the same
4609 day or 2 height or weight values equally distant from the collection date, then the mean will
4610 be used. The eGFR will be summarized separately for each method.

4611 Where laboratory samples are repeated, the baseline value is defined as the final recorded
4612 value prior to the first dose of IMP. If the Visit 2 data are missing then, where possible, the
4613 Visit 1 measurements will be used as baseline.

4614 Shift tables for hematology and biochemistry parameters will be constructed, based upon
4615 normal ranges and GW toxicity limits (See Section 8), to determine the categorical shifts
4616 from baseline to each post-baseline visit. Values will be categorized as ‘Normal’, ‘Low’ or
4617 ‘High’ based on normal ranges and ‘Toxically Low’, ‘Toxically Normal’ or ‘Toxically High’

4618 based on GW toxicity limits.

4619 For eGFR, results will be assigned to the following grades:

- 4620 • Normal: >60 ml/min/1.73 m²
- 4621 • Grade 1: 60 ml/min/1.73 m²
- 4622 • Grade 2: ≥ 30 and <60 ml/min/1.73 m²
- 4623 • Grade 3: ≥ 15 and <30 ml/min/1.73 m²
- 4624 • Grade 4: <15 ml/min/1.73 m²

4625 A separate shift table will be produced for eGFR based upon the above grades to determine
4626 the categorical shifts from baseline to each post-baseline visit.

4627 Scatter plots will be produced for each laboratory parameter presenting the maximum post
4628 baseline result divided by the upper limit of normal (ULN) on the Y-axis, and the baseline
4629 result divided by the ULN on the X-axis. However, for prothrombin international
4630 normalized ratio (INR), both axes will present the raw results rather than dividing by ULN.
4631 An additional table will be produced, summarizing the number of patients meeting the
4632 following criteria:

- 4633 • Alanine aminotransferase (ALT) $> 1 \times$ ULN at baseline
- 4634 • Aspartate aminotransferase (AST) $> 1 \times$ ULN at baseline
- 4635 • AT $> 1 \times$ ULN at baseline
- 4636 • Treatment emergent ALT $> 3 \times$ ULN, $> 5 \times$ ULN and $> 8 \times$ ULN
- 4637 • Treatment emergent AST $> 3 \times$ ULN, $> 5 \times$ ULN and $> 8 \times$ ULN
- 4638 • Treatment emergent AT $> 3 \times$ ULN, $> 5 \times$ ULN and $> 8 \times$ ULN
- 4639 • Treatment emergent AT $> 3 \times$ ULN and either bilirubin $> 2 \times$ ULN or INR > 1.5

4640 where AT is AST or ALT, and treatment emergent is defined as criteria not met at baseline,
4641 but met at any time post-baseline. The above will be summarized overall and for the
4642 following subgroups: Sex (Male, Female).

- 4643 • Valproic acid use (Yes, No).
- 4644 • Clobazam use (Yes, No).
- 4645 • Valproic acid use and Clobazam use (Yes/Yes, Yes/No, No/Yes, No/No).
- 4646 • Patients taking 3 or more current AEDs.
- 4647 • Patients taking 4 or more current AEDs.

4648 A separate table will be produced, by treatment group and visit, presenting the incidence of
4649 patients with urinalysis or blood results indicative of a medical condition at Visit 1 and
4650 indicative of an AE after Visit 1.

4651 All laboratory data will be listed; listings will include limited demographic information
4652 about the patient (age, sex, race and weight at baseline). Abnormal laboratory values will be
4653 listed separately. A further listing will be created for the laboratory reference ranges and
4654 toxicity limits.

4655 **5.6.3.2 Urinalysis**

4656 Urinalysis is assessed, using dipsticks, at the same visits as biochemistry and hematology.

4657 Urinalysis results will be listed only.

4658 **5.6.3.3 Pregnancy Test and Urine THC Screen**

4659 Serum pregnancy test results and urine THC screen results will be summarized by treatment
4660 group and visit.

4661 **5.6.4 Vital Signs, Other Physical Findings and Other Safety Data**

4662 **5.6.4.1 Vital Signs**

4663 Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature and
4664 respiratory rate) are measured at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6,
4665 Visit 8 (end of treatment) and Visit 9 (end of taper).

