# AN OPEN-LABEL, SINGLE-ARM STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF ADJUNCTIVE CANNABIDIOL ORAL SOLUTION (GWP42003-P) IN PARTICIPANTS WITH TUBEROUS SCLEROSIS COMPLEX (1 MONTH TO < 2 YEARS OF AGE), DRAVET SYNDROME (1 YEAR TO < 2 YEARS OF AGE), OR LENNOX-GASTAUT SYNDROME (1 YEAR TO < 2 YEARS OF AGE) WHO EXPERIENCE INADEQUATELY-CONTROLLED SEIZURES.

**Study Code: GWEP17005**

**EU CTR Number: 2023-505851-33-00**

# CLINICAL PROTOCOL

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**Investigator Agreement**

I have read the attached clinical protocol titled "An Open-label, Single-Arm Study to Assess the Safety, Pharmacokinetics, and Efficacy of Adjunctive Cannabidiol Oral Solution (GWP42003-P) in Participants with Tuberous Sclerosis Complex (1 Month to < 2 Years of Age), Dravet Syndrome (1 Year to < 2 Years of Age), or Lennox-Gastaut Syndrome (1 Year to < 2 Years of Age) who Experience Inadequately-controlled Seizures" and agree to abide by all provisions set forth therein.

I agree to comply with applicable regulatory requirement(s); the United States (US) Food and Drug Administration (FDA) regulations relating to good clinical practice (GCP) and clinical studies, and subsequent applicable regulatory/statutory instruments, or the International Council for Harmonisation Tripartite Guidelines for GCP where the EU Clinical Trials Register and EU GCP Directive do not apply, and to complete Form FDA 1572, if required. I accept responsibility for the overall medical care of participants during the study and for all study-related medical decisions.

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

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

Site No: _____

Print name: _____ Date: _____

Principal investigator (DD Month YYYY)

Signature: _____

Sponsor signatory

Print name: _____ Date: _____

Clinical physician (DD Month YYYY)

Signature: _____

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**Amendment 6**

**Overall Rationale for the Amendment:**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and EU Regulation No 536/2014. Although there is no significant impact on the safety or physical/mental integrity of participants nor the scientific value of the study, as the additional neurodevelopmental assessment have been added under the primary endpoint along with the other minor changes, the amendment has been classified as substantial.

Specific updates incorporated into Amendment 6.0 are listed below.

| Section # and Name | Description of Change | Brief Rationale |
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Abbreviations: CBD-OS = cannabidiol oral solution; CGIC = Clinician Global Impression of Change; CGIS = Clinician Global Impression of Severity; COVID-19 = Coronavirus disease 2019; EOT = end of treatment; EU = European Union; EU CTR = European Union Clinical Trial Register; GW = GW Research Ltd; ITQOL = Infant and Toddler Quality of Life Questionnaire; SAP = statistical analysis plan; SUSAR = serious unexpected serious adverse reaction; TSC = tuberous sclerosis complex; VEEG = video electroencephalogram; UK = United Kingdom.

# 1. PROTOCOL SYNOPSIS

<table>
<tr><td>Study Title</td><td colspan="2">An Open-label, Single-arm Study to Assess the Safety, Pharmacokinetics, and Efficacy of Adjunctive Cannabidiol Oral Solution (GWP42003-P) in Participants with Tuberous Sclerosis Complex (Age 1 Month to < 2 Years of Age), Dravet Syndrome (1 Year to < 2 Years of Age), or Lennox-Gastaut Syndrome (1 Year to < 2 Years of Age) who Experience Inadequately-controlled Seizures</td></tr>
<tr><td>Clinical Study Type</td><td colspan="2">Phase 3</td></tr>
<tr><td>Indication</td><td colspan="2">Seizures in participants with tuberous sclerosis complex (TSC), Dravet syndrome (DS), or Lennox-Gastaut syndrome (LGS)</td></tr>
<tr><td>Objectives and Endpoints</td><td>Primary Objectives</td><td>Primary Endpoints</td></tr>
<tr><td></td><td>To evaluate the safety and tolerability of adjunctive GWP42003-P assessed during the 52-week treatment period.</td><td>The safety profile of adjunctive GWP42003-P will be assessed by measuring:<ul><li>Adverse events (AEs) (frequency, type, and severity).</li><li>Vital signs.</li><li>Physical examination.</li><li>12-lead electrocardiogram (ECG).</li><li>Clinically significant changes in laboratory parameters.</li><li>Emergence of new seizure types as recorded by AE reporting.</li><li>Comprehensive neurodevelopmental assessment.</li></ul></td></tr>
<tr><td></td><td>To investigate the exposure of GWP42003-P and its major metabolites following multiple doses of GWP42003-P.</td><td>Trough, 3-hour and 6-hour postdose plasma concentrations of GWP42003-P and its major metabolites following multiple doses of GWP42003-P.</td></tr>
<tr><td></td><td>To evaluate the efficacy of GWP42003-P in reducing the frequency of indication-specific countable seizures.</td><td>Percentage change from baseline in indication-specific* countable seizures (average per 28 days) as recorded by caregivers in seizure diaries at Week 12, every 4 weeks thereafter, and during the 4-week period prior to end of treatment (EOT).<br>*Focal/generalised seizures (TSC), drop seizures (LGS), or convulsive seizures (DS).</td></tr>
<tr><td></td><td>Secondary Objectives</td><td>Secondary Endpoints</td></tr>
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| | To evaluate the efficacy of GWP42003-P in reducing the frequency of total countable seizures. | Measurements of total countable seizures (average per 28 days) as recorded by caregivers on seizure diaries at Week 12, every 4 weeks thereafter, and during the 4-week period prior to EOT will be used to determine the following endpoints:<br>• Number and percentage of participants considered treatment responders, defined as those with a ≥ 50% reduction from baseline in total countable seizures.<br>• Categorical percentage change from baseline to EOT in total countable seizures as follows:<br>o > 25% (increase);<br>o ≥ 0% to ≤ 25% (increase);<br>o > –25% to < 0% (reduction);<br>o > –50% to ≤ –25% (reduction);<br>o > –75% to ≤ –50% (reduction);<br>o ≤ –75% (reduction).<br>• Seizure freedom, defined as 100% reduction from baseline in total countable seizures. |
| | To assess the retention of participants receiving GWP42003-P. | Percentage of participants still taking GWP42003-P at Week 12 and every 4 weeks thereafter. |
| | **Exploratory Objectives** | **Exploratory Endpoints** |
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| Study Design | • This is a phase 3, multicentre, open-label, single-arm study to evaluate the safety, PK, efficacy, and exploratory QoL of adjunctive GWP42003-P in participants < 2 years of age with TSC, DS, or LG. Enrolment will be stratified via the Randomisation and Trial Supply Management (RTSM) to ensure the study includes at least 5 participants each (aged 1 to < 2 years of age) with LGS and DS and 8 participants (4 participants < 1 year of age and 4 participants aged 1 to < 2 years of age) with TSC in order to achieve 18 evaluable participants.<br>• The study duration will be up to approximately 62 weeks, including a 4-week screening/baseline period, a 52-week dose optimisation period (which includes a fixed 2-week titration period followed by flexible dose optimisation), a 10-day taper period, and a safety follow-up period (4 weeks after the end-of-taper visit). Throughout the study, participants should complete all visits and assessments as outlined in the Schedule of Activities (SoA). After the informed consent form (ICF) has been signed by the parent(s)/legally authorised representative (LAR), participants will be considered enrolled and enter the screening/baseline period (Visit 1 and Visit 2 [phone visit]). Participants can be rescreened once, at the discretion of the investigator and following approval from the medical monitor. Rescreened participants will be assigned a new participant number and all screening assessments will be repeated.<br>• Following enrolment, dose adjustments to concomitant antiseizure medications (ASMs) should not be made without prior discussion with and approval by the medical monitor. All ASM dose adjustments must be captured within the electronic case report form (eCRF).<br>• Starting at Visit 3, participants who continue to meet eligibility criteria will initiate the 52-week treatment period with the study intervention (GWP42003-P) as adjunctive therapy (i.e., in addition to their current ASM regimen). The study intervention will be taken orally or with a gastric or nasogastric tube (G-or NG-tube) twice a day (b.i.d.) (e.g., morning and evening) at about the same time each day, consistently with or without food. The time of GWP42003-P administration in relation to food should be kept consistent throughout the study. During the first 2 weeks of treatment (i.e., the fixed titration period), participants should begin titrating GWP42003-P at a rate of 5 mg/kg/week, reaching the target dose level of 10 mg/kg/day (unless the participant cannot tolerate this dose). |

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| | • Starting at Visit 5, after titrating to the target dose level (10 mg/kg/day), investigators will have the option to titrate a participant's dose no more rapidly than 5 mg/kg (≤ 2.5 mg/kg b.i.d.) every 7 days, up to a maximum dose of 20 mg/kg/day (for LGS and DS) or 25 mg/kg/day (for TSC), as recommended in Section 8.1.2 and based on the participant's individual response and tolerability. The investigator will determine if additional dose adjustments are warranted during scheduled or unscheduled visits throughout the remainder of the 52-week treatment period.<br>• If a participant experiences tolerability issues related to the study intervention or an AE occurs at any time during the 52-week treatment period, the investigator may consider temporarily or permanently reducing the current dosage, following discussion with the medical monitor. Doses may be decreased below the target dose level (i.e., < 10 mg/kg/day) based on safety and tolerability (refer to Section 8.1.2). Where possible, participants should be encouraged to return to the target dose level (10 mg/kg/day). Investigators should regularly monitor a participant's response to treatment and re-evaluate the need for adjustments to dosage (i.e., increase, maintain, or decrease) at the next study visit, if applicable.<br>• In general, doses should not be adjusted within the 3 days prior to PK study visits (as specified in the Schedule of Activities (SoA; APPENDIX 1), unless clinically indicated for safety. If a dose adjustment is needed during the 3 days prior to a PK study visit, the PK study visit should be rescheduled to occur > 3 days after the dose adjustment. Doses may be adjusted during PK study visits after all PK samples have been collected. The rationale for any dosage changes will be documented in the appropriate eCRF.<br>• Participants will continue study intervention treatment until the EOT visit, after which they will initiate a taper period to titrate off the study intervention at home. The taper period will last 10 days and end with the end-of-taper visit. A safety follow-up visit (phone call or visit) will occur 4 weeks after the end-of-taper visit (i.e., 4 weeks after the last dose of the GWP42003-P).<br>• If a participant discontinues the study intervention or study prematurely (i.e., before the EOT visit), the participant should be encouraged to complete an early termination (ET) visit as soon as possible, followed by a 10-day taper period if clinically indicated (i.e., unless the participant must discontinue treatment due for reasons related to safety and tolerability). A safety follow-up visit (phone call or visit, if needed) will occur 4 weeks after the participant's last dose of GWP42003-P. |
| Sample Size | Up to 27 participants will be assigned to receive the study intervention in order to achieve 18 evaluable participants. |
| Summary of Participant | **Inclusion Criteria**<br>For inclusion in the study, participants must fulfil ALL of the following criteria: |

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| Eligibility Criteria | 6.1.1 Participants with TSC (1 month to < 2 years of age), or DS (1 year to < 2 years of age), or LGS (1 year to < 2 years of age) within the specified age range at the time of initial informed consent.<br>6.1.2 Participants with TSC must have a diagnosis per the 2012 International Tuberous Sclerosis Complex Consensus Conference (APPENDIX 3)(Northrup 2013). Participants with LGS or DS must have a diagnosis that is consistent with International League Against Epilepsy (ILAE) guidelines and confirmed by ESCI (Specchio 2022, Zuberi 2022).<br>6.1.3 Participants who have uncontrolled seizures, and who are currently receiving 1 or more ASMs.<br>6.1.4 Parent(s)/LAR is/are willing and able to give informed consent for participation in the study.<br>6.1.5 Parent(s)/LAR is/are willing and able (in the investigator's opinion) to comply with all study requirements (including accurate electronic patient reported outcome [ePRO] diary completion).<br>6.1.6 Caregiver completes at least 75% of ePRO and paper seizure diary entries during the 28 days of the screening/baseline period (≥ 21 days of entries).<br>6.1.7 A suitable VEEG, as available in the medical records, within 1 year of Visit 1. When a historical VEEG is not available, and if clinically indicated and appropriate (due to uncertainties or new seizures), a VEEG will be completed and read to confirm diagnosis prior to Visit 3. All VEEGs are to be read at baseline by the investigator and by an independent reviewer.<br>• A suitable VEEG meets all the following criteria:<br>i. Multichannel (minimum 8-channel)<br>ii. Prolonged continuous recording up to 24 hours<br>iii. Completed within 1 year of Visit 1<br>iv. Consistent with the participant's current seizures (in the investigator's opinion)<br>v. Can be reviewed by the investigator and an independent reviewer prior to Visit 3<br>vi. Consistent with a diagnosis of inadequately -controlled seizures<br>6.1.8 Currently taking ≥ 1 ASMs at a dose that remains stable 2 weeks prior to Visit 3 and during the treatment period. Where required for participant safety, adjustments of concomitant ASM(s) or addition of new ASM may be permitted following discussion with the medical monitor.<br>• Adrenocorticotropic hormone (ACTH) or high dose corticosteroids for the treatment of infantile/epileptic spasms (IS/ES) are counted as ASMs.<br>6.1.9 Has seizures that are not adequately controlled through their current ASMs, defined as ≥ 1 seizure reported on the seizure diary during the screening/baseline period. |

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| | 6.1.10 Parent(s)/LAR is/are willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.<br>6.1.11 Parent(s)/LAR is/are willing to allow the participant's primary care practitioner (if they have one) and consultant (if they have one) to be notified of participation in the study if the primary care practitioner/consultant is different from the investigator.<br>**Exclusion Criteria**<br>The participant may not enter the study if ANY of the following apply:<br>6.2.1 Has clinically significant unstable medical condition other than epilepsy.<br>6.2.2 Has had clinically significant symptoms or a clinically significant illness within the 4 weeks prior to Visit 1, other than epilepsy, which in the opinion of the investigator could affect seizure frequency.<br>6.2.3 Has undergone general anaesthesia within 4 weeks prior to Visit 1.<br>6.2.4 Has undergone surgery for epilepsy within 6 months prior to Visit 1 or has plans to undergo surgery for epilepsy during the study.<br>6.2.5 Has taken felbamate for < 1 year prior to Visit 1.<br>6.2.6 Is < 1 year of age and taking valproic acid.<br>6.2.7 Has tumour growth which, in the opinion of the investigator, could affect participant safety.<br>6.2.8 Has clinically significant abnormal laboratory values, in the investigator's opinion, at screening/baseline.<br>6.2.9 Has clinically significant abnormalities in the ECG measured at screening/baseline.<br>6.2.10 Has any concurrent cardiovascular conditions that will, in the investigator's opinion, interfere with the ability to assess their ECGs.<br>6.2.11 Has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the study intervention such as sesame seed oil.<br>6.2.12 Has significantly impaired hepatic function prior to Visit 3, defined as:<br>• Serum alanine aminotransferase (ALT) **or** aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) **and** (total bilirubin [TBL] > 2 × ULN **or** international normalised ratio [INR] > 1.5).<br>• Serum ALT or AST > 5 × ULN.<br>• Serum ALT or AST > 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).<br>• Elevated ALT or AST should be discussed with the medical monitor prior to Visit 3; the medical monitor may allow for a confirmatory redraw prior to Visit 3. |

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| | 6.2.13 Has received another study intervention within 4 weeks prior to Visit 1 or plans to take another study intervention during the study.<br>6.2.14 Caregiver is currently giving or has given recreational or medicinal cannabis, cannabinoid-based medications (including Sativex) or cannabidiol (CBD; including Epidiolex/Epidyolex [GWP42003-P]) to the participant within the 4 weeks prior to Visit 1 **or** is unwilling to abstain from doing so for the duration of the study.<br>6.2.15 Mother (if breastfeeding) is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex) or CBD (including Epidiolex/Epidyolex [GWP42003-P]) within the 4 weeks prior to Visit 1 **or** is unwilling to abstain from doing so for the duration of the study.<br>6.2.16 Has any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the participant, other participants, or site staff at risk because of participation in the study, may influence the result of the study, or may affect the participant's ability to take part in the study.<br>6.2.17 Any clinically significant abnormalities identified following a physical examination of the participant that, in the opinion of the investigator, would jeopardize the safety of the participant if they took part in the study.<br>6.2.18 Has previously been enrolled into this study.<br>6.2.19 Has plans to travel outside their country of residence during the study, unless the participant has confirmation that the study intervention is permitted in the destination country, and all stops along the way. |
| Criteria for Withdrawal | **Discontinue Study Intervention:**<br>• Parent(s)/LAR may decline to continue participating in study intervention and/or other protocol-required therapies or procedures at any time during the study.<br>• Parent(s)/LAR who choose to discontinue participation in study intervention and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, and in agreement with the sponsor, the participants should remain in the study to ensure safety surveillance and/or collection of outcome data.<br>• The investigator is to discuss with the participant's parent(s)/LAR the appropriate processes for discontinuation from study intervention or other protocol-required therapies. These participants should complete an early termination (ET) visit followed by 10-day taper period if clinically indicated (i.e., if no safety reasons prohibit continued treatment; refer to Section 8.1.2). A safety follow-up visit should be conducted 4 weeks after the participant's last dose of GWP42003-P. The investigator must discuss with the participant's parent(s)/LAR the possibilities for continuation of activities described in the |

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| | SoA (APPENDIX 1) and must document this decision in the eCRF.<br>Reasons for removal from study intervention or procedural assessments include any of the following:<br>• Decision by the investigator.<br>• Decision by sponsor.<br>• Decision by regulatory authority.<br>• Withdrawal of parent(s)/LAR consent.<br>• Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects participant safety, as determined by the investigator (or designee).<br>• Protocol deviation that is considered to potentially compromise the safety of the participant.<br>• Noncompliance with study intervention.<br>• Noncompliance with any of the study assessments.<br>• Any clinically relevant sign or symptom that in the opinion of the investigator (or designee) warrants participant removal from study intervention.<br>• Liver Chemistry - Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the following conditions outlined or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.<br>o ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).<br>o ALT or AST > 8 × ULN.<br>o ALT or AST > 5 × ULN for more than 2 weeks.<br>o ALT **or** AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).<br>Note: Prior to treatment discontinuation for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests, tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase (GGT) and alkaline phosphatase (also refer to Section 12.7). **Should the above transaminase elevation criteria be confirmed, the participant must permanently discontinue the study intervention. In cases where transaminase elevation withdrawal criteria are not met or confirmed, the dose of study intervention or a concomitant medication with known hepatotoxicity may be reduced following discussion with the medical monitor. The final decision regarding dose adjustments should be taken by the investigator.**<br>• Disease progression that compromises the ability of the participant to safely continue study intervention.<br>• Participants who are withdrawn for nondrug related reasons may be replaced following discussion between the investigator and the sponsor. Participants withdrawn as a result of AEs |

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| | thought to be related to study intervention, as determined by the investigator, will generally not be replaced. The decision regarding the replacement of participants will be documented.<br>The participant may also be permanently discontinued from treatment for any of the following:<br>• Participant or parent(s)/LAR noncompliance.<br>• An AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the participant in the study.<br>• Not meeting eligibility criteria.<br>• Any evidence of drug abuse or drug diversion.<br>• Disease progression that compromises the ability of the participant to safely continue participating in the study.<br>**Participant Discontinuation/Withdrawal From the Study:**<br>• A participant's parent(s)/LAR may decide to withdraw the participant from the study at any time at their own request or the participant may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or compliance reasons.<br>• The participant will be permanently discontinued both from the study intervention and from the study at that time.<br>• If a participant is withdrawn from the study, the study monitor will be informed immediately. If there is a medical reason for withdrawal, the participant will be followed up by the investigator until satisfactory health has returned.<br>• At the time of discontinuing from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, an ET visit should be conducted, followed by a 10-day taper period if clinically indicated (refer to Section 8.1.2). A safety follow-up visit should be completed 4 weeks after the participant's last dose of GWP42003-P. See the SoA (APPENDIX 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.<br>• If the participant's parent(s)/LAR withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.<br>• If a participant withdraws from the study, her/his parent(s)/LAR may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.<br>Reasons for removal of a participant from the study are:<br>• Decision by the investigator.<br>• Decision by sponsor.<br>• Decision by regulatory authority.<br>• Withdrawal of parent(s)/LAR consent.<br>• Death.<br>• Lost to follow-up. |

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| | • Participant or parent(s)/LAR(s) noncompliance with study schedule.<br>• Participant or parent(s)/LAR noncompliance with study intervention administration. |
| Study Intervention: Formulation, Mode of Administration, Dose and Regimen | The study intervention is GWP42003-P oral solution (100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol [10% v/v], with sweetener [sucralose], and strawberry flavouring).<br>Mode of administration: to be taken orally b.i.d. (morning and evening) using the syringe(s) provided. In participants with G- or NG-tubes but where oral dosing of GWP42003-P is possible, oral dosing is preferable. Only in participants where oral dosing is not possible, and following consultation with the medical monitor, should GWP42003-P be administered via G- or NG-tubes made from silicon only (feeding tubes must be flushed with 15 to 30 mL of water before and after GWP42003-P dosing and also flushed after administration of concomitant medications to be taken before GWP42003-P [volume of water may be modified in participants with fluid restrictions]). The volume of GWP42003-P will be determined by participant's weight and assigned dose.<br>The GWP42003-P should be taken at about the same time each day consistently with or without food. The time of GWP42003-P administration in relation to food should be kept consistent throughout the study.<br>On Day 1 of treatment with the GWP42003-P, participants will begin dosing with 5 mg/kg/day (2.5 mg/kg b.i.d.). On Day 8 (± 3 days), the dose will be increased to 10 mg/kg/day (5 mg/kg b.i.d.). Participants will be observed on Day 15 and, subsequently, the dose may be escalated further based on individual clinical response and tolerability; doses may increase up to a maximum of 20 mg/kg/day (10 mg/kg b.i.d.) for LGS and DS or 25 mg/kg/day (12.5 mg/kg b.i.d.) for TSC. If clinically indicated for safety, participants may decrease their dose at any time.<br>Participants discontinuing GWP42003-P treatment at the end of the study, or at any other time if they discontinue treatment early, should undergo a 10-day taper period if clinically indicated (i.e., if no safety reasons prohibit continued treatment). |
| Procedures | **Screening/Baseline Period Assessments**<br>Starting at Visit 1, after completion of the ICF, the following assessments will be performed: eligibility criteria will be reviewed, along with demographics, medical history, and prior and concomitant medications. Participants will undergo full physical examinations (including height/length, body weight, and head circumference); vital signs, ECG, and VEEG will also be reviewed. Clinical laboratory samples will be collected, including chemistry, haematology, and urinalysis (when possible). Participants' seizures will be classified, and the following forms should be completed and submitted to the Epilepsy Study Consortium (ESCI): the Seizure Identification Form (SIF) (for TSC) or the Seizure Identification and Diagnostic Review Form (SIF/DRF) (for LGS and DS), along with the Epilepsy Diary Reference Sheet (EDRF) (for all participants). |