4666 At Visit 1 and Visit 2, systolic and diastolic blood pressure are collected in the sitting, supine
4667 and standing positions. At all other visits, systolic and diastolic blood pressure are collected
4668 in the sitting position only.

4669 Summaries will be presented by treatment group for each vital sign parameter at each visit.

4670 Change from baseline to each post-baseline visit will also be presented.

4671 A separate table will be produced, by treatment group and visit, presenting the incidence of
4672 patients with vital signs indicative of a medical condition at Visit 1 and indicative of an AE
4673 after Visit 1.

4674 Based on the criteria presented in Section 8, potentially clinically significant changes from
4675 baseline in vital signs measurements and other defined flagged values will be identified at
4676 each visit. The number of patients with a potentially clinically significant change from
4677 baseline will be summarized by parameter, visit and treatment group. The number of
4678 patients with at least one post-baseline flagged vital sign parameter value will be
4679 summarized by parameter, flagged criteria and treatment group.

4680 **5.6.4.2 Electrocardiogram**

4681 An ECG will be performed at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6,
4682 Visit 8 (end of treatment) and Visit 9 (end of taper).

4683 Summaries will be presented by treatment group for ventricular rate, PR interval, QRS
4684 duration, QT interval and QTcB, at each visit. Change from baseline to each post-baseline
4685 visit will also be presented.

4686 A separate table will be produced, by treatment group and visit, presenting the incidence of
4687 patients with an ECG indicative of a medical condition at Visit 1 and indicative of an AE
4688 after Visit 1.

4689 Based on the criteria presented in Section 8, defined flagged values will be identified at each
4690 visit. The number of patients with at least one post-baseline flagged ECG parameter value
4691 will be summarized by parameter, flagged criteria and treatment group.

4692 **5.6.4.3 Physical Examination**

4693 A physical examination will be performed at Visit 1 (screening), Visit 2 (Day 1), Visit 3,
4694 Visit 4, Visit 6, Visit 8 (end of treatment) and Visit 9 (end of taper).

4695 Any relevant findings at screening are included as part of the patient's medical history. Any
4696 changes seen after screening that are indicative of an AE are to be recorded as such on the
4697 AE form and included as part of the AE summaries.

4698 Additionally, height and weight are recorded as part of the physical examination. Height and
4699 weight will be summarized and listed together with the vital signs parameters.

4700 Incidence of patients with a physical examination indicative of a medical condition at Visit 1

4701 and indicative of an AE after Visit 1 will be summarized by treatment group and visit.

4702 **5.6.4.4 Columbia-Suicide Severity Rating Scale (Children's)**

4703 The C-SSRS is completed at Visit 1 (screening), Visit 2 (Day 1), Visit 3, Visit 4, Visit 6, Visit 8 (end
4704 of treatment) and Visit 9 (end of taper), for patients who are 6 years and older and capable of
4705 understanding and answering the questions, in the investigator's opinion. Questions are asked on
4706 suicidal behavior, suicidal ideation and intensity of ideation. At the screening visit, questions are in
4707 relation to lifetime experiences and all subsequent questioning in relation to the last assessment.
4708 The following C-SSRS data will be summarized by treatment group at each visit for patients in the
4709 safety analysis set:

- 4710 • Incidence of the following suicidal ideation:
- 4711 ○ Wish to be dead.
- 4712 ○ Non-specific active suicidal thoughts.
- 4713 ○ Active suicidal ideation with any methods (not plan) without intent to act.
- 4714 ○ Active suicidal ideation with some intent to act, without specific plan.
- 4715 ○ Active suicidal ideation with specific plan and intent.
- 4716 • Incidence of the following suicidal behavior:
- 4717 ○ Actual attempt.
- 4718 ○ Interrupted attempt.
- 4719 ○ Aborted attempt.
- 4720 ○ Preparatory acts or behavior.
- 4721 ○ Suicidal behavior.
- 4722 ○ Completed suicide.

4723 In addition, the number of patients with any suicidality, any suicidal ideation and any suicidal
4724 behavior will be summarized by treatment group at screening, baseline and at any time post-baseline.
4725 Suicidality is defined as at least one occurrence of suicidal behavior or suicidal ideation.

4726 The number of patients experiencing the following, at any time post-baseline, will also be
4727 summarized:

- 4728 • Complete suicidality.
- 4729 • Emergence of suicidal ideation.
- 4730 • Worsening of suicidal ideation.
- 4731 • Emergence of suicidal behavior.