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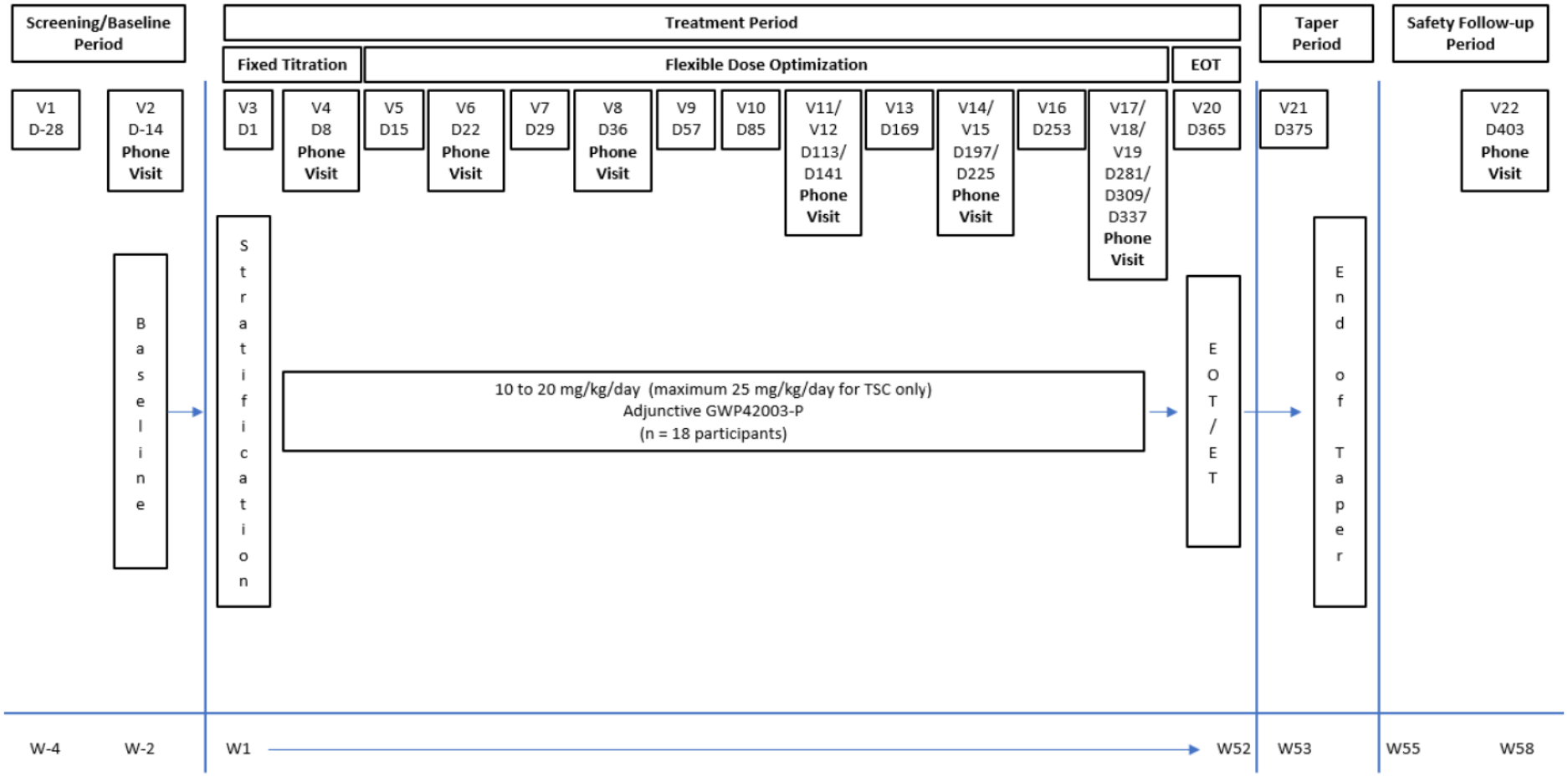
| | Caregivers will be trained to use paper and ePRO seizure diaries, and diary entries will be reviewed.<br>**Treatment Period Assessments**<br>Participants who continue to satisfy all inclusion criteria, and none of the exclusion criteria, will receive the study intervention, which will be dispensed and collected, with compliance reviewed, at timepoints specified in the SoA (APPENDIX 1). Participants will undergo the following assessments as specified in the SoA: abbreviated physical examination (including height/length, body weight, and head circumference), neurodevelopmental assessments, CGIC/CGIS, vital signs, and ECG. Concomitant medications and AEs will be recorded, and seizure type(s), and ePRO diary entries will be reviewed. Clinical laboratory samples will be collected, including chemistry, haematology, and urinalysis (when possible). Pharmacokinetic assessments will be completed for all participants.<br>**End-of-Taper Assessments:**<br>The following assessments will be performed: abbreviated physical examination (including height/length, body weight, and head circumference), neurodevelopmental assessments, CGIC/CGIS, and vital signs, concomitant medications recorded, and AEs, seizure types, and ePRO diary entries will be reviewed. The study intervention will be collected, and compliance will be reviewed.<br>**Safety Follow-up Assessments:**<br>Concomitant medications and AEs will be recorded by a telephone call or visit. |
| Pharmacokinetics | Pharmacokinetic samples will be collected for all participants. Morning trough (i.e., taken within 60 minutes prior to the morning dose of study intervention), 3-hour, and 6-hour postdose samples will be collected as specified in the SoA (APPENDIX 1).<br>Adjustments to dosage should be avoided within 3 days prior to PK visits, unless clinically indicated for safety. If a participant's dose is adjusted, PK sample collection should not occur until > 3 days after the dose adjustment. Dose adjustments may be made during PK study visits after all PK samples have been collected. |
| Statistical Considerations | No formal hypothesis testing will be performed in this study.<br>Endpoints will be analysed and reported using appropriate summary statistics including mean, standard deviation or standard error, median, interquartile range, minimum and maximum, counts and percentages. Details will be provided in a separate statistical analysis plan. |
| Safety Monitoring Committee (SMC) | An independent SMC will be used in this study to evaluate participant safety. Details are provided in the charter. |
| Sponsor | Jazz Pharmaceuticals Research UK Limited (formally known as GW Research Ltd)<br>Building 730 Kent Science Park<br>Sittingbourne, Kent<br>United Kingdom, ME9 8AG |

**Figure 1 Study Schema**




Abbreviations: D = Day; EOT = end of treatment; ET = early termination; TSC = tuberous sclerosis complex; V = Visit; W = weeks
Note: Visit 3 will occur 14 days (+ 3 days) after Visit 2 (phone visit occurs 14 days after Visit 1), however, not earlier than 28 days after Visit 1.

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| | |
|---|---|
| 7-COOH-CBD | 7-carboxy-cannabidiol |
| 7-OH-CBD | 7-hydroxy-cannabidiol |
| ACTH | Adrenocorticotropic hormone |
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| ASM | Antiseizure medication |
| AST | Aspartate aminotransferase |
| b.i.d. | Twice a day |
| CBD | Cannabidiol |
| CBD-OS | Cannabidiol oral solution |
| CB1 | Cannabinoid receptor 1 |
| CB2 | Cannabinoid receptor 2 |
| CFR | Code of Federal Regulations |
| CGIC | Clinician Global Impression of Change |
| CGIS | Clinician Global Impression of Severity |
| CIOMS | Council for International Organizations of Medical Sciences |
| COVID-19 | Coronavirus disease 2019 |
| CRO | Clinical Research Organisation |
| CSR | Clinical Study Report |
| CTIS | Clinical Trials Information System |
| DRF | Diagnostic Review Form |
| DS | Dravet syndrome |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EC | Ethics Committee |
| EDC | Electronic data capture |
| EDRS | Epilepsy Diary Reference Sheet |
| EEG | Electroencephalogram |
| EMA | European Medicines Agency |
| EOT | End of treatment |
| ePRO | Electronic patient-reported outcome |
| ES | Epileptic spasms |
| ESCI | Epilepsy Study Consortium |
| ET | Early termination |
| EU | European Union |
| EU CTD | European Union Clinical Trial Directive |

| | |
|---|---|
| EU CTR | European Union Clinical Trial Register |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials Database |
| FDA | Food and Drug Administration |
| G | Gastric |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| G-tube | Gastric-tube |
| GW | GW Research Ltd |
| GWP42003-P | Cannabidiol oral solution |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Human Use |
| IEC | Independent Ethics Committee |
| ILAE | International League Against Epilepsy |
| INR | International Normalised Ratio |
| IRB | Institutional Review Board |
| IS | Infantile spasms |
| ITQOL-SF47 | Infant and Toddler Quality of Life-Short Form 47 |
| LAR | Legally authorised representative |
| LGS | Lennox-Gastaut syndrome |
| mTOR | Mammalian target of rapamycin |
| NG | Nasogastric |
| PI | Principal investigator |
| PK | Pharmacokinetic |
| PLN | Packaging lot number |
| PT | Prothrombin time |
| QoL | Quality of life |
| QTcB | Corrected QT interval with Bazett correction |
| RTSM | Randomisation and Trial Supply Management |
| SAE | Serious Adverse Event |
| SAP | Statistical analysis plan |
| *SCN1A* | Sodium voltage-gated channel alpha subunit 1 |
| SE | Status epilepticus |
| SEGA | Subependymal giant cell astrocytoma |
| SEN | Subependymal nodules |
| SIF | Seizure Identification Form |

| | |
|---|---|
| SMC | Safety monitoring committee |
| SoA | Schedule of Activities |
| SOC | System Organ Class |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TBL | Total bilirubin |
| TEAE | Treatment-emergent adverse event |
| THC | $\Delta^9$-tetrahydrocannabinol |
| $T_{max}$ | Time to maximum plasma concentration |
| TSC | Tuberous sclerosis complex |
| ULN | Upper Limit of Normal |
| UK | United Kingdom |
| US | United States |
| VEEG | Video electroencephalogram |

# Definition of Terms

| Term | Definition |
|---|---|
| Adjunctive therapy | Therapy administered in addition to a participant's current ASM regimen. |
| Caregiver | Parent(s) or guardian(s) who provide and manage the everyday care for the participant. |
| End of study | Last participant last visit or last contact, whichever occurs last. |
| Enrolled participant | Any participant whose parent(s)/legally authorised representative has provided written informed consent to take part in the study. |
| International normalised ratio | A calculation made to standardize prothrombin time. |
| Investigator | Study principal investigator or a formally delegated study physician. |
| Screening/baseline | The 28-day period from Visit 1 to Visit 3 (Day 1). |
| Status epilepticus | Any seizure lasting 30 minutes or longer. |
| Study intervention | Term used to describe the active investigational product. |

# 2. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety and tolerability of adjunctive GWP42003-P assessed during the 52-week treatment period. | The safety profile of adjunctive GWP42003-P will be assessed by measuring:<br>• Adverse events (AEs [frequency, type, and severity]).<br>• Vital signs.<br>• Physical examination.<br>• 12-lead electrocardiogram (ECG).<br>• Clinically significant changes in laboratory parameters.<br>• Emergence of new seizure types as recorded by AE reporting.<br>• Comprehensive neurodevelopmental assessment. |
| To investigate the exposure of GWP42003-P and its major metabolites following multiple doses of GWP42003-P. | Trough, 3-hour and 6-hour postdose plasma concentrations of GWP42003-P and its major metabolites following multiple doses of GWP42003-P. |
| To evaluate the efficacy of GWP42003-P in reducing the frequency of indication-specific countable seizures. | Percentage change from baseline in indication-specific* countable seizures (average per 28 days) as recorded by caregivers on seizure diaries at Week 12, every 4 weeks thereafter, and during the 4-week period prior to end of treatment (EOT).<br>*Focal/generalised seizures (tuberous sclerosis complex [TSC]), drop seizures (Lennox-Gastaut syndrome [LGS]), or convulsive seizures (Dravet syndrome [DS]) |
| **Secondary** | |
| To evaluate the efficacy of GWP42003-P in reducing the frequency of total countable seizures. | Measurements of total countable seizures (average per 28 days) as recorded by caregivers on seizure diaries at Week 12, every 4 weeks thereafter, and during the 4-week period prior to EOT will be used to determine the following endpoints:<br>• Number and percentage of participants considered treatment responders, |

| Objectives | Endpoints |
|---|---|
| | defined as those with a ≥ 50% reduction from baseline in total countable seizures.<br>• Categorical percentage change from baseline to EOT in total countable seizures as follows:<br>o > 25% (increase);<br>o ≥ 0% to ≤ 25% (increase);<br>o > –25% to < 0% (reduction);<br>o > –50% to ≤ –25% (reduction);<br>o > –75% to ≤ –50% (reduction);<br>o ≤ –75% (reduction).<br>• Seizure freedom, defined as 100% reduction from baseline in total countable seizures. |
| To assess the retention of participants receiving GWP42003-P. | Percentage of participants still taking GWP42003-P at Week 12 and every 4 weeks thereafter. |
| **Exploratory** | |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

# 3. BACKGROUND AND RATIONALE

## 3.1. Disease

Tuberous sclerosis complex, LGS, and DS are rare, early-onset encephalopathic epilepsies with poor prognoses and associated comorbidities. Current options for antiseizure medications (ASMs) in these conditions have substantial limitations, including pharmacoresistance leading to low seizure control and intolerable side effects. Moreover, less effective seizure control is often associated with additional comorbidities and a lower QoL. Therefore, early treatment and control of seizures may be critical in improving the developmental outcomes for patients with these conditions (van der Poest Clement 2020).

***Tuberous Sclerosis Complex***

Tuberous sclerosis complex is a genetic disorder characterised by the formation of nonmalignant tumours (tubers) in multiple organ systems. The clinical signs of TSC arise as a result of inactivating mutations in tumour suppressor genes: *TSC1* (located on chromosome 9q34.13) or *TSC2* (located on chromosome 16p13.3) (European Chromosome 16 Tuberous Sclerosis Consortium 1993, van Slegtenhorst 1997). The *TSC1* gene encodes the 130 kDa protein *TSC1* (hamartin) whilst *TSC2* encodes the 200 kDa protein *TSC2* (tuberin) (European Chromosome 16 Tuberous Sclerosis Consortium 1993, van Slegtenhorst 1997). The *TSC1* and *TSC2* share no homology yet bind to each other with high affinity to form a functional heterodimer (Van Slegtenhorst 1998), which suppresses mTOR, a key regulator of cell growth and proliferation (Inoki 2002). Thus, inactivating mutations in *TSC1* and *TSC2* lead to inadequate suppression of mTOR signalling, resulting in abnormal cellular growth and tumorigenesis (Chan 2004, Huang 2008). Tuberous sclerosis complex is transmitted in an autosomal-dominant pattern of inheritance, although two-thirds of all cases are caused by *de novo* mutations (European Chromosome 16 Tuberous Sclerosis Consortium 1993, Webb 1996b, Jones 1999). Mutations in *TSC1* account for approximately 15% of all cases, while approximately 70% of all cases are due to mutations in *TSC2*; approximately 15% of patients have no identifiable mutation in the coding regions of either gene (Jones 1999, Dabora 2001). Generally, *TSC2* mutations result in a more severe disease phenotype compared with *TSC1* mutations (Jones 1999, Dabora 2001). The birth incidence of TSC is estimated to be 1 in 6000, with approximately 50,000 individuals in the United States and 1 million individuals worldwide affected (Osborne 1991, Tuberous Sclerosis Alliance 2019).

Tumours in patients with TSC can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin, and lungs (Crino 2006). The random location, number, size, and distribution of tumours result in a great variety of clinical manifestations, yet most patients exhibit dermatological, renal and/or neurological abnormalities, which appear at distinct developmental points (Curatolo 2008). Dermatological abnormalities generally first appear in infancy or early childhood and include hypomelanotic macules, which are present in more than 90% of patients with TSC, and facial angiofibromas, found in approximately 75% of patients with TSC (Webb 1996a, Webb 1996b, Józwiak 2000). In contrast, renal abnormalities tend not to develop until late childhood/adolescence and include angiomyolipomas (found in 50% to 70% of patients), renal cysts (found in 25% to 35% of patients) and, very

rarely, renal-cell carcinomas (found in 2% to 3% of patients) (Cook 1996, O'Callaghan 2004, Rakowski 2006). Neurological abnormalities first appear during embryogenesis and include cerebral cortical tubers and subependymal nodules (SENs), each of which are found in 80% to 90% of patients, as well as subependymal giant cell astrocytomas (SEGAs), which are presumed to derive from SENs and are found in 5% to 15% of patients (Northrup 2013). Whereas SENs and SEGAs are usually asymptomatic, the presence of cortical tubers is widely believed to contribute to the neurologic manifestations of TSC, which include epilepsy, cognitive disability, and autism (Crino 2006, Curatolo 2008, Northrup 2013).

Epileptic seizures are the most common clinical manifestation of TSC, affecting more than 70% of patients (Dabora 2001, Chu-Shore 2009, Wang 2014). Seizure onset occurs within the first year of life in approximately 60% of patients and within the first 3 years of life in approximately 80% of patients (Chu-Shore 2009). The onset of epilepsy in TSC commonly manifests as focal motor seizures, which coexist with infantile spasms (IS) in approximately one-third of patients (Chu-Shore 2009). Interictal EEG recordings at onset typically show hypsarrhythmia, characterised by focal or multifocal spike discharges and irregular slow-wave activity (Curatolo 2002). Virtually all patients with TSC who have a history of IS and approximately half of those without IS develop multiple seizure types, including complex focal seizures (with or without secondary generalisation), generalised tonic-clonic seizures, atonic seizures, and atypical absences (Chu-Shore 2009). Although IS resolve with time, the frequency and severity of other seizures tend to increase throughout early childhood, and nearly two-thirds of patients with TSC develop medically intractable epilepsy, including LGS (Chu-Shore 2009). Cognitive impairment (intelligence/developmental quotient < 70) is observed in around 60% of all patients with TSC who have a history of seizures and in approximately three-quarters of all patients with TSC with a history of refractory epilepsy (Chu-Shore 2009). Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences (Bombardieri 2010, Wang 2014).

***Lennox-Gastaut Syndrome***

Lennox-Gastaut syndrome is a rare epileptic encephalopathy in which frequent and debilitating seizures are believed to contribute to intellectual and behavioural disability. The onset of LGS symptoms usually occurs between 3 and 5 years of age but can also, in rare cases, occur during the first year of life (Trevathan 1997, Arzimanoglou 2009b). The disease is characterised by the presence of multiple seizure types (predominantly tonic, atonic, and atypical absence seizures but can include generalised tonic-clonic, focal, and myoclonic seizures), possibly slow EEG spike waves (< 3 Hz) with abnormal background activity when awake, and intellectual impairment (Trevathan 1997, Arzimanoglou 2009b). However, diagnosis can be delayed beyond the onset of seizures, as the electroencephalogram (EEG) findings often do not fully develop until 1 to 8 years of age (Arzimanoglou 2009b). Seizures in LGS may progress to status epilepticus (SE), which may occur frequently in some patients and carries great risks, including death. Lennox–Gastaut syndrome can be subdivided into cases of known origin (genetic, structural, metabolic, immune, and infectious) and idiopathic cases, in which the first clinical sign is often the occurrence of abrupt falls (commonly referred to as drop attacks/seizures). Drop seizures are common in LGS and can lead to physical injury leading to increased

morbidity and mortality. Cognitive impairment is apparent in ≥ 75% of all patients with LGS within 5 years of disease onset (Arzimanoglou 2009b). Thus, the need for treatment for patients with LGS often emerges early and prior to formal diagnosis.

***Dravet Syndrome***

Dravet syndrome, a severe myoclonic epilepsy in infancy, is a rare form of severe, treatment-resistant epilepsy with onset in early childhood and a distinctive yet complex electroencephalographic and clinical presentation (Scheffer 2012, Dravet 2013). It is characterised by a variety of treatment-resistant seizures (febrile and afebrile, generalised, and unilateral, clonic, or tonic-clonic) that occur in the first year of life, with a poor cognitive prognosis. Dravet syndrome is caused by pathogenic variants in the sodium voltage-gated channel alpha subunit 1 (*SCN1A*) in the majority (> 70%) of patients (Claes 2001, Mulley 2006, Suls 2006, Depienne 2009, Nakayama 2010). Onset usually occurs between 4 and 8 months of age and manifests typically as a prolonged (> 15 minutes) clonic, generalised or unilateral convulsive seizure, often triggered by fever, that can evolve into SE (Arzimanoglou 2009a, Dravet 2011, Dravet 2013). In fact, the occurrence of the first seizure in the first year of life is part of the criteria for diagnosis of DS, which have been confirmed in a clinical study (Cetica 2017). Dravet syndrome is extremely resistant to treatment during childhood and patients continue to have uncontrolled seizures throughout their lifetime. In addition to convulsive seizures, other seizure types appear between the ages of 1 and 4 years, including myoclonic seizures, focal seizures, atypical absences, and obtundation statuses (in which consciousness is impaired). Intellectual impairment affects nearly all patients and is severe in 50% of cases, often resulting in dependency in adulthood due to the chronic significant disability (Genton 2011).

## 3.2. Cannabidiol Background

GWP42003-P (Epidiolex/Epidyolex) is the substance code for the study intervention, purified GWP42003-P, a nonpsychoactive cannabinoid under development by Jazz Pharmaceuticals Research UK Ltd. for the treatment of a number of conditions. In the United States, Epidiolex is indicated for the treatment of seizures associated with LGS, DS, or TSC in patients 1 year of age and older. Epidyolex has received approval in the European Union for adjunctive use to treat seizures associated with LGS and DS, in conjunction with clobazam, in patients 2 years of age and older, and for adjunctive use to treat seizures associated with TSC in patients 2 years of age and older. The product has received Orphan Drug Designation from the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for the treatment of seizures associated with LGS, DS, and TSC.