4732 Emergence of suicidal ideation is defined as having no suicidal ideation at baseline and having
4733 reported any type of suicidal ideation at any time post-baseline. Worsening of suicidal ideation is
4734 defined to occur when the most severe suicidal ideation rating at any time post-baseline is more
4735 severe than its rating at baseline. Emergence of suicidal behavior is defined as having no suicidal
4736 behavior at baseline and reporting any type of suicidal behavior at any time post-baseline. If the C-
4737 SSRS was not completed at screening or baseline then the patient will not be included in summaries
4738 of emergence or worsening of suicidal ideation or behavior.

4739 **5.6.4.5 Growth and Development**

4740 IGF-1 levels will be analyzed as part of the clinical laboratory testing. IGF-1 levels will be
4741 summarized on a continuous scale, including change from baseline, by treatment group.
4742 Change from baseline to the end of treatment visit for IGF-1 levels will also be plotted against the
4743 Tanner Stages, weight, and height recorded at baseline.

4744 The pubic hair growth (both sexes), genital (males only) and breast (females only) development of all
 4745 adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the informed consent
 4746 form, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty) will
 4747 be assessed using Tanner Staging. The patients will undergo a discreet physical examination and be
 4748 assigned a value under each category of Pubic Hair Growth (both sexes), Genitals (male patients
 4749 only), and Breasts (female patients only).
 4750 Patients will be examined at Visit 2 (Day 1) and Visit 8 (end of treatment). Once a patient reaches a
 4751 score of V (i.e., 5) the examination need not be performed again.
 4752 Tanner Stages will be summarized on a categorical scale, by treatment group.

4753 **5.6.4.6 Menstruation**

4754 Caregivers will be asked if the female patient is menstruating and details will be recorded as part of
 4755 their medical history (Visit 2); any changes in normal cycles will be captured at Visit 8 (end of
 4756 treatment).
 4757 Menstruation details will be summarized as appropriate, including any changes in normal cycles at
 4758 the end of treatment, by treatment group.

4759 **5.6.4.7 Cannabis Withdrawal Scale (18 Years)**

4760 The CWS is a 19-item scale with each item (withdrawal symptom) measured on a 0–10 NRS (0 =
 4761 Not at all; 5 = Moderately; 10 = Extremely). The patient or their caregiver is asked to record the
 4762 extent to which each withdrawal symptom was experienced in the last 24 hours and also to rate the
 4763 negative impact on normal daily activities (i.e., 2 separate scores are recorded for each item using the
 4764 same 0–10 NRS). Scores are calculated as the sum of the 19 items for each measure, i.e., each
 4765 separate score has a theoretical maximum of 190.
 4766 The CWS will be used at Visit 2, to establish a baseline score, and then again at Visit 9, the safety
 4767 follow-up telephone call on Day 123 and Visit 10 for any patient completing the study or
 4768 withdrawing early. Patients entering the OLE on the day of Visit 8 will continue taking IMP; in this
 4769 instance withdrawal will be evaluated at the end of their participation in the OLE.
 4770 The 2 derived scores, recorded at each visit, will be summarized, on a continuous scale, by treatment
 4771 group. The change from baseline (Visit 2) will also be included.
 4772 If any of the individual items are missing, for each measure, then the corresponding derived score
 4773 will not be calculated.
 4774 The summary will be presented separately for all patients with a completed scale and patients 18
 4775 years of age.