GWP42003-P is extracted from *Cannabis sativa* L. plants, has a defined chemical profile, and contains consistent levels of cannabidiol (CBD) as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (≥ 98%) CBD that typically contains less than 0.10% (w/w) $\Delta^9$-tetrahydrocannabinol (THC). The pure CBD is subsequently dissolved in excipients with added sweetener and flavouring.

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 cannabidiol receptor 1 ($CB_1$) and cannabidiol receptor 2 ($CB_2$) receptors; CBD does not bind to either of these receptors with any great affinity but does modulate the metabolising enzymes of the endocannabinoid system. Cannabidiol also affects ion channel conductance and acts on other G protein-coupled receptors, such as the transient receptor potential channel, TRPV1 (Bisogno 2001), and the orphan GPR55 (Whyte 2009). Cannabidiol also inhibits adenosine reuptake via equilibrative nucleoside transporter 1, thereby enhancing the anticonvulsive and anti-inflammatory effects of adenosine via agonism of $A_1$ and $A_{2A}$ receptors (Sebastião 2000, Carrier 2006, Ribeiro 2012, Amorim 2016). Importantly, in contrast to THC, CBD lacks detectable psychoactivity. Cannabidiol has demonstrated anticonvulsant, antipsychotic, anxiolytic, neuroprotective, antioxidant, and anti-inflammatory activity (Pertwee 2004).

## 3.3. Rationale

The rationale for this study is to further characterize the safety, PK, and efficacy of GWP42003-P in participants with TSC, DS, and LGS who are < 2 years of age. Current treatment options for these patients are inadequate, especially because these conditions often present within the first years of life and can manifest in infants < 12 months of age. New, efficacious pharmaceutical treatments are needed for the youngest patients with these typically refractory epilepsy syndromes.

### 3.3.1. Justification for Dose

The rationale behind the dosing schedule is from the well-established clinical development programme including 5 positive pivotal studies that have supported its commercialisation as an ASM in the US, EU, and other geographic expansion areas. CBD-OS has been approved up to a maximum maintenance dose of 20 mg/kg/day for the treatment of DS and LGS, and up to a maximum maintenance dose of 25 mg/kg/day for the treatment of TSC. It has also been prescribed by physicians for the treatment of patients with intractable epilepsy resulting from a variety of aetiologies as part of the investigator-initiated expanded access program with daily dosages up to 50 mg/kg/day. Based on safety results from previous studies, and since the current study is designed to allow for individualised dosing, a daily maximum dosage of 20 mg/kg/day CBD-OS for participants with DS and LGS and a maximum dosage of 25 mg/kg/day CBD-OS for participants with TSC was selected.

The 52-week treatment period of Study GWEP17005 includes a fixed 2-week titration schedule followed by flexible dose optimisation. The optimal dose will be based on the participant's observed efficacy, safety, and tolerability per the investigator's clinical judgement.

## 3.4. Clinical Hypothesis

The primary clinical hypothesis underlying this study is that GWP42003-P has a positive risk/benefit outcome in the adjunctive treatment of seizures in participants with TSC, LGS, or DS.

## 3.5. Benefit/Risk Assessment

Cannabidiol oral solution has been approved for use in treatment of seizures associated with LGS, DS, and TSC. [redacted]

[redacted]

Participants in the current study may experience some improvement of symptoms and will receive comprehensive clinical exams and clinical monitoring associated with the study. The risks of participation are primarily associated with adverse reactions to GWP42003-P, although there may also be some discomfort from collection of blood samples and other study procedures. Cannabidiol oral solution contains 79 mg/mL ethanol. In this study in young children, there may be a potential risk of accumulation when CBD-OS is chronically coadministered with other medicines containing ethanol or other substrates for alcohol dehydrogenase (such as propylene glycol). Clinical judgment should be used weigh potential benefit from CBD-OS against this potential risk. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with GWP42003-P may be found in the current approved version of the Investigator's Brochure (IB) (CBD-OS IB).

The most commonly reported side effects include somnolence; decreased appetite; diarrhoea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor-quality sleep; infections; pyrexia; and vomiting. Serious side effects include hepatocellular injury, somnolence and sedation, suicidal behaviour and ideation, and hypersensitivity reactions. Further information is included in the latest CBD-OS IB.

Overall, the extensive clinical safety and efficacy results of GWP42003-P were demonstrated across 5 Phase 3 studies, an open-label study, and the expanded access program in the treatment of paediatric epilepsy syndromes. And it is believed that GWP42003-P has a favourable benefit risk profile for the treatment of seizures associated with TSC, DS, and LGS in the participant age ranges being investigated in this study.

# 4. EXPERIMENTAL PLAN

## 4.1. Study Design

This is a phase 3, multicentre, open-label, single-arm study that will evaluate the safety, PK, efficacy, and exploratory QoL of adjunctive GWP42003-P in participants < 2 years of age with TSC, LGS, or DS. Enrolment will be stratified via the Randomisation and Trial Supply Management (RTSM) to ensure at least 5 participants each with DS or LGS (1 to < 2 years of age) and 8 participants with TSC (4 participants < 1 year of age and 4 participants 1 to < 2 years of age) are included in this study in order to achieve 18 evaluable participants.

The study duration will be up to approximately 62 weeks, including a 4-week screening/baseline period, a 52-week dose optimisation treatment period (which includes a fixed 2-week titration period followed by flexible dose optimisation), a 10-day taper period, and a safety follow-up period (4 weeks after the end-of-taper visit). Throughout the study, participants should complete all visits and assessments as outlined in the Schedule of Activities (SoA) (APPENDIX 1).

After the informed consent form (ICF) has been signed by the parent(s)/legally authorised representative (LAR), participants will be considered enrolled and enter the screening/baseline period (Visit 1 and Visit 2 [phone visit]). Participants can be rescreened once, at the discretion of the investigator and following approval from the medical monitor. Rescreened participants will be assigned a new participant number and all screening assessments will be repeated.

Following enrolment, dose adjustments to ASMs should not be made and new ASMs should not be added without prior discussion with and approval by the medical monitor. All ASM dose adjustments must be captured in the electronic case report form (eCRF).

Starting at Visit 3, participants who continue to meet all eligibility criteria will initiate the 52-week treatment period with the study intervention (GWP42003-P) as adjunctive therapy (i.e., in addition to their current ASM regimen). The study intervention will be taken orally or with a gastric or nasogastric tube (G-or NG-tube) twice a day (b.i.d.) (e.g., morning and evening) at about the same time each day, consistently with or without food. The time of GWP42003-P administration in relation to food should be kept consistent throughout the study. During the first 2 weeks of treatment (i.e., the fixed titration period), participants should begin titrating GWP42003-P at a rate of up to 5 mg/kg/week, reaching the target dose level of 10 mg/kg/day (unless the participant cannot tolerate this dose).

Starting at Visit 5, after titrating to the target dose level (10 mg/kg/day), investigators will have the option to titrate a participant's dose no more rapidly than 5 mg/kg (≤ 2.5 mg/kg b.i.d.) every 7 days, up to a maximum dose of 20 mg/kg/day (for LGS and DS) or 25 mg/kg/day (for TSC), as recommended in Section 8.1.2 and based on the participant's individual response and tolerability. The investigator will determine if additional dose adjustments are warranted during scheduled or unscheduled visits throughout the remainder of the 52-week treatment period.

If a participant experiences tolerability issues related to the study intervention or an AE occurs at any time during the 52-week treatment period, the investigator may consider temporarily or permanently reducing the participant's dosage, following

discussion with the medical monitor. Doses may be decreased below the target dose level (i.e., < 10 mg/kg/day) based on safety and tolerability (refer to Section 8.1.2). Where possible, participants should be encouraged to return to the target dose level (10 mg/kg/day). Investigators should regularly monitor a participant's response to treatment and re-evaluate the need for adjustments to dosage (i.e., increase, maintain, or decrease) at the next study visit, if applicable.

In general, doses should not be adjusted within the 3 days prior to PK study visits (as specified in the SoA [APPENDIX 1]) unless clinically indicated for safety. If a dose adjustment is needed during the 3 days prior to a PK study visit, the PK study visit should be rescheduled to occur > 3 days after the dose adjustment. Doses may be adjusted during PK study visits after all PK samples have been collected. The rationale for any dosage changes will be documented in the appropriate eCRF.

- Participants will continue treatment with the study intervention until the EOT visit, after which they will initiate a taper period to titrate off the study intervention at home. The taper period will last 10 days and end with the end-of-taper visit. A safety follow-up visit (phone call or visit) will occur 4 weeks after the end-of-taper visit (i.e., 4 weeks after the last dose of GWP42003-P).

If a participant discontinues the study intervention or study prematurely (i.e., before the EOT visit), the participant should be encouraged to complete an early termination (ET) visit as soon as possible, followed by a 10-day taper period if clinically indicated (i.e., unless the participant must discontinue treatment due for reasons related to safety and tolerability). A safety follow-up visit (phone call or visit, if needed) will occur 4 weeks after the participant's last dose of GWP42003-P.

A schematic for the overall study design is presented in Figure 1. More detailed information on treatment and study procedures is provided in Section 8 and Section 9, respectively.

## 4.2. Number of Clinical Study Sites

Approximately ■ clinical trial centres are expected to participate in this study. Additional sites may be used in order to supplement recruitment.

## 4.3. Number of Participants

Up to 27 participants will be assigned to receive the study intervention in order to achieve 18 evaluable participants for this study. Additional information is provided in Section 13.1.

## 4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study, including the last scheduled procedure shown in the SoA (APPENDIX 1).

The end of the study is defined as the date of the last visit of the last participant in the study or last contact, whichever occurs last.

# 5. STUDY INTERVENTION

Please refer to the separate pharmacy manual for more detailed information about the study intervention.

The study intervention, GWP42003-P oral solution, contains 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol (10% v/v), with sweetener (sucralose), and strawberry flavouring (Table 1).

**Table 1 Formulation of GWP42003-P Oral Solution**

| Ingredients | Quantity |
|---|---|
| CBD | 100 mg/mL |
| Anhydrous ethanol | 79 mg/mL |
| Sucralose | 0.5 mg/mL |
| Strawberry flavour | 0.2 mg/mL |
| Refined sesame oil | make up to 1 mL |

Abbreviations: CBD = cannabidiol.

## 5.1. Packaging, Storage and Drug Accountability

### 5.1.1. Packaging and Labelling

The study intervention will be manufactured, packaged, labelled, and/or distributed by the sponsor or delegated contractors. The study intervention will be presented in 105 mL amber glass bottles containing 100 mL of 100 mg/mL CBD solution with child resistant screw caps and packed in cartons. Sufficient study intervention will be dispensed at each relevant visit considering the dose group and the weight of the participant. A unique identification number will be used to identify each box and the study intervention it contains. The unique identification number together with the packaging lot number (PLN) will permit full traceability of manufacture, pack and label activities conducted at or on behalf of sponsor and the study intervention information held on the RTSM system. The sponsor will ensure that all study intervention provided is fully labelled and packaged. Label text will include the following information, as a minimum:

- Sponsor's name and address.
- Product identification (e.g., GWP42003-P or CBD-OS).
- Dose and/or potency (e.g., "100 mg/mL GWP42003-P").
- Study code number.
- Expiry date.
- Storage conditions.
- Instruction: "For clinical trial use only".
- Instruction: "Keep out of the sight and reach of children".
- Any other information required by local regulatory authorities.

Directions for use will be provided separately to the participant.

### 5.1.2. Storage

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

The study intervention must be stored in compliance with the local regulations for a controlled drug (if applicable to the country). The sponsor must approve the storage location and facilities. Temperature records of the clinical site storage location must be maintained (recording a minimum of Monday through Friday, excluding public holidays) from date of receipt of first shipment until end of study dispensing period at each site. These records must contain at least the minimum and maximum daily temperatures and must be made available to the appropriate sponsor personnel for review throughout the study. Temperature during transit of GWP42003-P to the site must be checked on receipt and compliance/noncompliance to the minimum and maximum recorded.

Should storage conditions deviate from these specified requirements, the sponsor study monitor must be contacted immediately to confirm if the study intervention remains suitable for use. The study intervention must be placed under quarantine until written confirmation is received that the study intervention is suitable for use.

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

### 5.1.3. Supply and Return of Study Intervention

At study initiation and as needed thereafter, the study intervention will be shipped to the identified responsible person, such as the pharmacist, at the investigator's site, who will check the amount received (against the RTSM Shipment Request) and condition of the drug (i.e., integrity, physical appearance, temperature during transit). Details of the study intervention received will be recorded in the study intervention accountability record (see Section 5.1.4). The site will acknowledge the study intervention receipt via the RTSM and will complete any receipt forms required. Study intervention will be dispensed and returned as detailed in Section 8.5. As directed, all supplies, including unused, partially used, or empty containers, will be returned to the sponsor or destroyed at a sponsor-approved site if agreed in writing by the study monitor.

### 5.1.4. Study Intervention Accountability

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

- Study code.
- Pack number, PLN, date of receipt, and quantity of study intervention received.
- Participant's study identification and/or treatment number.
- Date and quantity of study intervention dispensed.
- The initials of the dispensing/dosing party.

- Date and quantity of study intervention returned to the investigator.
- Study intervention expiry dates.

Refer to APPENDIX 1 for when the study intervention will be dispensed. Participants' caregivers will be asked to return all study intervention (unused, partially used, and empty containers) at each relevant visit. The site will check the returned study intervention against the usage recorded in the diary. Any discrepancies will be discussed with the caregiver at the time of the visit and documented accordingly within the participant's source documents.

The investigator must inform the sponsor promptly of all missing or unaccountable study intervention.

A record of returned study intervention must be completed and included in the shipment of used and unused study intervention to the relevant drug distribution depot. At the end of the study, a record/statement of reconciliation must be completed and provided to the sponsor.

These inventories must be made available for inspection by an authorised sponsor representative and local officials or regulatory agency inspectors.

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

### 5.1.5. Post-Study Provision

Participants will not have access to GWP42003-P through an expanded access program after the study is completed; participants may have access to the commercial product upon completing the study as permitted per local health authorities.

A summary of the results of this study will be made available on http://www.clinicaltrials.gov and https://euclinicaltrials.eu/(as applicable), as required by US and EU law.

# 6. PARTICIPANT ELIGIBILITY

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

## 6.1. Inclusion Criteria

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

6.1.1 Participants with TSC (1 month to < 2 years of age), or DS (1 year to < 2 years of age), or LGS (1 year to < 2 years of age) within the specified age range at the time of initial informed consent.

6.1.2 Participants with TSC must have a diagnosis per the 2012 International Tuberous Sclerosis Complex Consensus Conference (Northrup 2013)(APPENDIX 3). Participants with LGS or DS must have a diagnosis that is consistent with International League Against Epilepsy (ILAE) guidelines and confirmed by the Epilepsy Study Consortium (ESCI) (also refer to Section 9.1.12.1) (Specchio 2022, Zuberi 2022).

6.1.3 Participants who have uncontrolled seizures, and who are currently receiving 1 or more ASMs.

6.1.4 Parent(s)/LAR is/are willing and able to give informed consent for participation in the study.

6.1.5 Parent(s)/LAR is/are willing and able (in the investigator's opinion) to comply with all study requirements (including accurate electronic patient-reported outcome [ePRO] diary completion).

6.1.6 Caregiver completes at least 75% of ePRO and paper seizure diary entries during the 28 days of the baseline period (≥ 21 days of entries).

6.1.7 A suitable VEEG, as available in the medical records, within 1 year of Visit 1. When a historical VEEG is not available, and if clinically indicated and appropriate due to uncertainties or new seizures, a VEEG will be completed and read to confirm diagnosis prior to Visit 3. All VEEGs are to be read at baseline by the investigator and an independent reviewer.

- A suitable VEEG meets all the following criteria:

  i. Multichannel (minimum 8-channel)
  ii. Prolonged continuous recording up to 24 hours
  iii. Completed within 1 year of Visit 1
  iv. Consistent with the participant's current seizures (in the investigator's opinion)
  v. Can be reviewed by the investigator and an independent reviewer prior to Visit 3
  vi. Consistent with a diagnosis of inadequately-controlled seizures

6.1.8 Currently taking ≥ 1 ASMs at a dose that remains stable 2 weeks prior to Visit 3 and during the treatment period. Where required for participant safety, adjustments of concomitant ASMs or addition of new ASM may be permitted following discussion with the medical monitor.

- Adrenocorticotropic hormone (ACTH) or high dose corticosteroids for the treatment of IS/ES are counted as ASMs.

6.1.9 Has seizures that are not adequately controlled through their current ASMs, defined as ≥ 1 seizure reported on the seizure diary during the screening/baseline period.
6.1.10 Parent(s)/LAR is/are willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law.
6.1.11 Parent(s)/LAR is/are willing to allow the participant's primary care practitioner (if they have one) and consultant (if they have one) to be notified of participation in the study if the primary care practitioner/consultant is different from the investigator.

## 6.2. Exclusion Criteria

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

6.2.1 Has clinically significant unstable medical condition other than epilepsy.
6.2.2 Has had clinically significant symptoms or a clinically significant illness within the 4 weeks prior to Visit 1, other than epilepsy, which in the opinion of the investigator could affect seizure frequency.
6.2.3 Has undergone general anaesthesia within 4 weeks prior to Visit 1.
6.2.4 Has undergone surgery for epilepsy within 6 months prior to Visit 1 or has plans to undergo surgery for epilepsy during the study.
6.2.5 Has taken felbamate < 1 year prior to Visit 1.
6.2.6 Is < 1 year of age and taking valproic acid.
6.2.7 Has tumour growth which, in the opinion of the investigator, could affect participant safety.
6.2.8 Has clinically significant abnormal laboratory values, in the investigator's opinion, at screening/baseline.
6.2.9 Has clinically significant abnormalities in the ECG measured at screening/baseline.
6.2.10 Has any concurrent cardiovascular conditions that will, in the investigator's opinion, interfere with the ability to assess their ECGs.
6.2.11 Has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the study intervention such as sesame seed oil.
6.2.12 Has significantly impaired hepatic function prior to Visit 3, defined as:

- Serum alanine aminotransferase (ALT) **or** aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) **and** (total bilirubin [TBL] > 2 × ULN **or** international normalised ratio [INR] > 1.5).
- Serum ALT or AST > 5 × ULN.
- Serum ALT or AST > 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- Elevated ALT or AST should be discussed with the medical monitor prior to Visit 3; the medical monitor may allow for a confirmatory re-draw prior to Visit 3.

6.2.13 Has received another study intervention within 4 weeks prior to Visit 1 or plans to take another study intervention during the study.
6.2.14 Caregiver is currently giving or has given recreational or medicinal cannabis, cannabinoid-based medications (including Sativex) or CBD (including

Epidiolex/Epidyolex [GWP42003-P]) to the participant within the 4 weeks prior to Visit 1 **or** is unwilling to abstain from doing so for the duration of the study.

6.2.15 Mother (if breastfeeding) is currently using or has used recreational or medicinal cannabis, cannabinoid-based medications (including Sativex) or CBD (including Epidiolex/Epidyolex [GWP42003-P]) within the 4 weeks prior to Visit 1 **or** is unwilling to abstain from doing so for the duration of the study.

6.2.16 Has any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the participant, other participants, or site staff at risk because of participation in the study, may influence the result of the study, or may affect the participant's ability to take part in the study.

6.2.17 Any clinically significant abnormalities identified following a physical examination of the participant that, in the opinion of the investigator, would jeopardize the safety of the participant if they took part in the study.

6.2.18 Has previously been enrolled into this study.

6.2.19 Has plans to travel outside their country of residence during the study, unless the participant has confirmation that the study intervention is permitted in the destination country and all stops along the way.

# 7. PARTICIPANT ENROLMENT

Before participants may be entered into the study, the sponsor requires a copy of the relevant site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) written approval of the protocol, ICF, and other participant information material. Participants will be considered enrolled in the study from the time of the parent(s)/LAR providing written informed consent. The participant's parent(s)/LAR must personally sign and date the ICF regulations, prior to any procedures being performed (refer to Section 9.1.1 and Section 15.2).

## 7.1. Enrolment Stratification

Enrolment will be stratified via the RTSM to ensure that at least 5 participants each with LGS and DS (1 to < 2 years of age) and 8 participants with TSC (4 participants < 1 year of age and 4 participants aged 1 to < 2 years) are included in this study in order to achieve 18 evaluable participants. All participants will receive open-label study intervention in this nonrandomised study.

# 8. TREATMENT PROCEDURES

## 8.1. Study Intervention Dosage, Administration and Schedule

For details regarding study intervention formulations, see Section 5.

### 8.1.1. Dose Administration

GWP42003-P will be administered as adjunctive therapy (i.e., in addition to the participant's current ASM regimen) orally b.i.d. (morning and evening) using the syringe(s) provided. In participants with G- or NG-tubes but where oral dosing of GWP42003-P is possible, oral dosing is preferable. Only in participants where oral dosing is not possible, and following consultation with the medical monitor, should GWP42003-P be administered via G- or NG-tubes made from silicon only (feeding tubes must be flushed with 15 to 30 mL of water before and after GWP42003-P dosing and also flushed after administration of concomitant medications to be taken before GWP42003-P [volume of water may be modified for participants with fluid restrictions]). Volume of GWP42003-P to be determined by participant's weight and assigned dose.

GWP42003-P should be taken at about the same time each day consistently with or without food. The time of GWP42003-P administration in relation to food should be kept consistent throughout the study.

Route of administration with GWP42003-P (oral or with G- or NG-tubes) should remain consistent throughout the study. Any changes in the route of administration should be captured in the participant's medical records.

### 8.1.2. Dose Escalation and Dose Adjustments

The 52-week treatment period includes a fixed 2-week titration schedule followed by flexible dose optimisation. The optimal dose will be based on the participant's observed efficacy, safety, and tolerability per the investigator's clinical judgement.

On Day 1 (Visit 3) of treatment with GWP42003-P, participants will initiate the fixed 2-week titration of GWP42003-P, beginning with a dose of 5 mg/kg/day (2.5 mg/kg b.i.d.). On Day 8 (± 3 days), the dose will be increased to the target dose level of 10 mg/kg/day (5 mg/kg b.i.d.). Participants will be observed on Day 15 (Visit 5).