4776 **5.6.4.8 Pediatric Cannabinoid Withdrawal Scale (4–17 Years)**

4777 The PCWS was developed from the 19-item validated CWS (adults) that assesses mood, behavioral
 4778 and physical symptoms associated with cannabis, which was based on the Marijuana Withdrawal
 4779 Checklist. The modified 10-item PCWS was developed from a low literacy version of the CWS.
 4780 Symptoms specific to adult cannabis withdrawal have been removed and the wording has been
 4781 amended to be comprehensible to children of the specified age range.
 4782 Ratings are based on a 4-point scale where 0 = none, 1 = a little bit, 2 = quite a bit, and 3 = a lot.
 4783 This rating scale has been compacted from the original 11-point Likert scale used for the CWS in
 4784 order to simplify the range of options to consider for potential intellectually disabled children. The
 4785 PCWS was designed with epileptic children in mind as a tool to assess the safety of cannabinoid
 4786 medications with respect to the stimulation of cannabinoid withdrawal syndrome when medications
 4787 are withdrawn. As there may be a wide range of intellectual or developmental difficulties in severely
 4788 epileptic children, from no intellectual or developmental impairment to extreme, the PCWS has been
 4789 designed to be administered by a treating clinician, either directly to the child, or to the parent or
 4790 caregiver of the child, reflecting on the child's symptoms within the chosen timeframe.
 4791 A derived score is calculated as the sum of the 10 items and has a theoretical maximum score of 30.
 4792 The PCWS will be used at Visit 2, to establish a baseline score, and then again at Visit 9, the safety
 4793 follow-up telephone call on Day 123 and Visit 10 for any patient completing the study or

4794 withdrawing early. Patients entering the OLE on the day of Visit 8 will continue taking IMP; in this
 4795 instance withdrawal will be evaluated at the end of their participation in the OLE.
 4796 The derived score, recorded at each visit, will be summarized, on a continuous scale, by treatment
 4797 group. The change from baseline (Visit 2) will also be included.
 4798 If any of the individual items are missing, then the derived score will not be calculated.
 4799 The summary will be presented separately for all patients with a completed scale and patients 4–17
 4800 years of age.

4801 **5.7 Other Measures**

4802 **5.7.1 Concomitant Medication**

4803 Medications will be coded using the World Health Organization Drug Dictionary, Version
 4804 June 2014.

4805 A medication will be considered concomitant if it has a start date on or after the first dose of
 4806 IMP or if it was started prior to the first dose of IMP and was ongoing. If a medication has a
 4807 partial or missing start/stop date and it is unclear from the date whether the medication was
 4808 taken after the first dose of IMP then it will be considered concomitant.

4809 For summaries and listings of medications the following approach will be used to determine
 4810 the Anatomical Therapeutic Chemical (ATC) term to be presented:

- 4811 • If coded to level 4 then the level 4 coded term will be presented.
- 4812 • If coding is not performed at level 4 but level 3 coding is present then level 3 coded
 4813 term will be presented.
- 4814 • If coding is not performed at level 3 but level 2 coding is present then the level 2
 4815 coded term will be presented.
- 4816 • If coding is not performed at level 2 but level 1 coding is present then the level 1
 4817 coded term will be presented.

4818 Summaries of each of the following by ATC term and preferred term will be summarized by
 4819 absolute counts (n) and percentages (%):

- 4820 • History of antiepileptic medications;
- 4821 • Concomitant antiepileptic medications;
- 4822 • Concomitant rescue medications; and
- 4823 • Other concomitant medications.

4824 The ATC term, preferred term, reported generic name and reported brand name will be
 4825 listed.

4826 An additional summary table will be produced for concomitant antiepileptic therapies,
 4827 displaying the number and percentage of patients with a vagus nerve stimulation device or
 4828 on a ketogenic diet.

4829 The start day and stop day will be included in the listing according to Section 5.1.2. If the
 4830 date is partial and the exact day is unknown then the text ‘pre’ or ‘post’ will replace the start
 4831 or stop day if it is clear from the partial date that the medication started or stopped prior to or
 4832 after the first dose of IMP.

4833 **5.7.2 Plasma Concentrations of Concomitant Antiepileptic Drugs**

4834 Blood sampling for AEDs will be performed at Visit 2 (Day 1), Visit 4, Visit 6 and Visit 8
 4835 (end of treatment). For each AED, plasma concentrations will be summarized by treatment

4836 group at each visit for patients in the safety analysis set.

4837 **5.7.3 Caregiver Impression of Investigational Medicinal Product Palatability**

4838 The caregiver's impression of palatability of the IMP will be assessed at Visit 8 (end of treatment).

4839 The Caregiver will be asked the following question to be rated on a 5-point scale:

- 4840
- Overall, how acceptable did your child find the study medication?

4841 The possible responses are: Liked it a lot; Liked it; Neither liked nor disliked it; Didn't like it; Didn't
4842 like it at all.

4843 The caregiver's impression of palatability of the IMP will be summarized, on a categorical scale, by
4844 treatment group.

4845 **5.7.4 Study Medication Use and Behavior Survey**

4846 This form consists of 18 questions regarding the use of the IMP. The trained investigator or
4847 study coordinator will complete this survey as an interview with the patient/caregiver at the
4848 final dosing visit (Visit 8 or Visit 9, as applicable).

4849 The form will be completed for all patients 12 years of age and older in the study.

4850 Each question will be summarized, on a categorical scale, by treatment group. Percentages
4851 will be based on the number of patients completing the survey, in each treatment group. The
4852 summary will be presented separately for all patients with a completed form and patients 12
4853 years of age and older.

4854 **5.7.5 Supplemental Drug Accountability Form**

4855 This form consists of 7 questions regarding various aspects of drug accountability and patient usage.
4856 It is completed as part of an interview with the patient/caregiver when a triggering drug
4857 accountability discrepancy is identified.

4858 The triggering drug accountability discrepancies are as follows:

- 4859
- Missing bottle(s).
 - Compliance issues where one or more bottles are used compared to what was the expected
4860 use, according to the IVRS report and paper diary.
 - Returned IMP supply with evidence of tampering.
 - Greater than the target daily dose as recorded in the IVRS report and paper diary.

4864 The number of patients completing a form will be summarized by treatment group. The summary
4865 will be presented separately for all patients with a completed form and patients 12 years of age and
4866 older.

4867 **5.7.6 Supplemental Adverse Event Form**

4868 This form consists of 15 questions regarding the AE and use of IMP. It is completed as part of an
4869 interview with the patient/caregiver when a triggering AE of interest is reported.

4870 The categories for triggering AEs of interest are:

- 4871
- Euphoria or inappropriate elation.
 - Inappropriate laughter or exhilaration.
 - Mood changes.
 - Drunk, high or intoxicated.
 - Hallucinations (visual or auditory), dissociations, disorientation, agitation.
 - Disturbance in cognition, memory, or attention.
- 4876

- 4877 • Drug abuse.
- 4878 • Drug withdrawal or drug withdrawal syndrome.
- 4879 • Addiction.
- 4880 • Overdose.
- 4881 • Misuse of IMP.
- 4882 • Thoughts of suicide, attempted suicide or suicide.

4883 The number of patients completing a form will be summarized by treatment group. The summary
 4884 will be presented separately for all patients with a completed form and patients 12 years of age and
 4885 older.

4886 **5.7.7 Site Classification Form**

4887 The investigator reviews the applicable Supplemental Adverse Event Form or Supplemental
 4888 Drug Accountability Form, and then completes a Site Classification Form. For each
 4889 Supplemental Adverse Event Form or Supplemental Drug Accountability Form completed,
 4890 there should be an associated Site Classification Form.

4891 The Site Classification Form requires the investigator to assign the finding to an appropriate
 4892 classification and then to also assign the possible relationship to the IMP. The investigator is
 4893 also required to indicate the level of the certainty of the classification.

4894 The number of patients completing a form and the possible relationship and level of the
 4895 certainty for each category will be summarized, on a categorical scale, by treatment group.
 4896 If more than one form is completed for a particular patient then they will be summarized
 4897 under each category for all forms. However, if more than one form is completed with and
 4898 assigned to the same category, then 'related' would be used over 'not related' and the highest
 4899 level of certainty will be used for the corresponding chosen relationship. The summary will
 4900 be presented separately for all patients with a completed form and patients 12 years of age
 4901 and older.

4902 **5.7.8 IVRS Compliance**

4903 The number of unreported days in IVRS, during the baseline and treatment periods, will be
 4904 summarized, on a continuous and categorical scale, by treatment group for patients in the ITT
 4905 analysis set. For the summary on a continuous scale, the lower and upper quartiles will also be
 4906 presented.

4907 The percentage IVRS compliance, during the baseline and treatment periods, will also be
 4908 summarized, on a continuous and categorical scale, and calculated as:

4909
$$[\text{Number of reported days in IVRS} \div (\text{Number of reported days in IVRS} + \text{Number of unreported days in IVRS})] \times 100$$

 4910

4911 **5.7.9 Meal Times**

4912 Patient meal times will be recorded for the day prior to and the day of Visit 2 (Day 1) and
 4913 Visit 8 (end of treatment). Meal times will be listed only.

4914

4915 **5.8 Changes in the Conduct of the Study or Planned Analysis**

4916 The identification of 3 key secondary endpoints and the hierarchical testing procedure were not
4917 defined in the protocol, but have been included in the SAP prior to unblinding.