After Day 15 (Visit 5), the GWP42003-P dose may be escalated further based on individual clinical response and tolerability using a flexible titration schedule, per the investigator's clinical judgement. If, in the investigator's opinion, the participant is experiencing a clinically meaningful improvement in seizures, investigators will have the option to maintain or increase a participant's dose at any time during or between scheduled visits until EOT. Doses may be increased up to a maximum of 20 mg/kg/day (10 mg/kg b.i.d.) for LGS and DS or 25 mg/kg/day (12.5 mg/kg b.i.d.) for TSC, in maximum weekly increments of 5 mg/kg/day (≤ 2.5 mg/kg b.i.d.). If possible, changes in dose should be avoided during the 3 days prior to PK visits or before PK samples have been collected on the day of PK study visits (as specified in APPENDIX 1) unless clinically indicated for safety (Section 9.1.10.1 provides additional details).

A titration schedule (including the fixed 2-week titration to the target dose and a suggested titration schedule up to the maximum dose) is provided in Table 2. Per the table, a participant's dose may be escalated to up to 15 mg/kg/day (≤ 7.5 mg/kg b.i.d.) on or after Days 15, up to 20 mg/kg/day (≤ 10 mg/kg b.i.d.) on or after Day 22, and up to 25 mg/kg/day (≤ 12.5 mg/kg b.i.d.; TSC only) on or after Day 29. However, the titration schedule starting at Day 15 in Table 2 is optional; investigators should use their clinical judgement when titrating a participant's dose. Any adjustments to a participant's dose will require follow-up within 7 days via an in-clinic visit or telephone follow-up, as determined by the investigator, to evaluate participant safety. An unscheduled phone contact (documented as an unscheduled phone visit) or unscheduled clinic visit must be recorded in the eCRF.

**Table 2 Dose Titration**

| Days | Daily Dose | Morning and Evening Dose |
|---|---|---|
| *Fixed titration to target dose* | | |
| 1 to 7 | 5 mg/kg/day | 2.5 mg/kg b.i.d. |
| 8 to 14 | 10 mg/kg/day | 5 mg/kg b.i.d. |
| *Suggested titration to the maximum dose* | | |
| ≥ 15 | ≤ 15 mg/kg/day | ≤ 7.5 mg/kg b.i.d. |
| ≥ 22 | ≤ 20 mg/kg/day | ≤ 10 mg/kg b.i.d. |
| ≥ 29 | ≤ 25 mg/kg/day (TSC only) | ≤ 12.5 mg/kg b.i.d. |

Abbreviations: b.i.d. = twice a day; DS = Dravet syndrome; LGS = Lennox–Gastaut syndrome; TSC = tuberous sclerosis complex.
Note: Participants with TSC may receive a maximum dose of 25 mg/kg/day; participants with LGS or DS may receive a maximum dose of 20 mg/kg/day.

- If a participant reports any tolerability issues related to GWP42003-P or an AE occurs at any time during the 52-week treatment period, the investigator may temporarily or permanently reduce the participant's dosage, following discussion with the medical monitor. For participants with poor tolerability, the daily dose should be reduced by 10 mg/kg every 7 days (unless smaller, larger, or more rapid dose reductions are clinically indicated per the investigator's opinion).
- At any time, the dose level may be decreased below the target dose (i.e., < 10 mg/kg/day), based on safety and tolerability, with 2.5 mg/kg/day being the minimum dose. Where possible, the participant should be encouraged to return to the target dose level (10 mg/kg/day); doses may increase in maximum weekly increments of 5 mg/kg/day (≤ 2.5 mg/kg b.i.d.) following consultation with the medical monitor. Investigators should regularly monitor a participant's response to treatment and re-evaluate the need for adjustments to dosage (i.e., increase, maintain, or decrease) at each study visit, if applicable. The rationale for any dosage changes will be documented in the appropriate eCRF.

Following the EOT visit, doses of GWP42003-P will be down-titrated at home (10% of the final dose per day for 10 days) until the end-of-taper visit.

Participants discontinuing the study intervention early should still complete a 10-day taper period (unless a continued dosing is not possible due to an AE or other safety or tolerability considerations); additional information is in Section 10.

Following enrolment, dose adjustments to ASM should not be made without prior consultation with the medical monitor. All adjustments must be captured within the eCRF (refer to Section 8.2).

## 8.2. Concomitant Therapy

It is theoretically possible that GWP42003-P may modify the metabolism of other drugs (including ASMs) administered concurrently and there remains the possibility of pharmacological interactions between GWP42003-P and other concurrently administered drugs. Doses of any concomitant or nonpharmacological ASMs must have been stable for at least 2 weeks prior to Visit 3 and must remain stable for the duration of the study. Any concomitant medication, including dose adjustments to concomitant medications, must be captured within the eCRF.

Where required for participant safety, adjustments of concomitant ASMs or addition of new ASM may be permitted following discussion with the medical monitor. If side effects are suspected of being related to an elevation in the concomitant ASM concentration, the investigator must contact the medical monitor to discuss best management. Decisions should be based on clinical symptoms and not plasma levels of ASMs. Further information on drug interactions can be found in the CBD-OS IB. Concomitant ASM dose reductions are permitted on clinical grounds (e.g., due to AEs or transaminase elevations not meeting withdrawal criteria specified in Section 10) following discussion with the medical monitor.

The use of rescue medication is allowed when necessary and each use should be recorded in the participant diary and eCRF.

## 8.3. Prohibited Therapy During Study Period

There are no medications that are specifically prohibited. There are 2 medications that are exclusionary in specific circumstances for study enrolment, per the Exclusion Criteria (Section 6.2), as follows:

- Felbamate taken < 1 year prior to Visit 1.
- Valproic acid for participants < 1 year of age.

Refer to Section 6.2 Exclusion Criteria for additional details.

However, any participants taking these medications/therapies after Visit 3 should not be discontinued from treatment 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 13.7.1).

- The addition of any new medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) are prohibited after the participant has been enrolled in the study. Where required for participant safety, adjustments of concomitant ASMs or the addition of

new ASM may be permitted following discussion with and approval by the medical monitor.

Refer to the SmPC and IB for additional information.

## 8.4. Precautionary Concomitant Medications

Additional care should be taken with drugs, or their metabolites, that are cytochrome P450 2C19 substrates, such as N-desmethylclobazam. Care should also be taken with drugs, or their metabolites, that are solely or primarily metabolised by UGT1A9 and UGT2B7. Specifically, care should be taken with the following medications that have known interactions with GWP42003-P:

- Sirolimus, everolimus, temsirolimus, or tacrolimus.
- Clobazam.

In addition, the following medications are considered precautionary: carbamazepine, lamotrigine, lorazepam, phenytoin, stiripentol,valproate, mitotane, morphine, diflunisal, efavirenz, theophylline, caffeine, propofol, simvastatin, fenofibrate, gemfibrozil, enzalutamide, bupropion, St. John's wort, rifampin, clarithromycin, erythromycin, and medicines used to treat acid reflux (e.g. omeprazole).

Cannabidiol oral solution contains 79 mg/mL ethanol. In this study in young children, there may be a potential risk of accumulation when CBD-OS is chronically coadministered with other medicines containing ethanol or other substrates for alcohol dehydrogenase (such as propylene glycol). Potential effects include central nervous system effects (such as drowsiness, behavioural changes, and ataxia) as well as hypothermia. Clinical judgment should be used to weigh the potential benefit from CBD-OS against this potential risk.

For additional details regarding these precautionary medications, refer to the SmPC and IB.

## 8.5. Compliance in Study Intervention Administration

The caregiver will record the volume of study intervention taken each morning and evening on each treatment day in the participant diary (refer to Section 9.1.12.2 for additional information).

Caregivers should return all study intervention (unused, partially used, and empty containers) at each visit. The diary-reported dosing information will be checked and any discrepancies discussed with the caregiver at the time of the visit and documented accordingly within the participant's source documents.

Records of study intervention accountability will be maintained according to Section 5.1.4.

# 9. STUDY PROCEDURES

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

## 9.1. Study Procedures

### 9.1.1. Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant's parent(s)/LAR prior to participation in this study. A signed copy of the ICF form should be given to the participant's parent(s)/LAR, and the original should be placed in the participant's medical records. The parent(s)/LAR of minor participants must personally sign and date the IRB/IEC approved ICF before any study specific procedures are performed or any participant related data is recorded for the study. Participants may be rescreened only once, at the discretion of the investigator and with approval from the medical monitor. The rescreened participants will be assigned a new participant number and all screening will be repeated.

For further details, see Section 15.2.

### 9.1.2. Demographics

The following information will be obtained for each participant: date of birth, sex, and race (as allowed per local regulations).

### 9.1.3. Medical History

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

- May affect the conditions under study. Including complete seizure history, lifetime history of epilepsy, history of SE, and any hospitalisations.
- Is ongoing upon entry into the study (prior to the initial dose at Visit 3).
- Has occurred within one year prior to screening (Visit 1).
- Historical vaccinations.
- For participants with TSC, the mutation status of the *TSC1* and *TSC2* genes, if known, will be obtained through the participant's medical records to support diagnosis.
- For participants with DS, the mutation status (positive or negative for mutation) of the *SCN1A* gene will be determined through the participant's medical records.
- For participants with DS and LGS, the ESCI will review and confirm diagnosis to ensure that the correct study population is enrolled. Investigators will submit a documented history of DS or LGS directly to the ESCI for confirmation of diagnosis. The ESCI will also verify seizure types for all participants (refer to Section 9.1.12.1).

### 9.1.4. Prior and Concomitant Medication and Therapies

Details of all current and recent medication (i.e., taken within the previous 3 months prior to Visit 3), and all ASMs, rescue medications, and vaccinations taken during the participant's life will be recorded in the eCRF and reviewed at each subsequent visit.

Any changes in concomitant medications (e.g., ASMs, rescue medication usage, vaccinations, or other medications), medical procedures (e.g., G-or NG-tube placement/revision. or changes to non-drug therapies during the study must be discussed with the medical monitor and recorded on the eCRF (also refer to Section 8.2).

### 9.1.5. Physical Examination

Physical examinations will include length (height), body weight, and head circumference measurements. A full physical examination will be completed at Visit 1; an abbreviated physical examination may be completed at each subsequent visit, as clinically indicated.

Any findings related to (neuro)developmental or growth issues considered to represent an AE must be documented on the eCRF.

### 9.1.6. Comprehensive Neurodevelopmental Assessment

In addition to standard physical examinations, a formalized neurodevelopmental examination will be performed at Visits 3, 13, and EOT. The standard physical examination will include many of the following components and duplication is not necessary. Visits with neurodevelopmental assessments should include recording of the following aspects:

- Paediatric neurological examination
  - Including mental status (level of alertness, attention, eye contact, etc.) cranial nerve examination I-XII, motor examination (tone, posture, strength, involuntary movements), sensory examination, coordination, deep tendon reflexes, developmental/primitive reflexes, gait (if age appropriate)
  - Including hearing and vision testing
  - Height, weight, and head circumference recorded during the physical examination (Section 9.1.5)
- Developmental milestones assessment
  - Including recording developmental interventions/educational service (i.e., early intervention services including speech, occupational, physical, developmental therapies)
  - Including feeding/sleep concerns and milestones
- Recording of ongoing health conditions as detailed in Section 9.1.12.2
- Longitudinal monitoring of neurodevelopment via Clinician Global Impression of Change/Severity (CGIC/CGIS) for sensory, motor, cognition, emotional/behavioural health, communication, social, and adaptive functioning

- Quality of life assessments via Infant and Toddler Quality of Life Questionnaire Short Form 47 (ITQOL-47) as detailed in Section 9.1.12.3 (Performed at Baseline, Visit 3, and EOT)

### 9.1.7. Vital Signs

Vital sign measurements (blood pressure, pulse rate, respiration rate, body temperature), including blood pressure taken in a supine position at rest for 5 minutes, will be completed alongside the physical examination. Blood pressure must be recorded using the same arm throughout the study, where possible.