4918 Upon blinded review of IVRS data for the number of convulsive seizures greater than 30 minutes in
4919 duration and the number of non-convulsive seizures greater than 30 minutes in duration, it was
4920 determined that there were insufficient numbers of patients reporting these seizures to perform
4921 analyses planned in the protocol.

4922 Upon blinded review of the number of patients with inpatient epilepsy-related hospitalizations, it was
4923 determined that there were insufficient numbers of patients to perform analyses planned in the
4924 protocol.

4925 The protocol included changes from baseline in usage of rescue medication as an efficacy endpoint.
4926 However, due to inconsistencies in the collection of this data, no analyses are proposed.

4927 The endpoint of number of patients experiencing a >25% worsening, -25 to +25% no change, 25-
4928 50% improvement, 50-75% improvement or >75% improvement in convulsive seizures from
4929 baseline has been updated to the following:

- 4930 • Number of patients experiencing a >25% increase, ≥ 0 to $\leq 25\%$ increase, >0 to <25%
4931 reduction, ≥ 25 to <50% reduction, ≥ 50 to <75% reduction or $\geq 75\%$ reduction in convulsive
4932 seizures from baseline.

4933 **6. References**

4934 ¹ Rubin DB: Multiple imputation for nonresponse in surveys. John Wiley & Sons, New
4935 York 1987.

4936 ² Mogg R, Mehrotra DV (2007). Analysis of antiretroviral immunotherapy trials with
4937 potentially non-normal and incomplete longitudinal data. Stat Med. 2007;26(3): 484-497.

4938 ³ Sabaz M, Cairns D, Lawson J, Nheu, N, Bleasel A, Bye A. Data instructions for the
4939 quality of life in childhood epilepsy questionnaire – parent form.

4940

4941

4942 **7. Amendments**

4943 Notable changes to the SAP that were completed prior to unblinding, are given below.
4944 Minor changes, clarifications and corrections are not listed.

Date	Section	Description of Change
------	---------	-----------------------

4945
4946

4947 **8. Attachments and Appendices**4948 **Appendix 1 Adverse Events of Special Interest – Abuse Liability**

Withdrawal	Drug withdrawal convulsions
	Drug withdrawal headache
	Drug withdrawal maintenance therapy
	Drug withdrawal syndrome
	Drug withdrawal syndrome neonatal
	Drug rehabilitation
	Rebound effect
	Steroid withdrawal syndrome
	Withdrawal arrhythmia
	Withdrawal syndrome
Drug abuse and dependence	Dopamine dysregulation syndrome
	Drug abuse
	Drug abuser
	Drug dependence
	Drug dependence, antepartum
	Drug dependence, postpartum
	Intentional drug misuse
	Intentional overdose
	Maternal use of illicit drugs
	Neonatal complications of substance abuse
	Polysubstance dependence
	Substance abuse
	Substance abuser
	Accidental overdose
	Dependence
	Disturbance in social behaviour
	Drug administered at inappropriate site
	Drug detoxification
	Drug diversion
	Drug level above therapeutic
	Drug level increased
	Drug screen
	Drug screen positive
	Drug tolerance
	Drug tolerance decreased
	Drug tolerance increased
	Medication overuse headache
	Narcotic bowel syndrome
	Needle track marks
	Overdose
	Prescribed overdose
	Prescription form tampering
	Substance use
Substance-induced mood disorder	
Substance-induced psychotic disorder	
Toxicity to various agents	

4949

4950

4951 **Appendix 2 Ranges for Clinically Significant Changes and Other Defined Flagged**
 4952 **Values in Vital Signs**

4953 The range of values that will be used to identify clinically significant changes in vital signs
 4954 parameters (See Section 5.6.4.1) are presented in Table 8.

4955 **Table 8 Ranges for Potentially Clinically Significant Changes in Vital Signs**
 4956

Vital Sign	Range
Sitting Systolic BP	Change: < -20, > 20
Sitting Diastolic BP	Change: < -10, > 10
Pulse Rate	Change: < -10, > 10
Weight	Percent Change: $\leq -7, \geq 7$

4957
 4958 Defined flagged values that will be used to identify low or high vital signs parameters (See Section
 4959 5.6.4.1) are presented in Table 9.

4960 **Table 9 Other Defined Flagged Values for Vital Signs**
 4961

Vital Sign	Flag
Sitting Systolic BP	< 90, > 140, > 160
Sitting Diastolic BP	< 50, > 90, > 100
Pulse Rate	< 60, > 100
Temperature	> 38.0, < 36.0
Respiratory Rate	< 12, > 20

4962
 4963 **Appendix 3 Defined Flagged Values in ECG Parameters**

4964 Defined flagged values that will be used to identify low or high ECG parameters (See Section
 4965 5.6.4.2) are presented in Table 10.

4966 **Table 10 Defined Flagged Values for ECG Parameters**
 4967

ECG Parameter	Flag
QTc	> 450, > 480, > 500

4968
 4969 **Appendix 4 Toxicity Criteria for Laboratory Parameters**

4970 The toxicity criteria that will be used to identify abnormal laboratory parameters are presented in
 4971 Table 11 and Table 12.

4972 **Table 11 Toxicity Criteria for Biochemistry Parameters**

Parameter	Toxicity Decrease	Toxicity Increase
Chloride	$\leq 0.96 \times LL$	$\geq 1.04 \times UL$
Calcium	$\leq 0.89 \times LL$	$\geq 1.16 \times UL$
Sodium	$\leq 0.96 \times LL$	$\geq 1.04 \times UL$
Potassium	$\leq 0.90 \times LL$	$\geq 1.10 \times UL$
Glucose (mmol/L)	≤ 3.2	≥ 16
Phosphate	$\leq 0.79 \times LL$	
Cholesterol	$\leq 0.85 \times LL$	$\geq 1.6 \times UL$
AST		$\geq 3 \times UL$
ALT		$\geq 3 \times UL$
Lactate Dehydrogenase		$\geq 2.6 \times UL$
Alkaline phosphatase		$\geq 2 \times UL$

Parameter	Toxicity Decrease	Toxicity Increase
Gamma GT		≥2.6xUL
Bilirubin		>2xUL
Albumin	≤0.84xLL	
Total protein	≤0.84xLL	≥1.16xUL
Urea		≥2.6xUL
Blood urea nitrogen		≥2.6xUL
Creatinine		≥2.6xUL
Uric acid		≥1.16xUL

4973 UL = upper limit of reference range LL = lower limit of reference range

4974

4975

Table 12 Toxicity Criteria for Hematology Parameters

Parameter	Toxicity Decrease	Toxicity Increase
Hemoglobin (g/dL)	≤9.4	
Hematocrit (%)	≤28	
Red cell count	≤0.84xLL	
Mean corpuscular volume	≤0.84xLL	≥1.11xUL
Mean corpuscular hemoglobin	≤0.84xLL	
Mean corpuscular hemoglobin concentration	≤0.84xLL	
Platelets (x10 ⁹ /L)	≤74	
Prothrombin time		>1.5xUL
Prothrombin international normalized ratio		>1.5
Total white blood cell count (x10 ⁹ /L)	≤2.9	≥21
Total neutrophil count (x10 ⁹ /L)	≤1.36	≥14.7
Segmented neutrophil count (x10 ⁹ /L)	≤0.75	≥12.3
Eosinophils (x10 ⁹ /L)		≥1.5
Basophils (x10 ⁹ /L)		≥0.31
Monocytes (x10 ⁹ /L)		≥2.1
Lymphocytes (x10 ⁹ /L) for patients <18 years (auto hematology)	≤1.0	
Lymphocytes (x10 ⁹ /L) for patients <18 years (manual hematology)	≤0.2	
Lymphocytes (x10 ⁹ /L) for patients ≥18 years	≤0.2	

4976 UL = upper limit of reference range LL = lower limit of reference range

4977

4978 **Appendix 5 List of Tables, Listings and Figures**

4979 Lists of the tables, listings and figures to be provided are given below in Table 13, Table 14
 4980 and Table 15, respectively.

4981 **Table 13 List of Tables**

Table Number	Title	Analysis Set
Table 1.1.1	Summary of Patient Disposition – Number of Patients Screened and Randomized by Site	All Screened Patients
Table 1.1.2	Summary of Patient Disposition – Number of Patients Screened and Randomized by Country	All Screened Patients
Table 1.2	Summary of Patient Disposition – Reasons for Screen Failure	All Screened Patients
Table 1.3.1	Summary of Patient Disposition – Numbers of Patients Randomized, Withdrawn or Completed the Treatment Period by Site	All Randomized Patients
Table 1.3.2	Summary of Patient Disposition – Numbers of Patients Randomized, Withdrawn or Completed the Treatment Period by Country	All Randomized Patients
Table 1.4	Summary of Overall Patient Disposition	All Randomized Patients
Table 2.1	Summary of Important Protocol Deviations	All Randomized Patients
Table 2.2	Summary of Analysis Sets	All Randomized Patients
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Table 3.2.3	Summary of Baseline Characteristics	PP Analysis Set
Table 4.1	Summary of Dravet Syndrome History	Safety Analysis Set
Table 4.2.1	Summary of Seizure Types No Longer Occurring	Safety Analysis Set
Table 4.2.2	Summary of Current Seizure Types	Safety Analysis Set
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Table 5.1	Summary of Previous Significant Non-Epilepsy Medical or Surgical History Now Resolved	Safety Analysis Set
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Table 6.1	Summary of History of Antiepileptic Medications	Safety Analysis Set
Table 6.2	Summary of Concomitant Antiepileptic Therapies	Safety Analysis Set
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Table 7.1	Summary of Treatment Compliance	Safety Analysis Set
Table 7.2	Summary of IVRS Compliance	ITT Analysis Set
Table 8.1.1	Summary of Convulsive Seizure Frequency	ITT Analysis Set
Table 8.1.2	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods	ITT Analysis Set
Table 8.2.1.1	Summary of Convulsive Seizure Frequency	PP Analysis Set
Table 8.2.1.2	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods	PP Analysis Set
Table 8.2.2	Analysis of Percentage Change from Baseline in Convulsive Seizure Frequency During the Treatment Period – Wilcoxon Rank-Sum Test	ITT Analysis Set

Table Number	Title	Analysis Set
Table 8.2.3	Analysis of Percentage Change from Baseline in Convulsive Seizure Frequency During the Treatment Period – Rank ANCOVA	ITT Analysis Set
Table 8.2.4	Analysis of Convulsive Seizure Frequency During the Treatment Period – Log-transformed ANCOVA	ITT Analysis Set
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Table 8.2.6	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and the Maintenance Periods	ITT Analysis Set
Table 8.2.7	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods After Imputing Unreported Days in IVRS	ITT Analysis Set
Table 8.2.8	Analysis of Percentage Change from Baseline in Convulsive Seizure Frequency During the Treatment Period After Multiple Imputation to Account for MNAR – Wilcoxon Rank-Sum Test	ITT Analysis Set
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Table 8.2.9.2	Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods	Safety Analysis Set
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Table 9.1.1.2	Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Treatment Periods	ITT Analysis Set
Table 9.1.2.1	Summary of Total Seizure Frequency	PP Analysis Set
Table 9.1.2.2	Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Treatment Periods	PP Analysis Set
Table 9.1.3	Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Maintenance Periods	ITT Analysis Set
Table 9.2.1	Summary and Analysis of Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom During the Treatment Period	ITT Analysis Set
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Table 9.2.3	Summary and Analysis of Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom During the Maintenance Period	ITT Analysis Set
Table 9.3.1.1	Summary of the Caregiver Global Impression of Change	ITT Analysis Set
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Table 9.3.2.2	Analysis of the Caregiver Global Impression of Change	PP Analysis Set
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Table 9.4.2	Summary of Occurrence of Status Epilepticus When Not Experienced During the Baseline Period	ITT Analysis Set
Table 9.5.1	Summary and Analysis of Total Seizure Treatment Responders and Total Seizure Freedom During the Treatment Period	ITT Analysis Set
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Table Number	Title	Analysis Set
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Table 9.7.3.3	Summary and Analysis of Atonic Seizure Treatment Responders and Atonic Seizure Freedom During the Treatment Period	ITT Analysis Set
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Table 9.7.4.1.1	Summary of Clonic Seizure Frequency	ITT Analysis Set
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Table Number	Title	Analysis Set
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4983 **Table 14 List of Listings**

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Listing 1.3	Inclusion/Exclusion Criteria Not Met	Safety Analysis Set
Listing 1.4	Visit Dates	Safety Analysis Set
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Listing 4.1.2	Dravet Syndrome History – Part 2	Safety Analysis Set
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