### 9.1.8. 12-Lead Electrocardiogram

A 12-lead ECG will be performed after 5 minutes in a supine position. A physician must review the ECG immediately (annotated, signed, and dated), and any clinically significant abnormal findings considered to indicate significant medical history or AEs must be recorded appropriately on the eCRF. Additional ECG measurements can be taken at any time during the study, if clinically indicated.

### 9.1.9. Video Electroencephalogram

Prolonged multichannel (minimum 8-channel) VEEG recording of up to 24 hours will be performed. Prior to Visit 3, a suitable VEEG must be reviewed by the investigator and an independent reviewer to establish a baseline VEEG for the participant and confirm participant eligibility (i.e., a VEEG pattern consistent with a diagnosis of inadequately-controlled seizures). See Section 6.1 for definition of a suitable VEEG.

Any VEEG findings considered to represent an AE must be documented on the eCRF.

### 9.1.10. Blood Sampling

For all blood samples, the maximum amount of blood taken at any single time will not exceed 1% of total blood volume and the cumulative maximum amount of blood taken in any 4-week period will not exceed 3% of total blood volume as per relevant EU guidance on ethical considerations for clinical studies on medicinal products conducted with minors (Appendix 3.3). Where required by the site's IRB/IEC, the volume of all blood collected from the participant during their participation in the study will be recorded on a blood draw record sheet. Where the required blood draw volume for study samples exceeds guidance at a particular visit, safety parameters (chemistry and haematology) should be prioritised.

The caregiver must be advised that it may not be safe for participants to undertake further blood tests within 1 month of any study-related blood draws and to inform the investigator if they suffered any blood loss during the 1-month period leading up to a planned blood draw.

#### 9.1.10.1. Clinical Laboratory Sampling

The investigator should use their judgment and knowledge of the participant to determine when best to collect the blood and urine samples in order to mitigate the risk that invasive procedures may cause the participant to become stressed, thereby affecting the results of other assessments.

Due to the young age and low body weight of the participants being studied, and to ensure compliance with blood draw limits (Appendix 3.3), it will be necessary to use

local laboratories for the clinical laboratory aspects of the study. The essential parameters in Table 3 should be prioritised, and the additional parameters should only be collected where possible based on blood draw limits outlined in Appendix 3.3.

Laboratory tests will include haematology, chemistry, and urinalysis (provided enough urine can be obtained).

The investigator and study monitor will be provided with a list of the normal ranges used by the site's local 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 3. Additional details will be provided in a separate laboratory manual.

**Table 3 Chemistry, Haematology, and Urinalysis**

| Chemistry (Serum) | Haematology (Whole Blood) | Urinalysis (Urine)[e] |
|---|---|---|
| **Essential Parameters[a]** | | |
| Alanine aminotransferase | Haematocrit | Glucose |
| Alkaline phosphatase | Haemoglobin | Nitrites |
| Aspartate aminotransferase | Mean corpuscular haemoglobin | pH |
| Creatinine | Platelet count | Protein |
| Gamma-glutamyl transferase | Red blood cell count | White blood cells |
| Potassium | White blood cell count with automated differential[c] | Haemoglobin (blood) |
| Prothrombin time/International Normalised Ratio (PT/INR[b]) (plasma) | | |
| Sodium | | |
| Total bilirubin | | |
| Triglycerides | | |
| Urea (blood urea nitrogen) | | |
| **Additional Parameters[d]** | | |
| Albumin | Mean corpuscular volume | |
| Calcium | | |
| Creatinine clearance | | |
| Total protein | | |
| Chloride | | |

Abbreviations: eCRF = electronic case report form; INR = international normalised ratio; PT = prothrombin time.
[a] Analysed as a priority.
[b] Both PT and INR will be recorded in the eCRF.
[c] Including absolute counts and percent for neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
[d] Analysed in addition to the essential parameters, wherever possible.

[e] Where possible, urine samples for biochemistry will be analysed at the site's local laboratory by use of a dipstick with any relevant findings being sent for further urinalysis (urinalysis, microscopy, culture, and sensitivity, as applicable).

All laboratory results will be reviewed, and the reports signed and dated by an investigator. Any results considered to be of clinical significance must be documented as AEs and followed up as clinically appropriate.

All laboratory results considered to represent an AE must be documented on the eCRF. For reporting and follow-up of potential cases of drug-induced liver injury, see Section 12.6.

Repeat samples will be taken, if required, for clinical follow-up or if the sample is lost or damaged. Any abnormal EOT 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 study intervention and needs no further investigation.

#### 9.1.10.2. Pharmacokinetic Blood Sampling

Pharmacokinetic samples will be collected from all participants.

Morning trough (i.e., taken within 60 minutes prior to the morning dose of GWP42003-P) PK samples will be collected along with 3-hour, and 6-hour postdose samples during certain study visits as specified in the SoA (APPENDIX 1). A minimum interval of at least 2 hours between each of the blood sampling time points must be maintained. The PK samples will be used to determine concentrations of GWP42003-P and its main metabolites (refer to Section 13.7.1.4 for additional details).

If possible, any changes in dose should be avoided during the 3 days prior to PK visits, unless clinically indicated for safety. If a participant's dose is adjusted, PK sample collection should not occur until > 3 days after the dose adjustment. Doses may be adjusted during a PK study visit after all PK samples have been collected on the day of the PK study visit.

Analysis of all PK samples will be conducted at a central bioanalytical laboratory. Blood sample volume requirements and processing procedures will also be detailed in a separate laboratory manual; the maximum amount of blood taken for PK analyses during the study will not exceed limits specified in Appendix 3.3.

The caregiver will record the timing and content of meals during the 24 hours prior to PK sample collection (refer to Section 9.1.12.2). These data will be included in an exploratory analysis along with the dose time and PK specimens to further understand the PK profile of GWP42003-P in this population.

#### 9.1.10.3. Optional Blood Sampling

The following samples are optional and will only be collected from participants whose parent(s)/LAR have consented to participate in these analyses.

Participation is optional. Participants whose parent(s)/LAR do not wish to participate in these analyses may still participate in the study.

Samples collected will be within the limits specified in Appendix 3.3.

Participant confidentiality will be maintained at all times by the blinding of samples.

Additional information is provided in APPENDIX 4. Details, including the processes for collection and handling of biological samples, as well as shipment and destruction of these samples, are provided in the laboratory manual. Results of these analyses will be reported separately.

#### 9.1.10.3.1. Pharmacogenomics

Optional blood samples may be collected from participants whose parent(s)/LAR have consented to participate in the genetic analysis component of the study as outlined in the SoA (APPENDIX 1).

- Blood samples will be analysed to detect polymorphisms in specific genes and determine if unique single nucleotide polymorphisms or more complex Mendelian factors might be a contributing factor in a participant's response to GWP42003-P.

#### 9.1.10.3.2. Exploratory Biomarkers

Optional plasma samples may be collected from participants whose parent(s)/LAR have consented to participate in the exploratory biomarker analysis as specified in the SoA (APPENDIX 1).

[redacted]

### 9.1.11. Randomisation and Trial Supply Management System

The RTSM will be used for enrolment stratification (refer to Section 7.1) and to manage study intervention supply. The RTSM system will be integrated with electronic data capture (EDC). Study site personnel must register in EDC in order to:

- Obtain a participant's number.
- Obtain dispensing information.
- Provide completion/taper/premature termination information.
- Training will be given to all trial centres prior to the start of the study.

### 9.1.12. Questionnaires and Assessments Completed at Scheduled Visits

Questionnaires and diaries should be completed by the main caregiver who has received training on completion of study assessments, as appropriate. In situations where this is not possible during a scheduled visit, the questionnaire should be completed within 3 days of scheduled visit. The same person should complete the questionnaires and diary assessments in order to maintain consistency.

#### 9.1.12.1. Confirmation of Diagnosis (DS and LGS) and Seizure Classification

For participants with DS or LGS only, the ESCI will confirm diagnosis during the screening/baseline period. Participants with DS or LGS whose diagnosis cannot be

confirmed by the ESCI must discontinue the study (refer to Section 6.2, Inclusion Criteria).

In addition, to promote accurate and consistent reporting of ILAE seizures associated with LGS, DS, or TSC for this study (APPENDIX 3) (Foundation 2017), the ESCI will verify the ILAE seizure types of screened participants during the screening/baseline period.

During Visit 1, investigators will collect a detailed medical history regarding the participant's seizure history using the following forms provided:

- The Seizure Identification Form (SIF; for TSC)
- The SIF/ Diagnostic Review Form (DRF; for LGS and DS)
- The Epilepsy Diary Reference Sheet (EDRS; for all participants)

The investigator will submit these forms directly to the ESCI, along with the following supporting information for confirmation of diagnosis (for DS and LGS) and verification of seizure types (for all participants) within 24 hours (1 business day) of Visit 1:

- Inter-Ictal-EEG summary reports (for all participants)
- Ictal-EEG summary (for all participants, where available)
- Neuroimaging summary (for LGS and DS)

The ESCI may ask the investigator for additional information to assist in their decision. The ESCI will provide written confirmation of diagnosis (for DS and LGS) and written confirmation of seizure types (for all participants) during the screening/baseline period.

Also during Visit 1, the investigator will review and train the caregiver to identify, count, and report the participant's expected seizures in the paper (screening/baseline period only) and ePRO daily seizure diary(ies) using the EDRS. Caregivers will begin daily tracking of the investigator-classified seizure types in both the paper seizure diary and the ePRO seizure diary.

After the ESCI has provided written confirmation of seizure types, the investigator must contact the caregiver immediately if any seizure type was misclassified by the investigator during the initial training. If a seizure type was misclassified, the investigator must retrain the caregiver and submit an updated EDRS to ESCI for review and approval.

The caregiver will continue daily tracking of the ESCI-approved seizure types in both the paper seizure diary and the ePRO seizure diary, using the ESCI-approved EDRS, through the remainder of the screening/baseline period. At Visit 3, the caregiver will return to the trial centre with the paper seizure diary and ePRO seizure diary for review.

After Visit 3, caregivers will only use the ePRO seizure diary for daily seizure reporting during the remaining course of the study.

Note: If a new seizure type occurs during the study that was not previously approved by ESCI, the investigator must complete a New Seizure Form and submit this form to ESCI for review and approval. Where agreed with the ESCI and medical monitor, the SIF or

SIF/DRF (as applicable) and EDRS may be updated to include the new seizure type(s). New seizure types may also meet the definition of an AE (refer to Section 12.1).

**Only seizures that are recognisable and countable will be reported by caregivers for this study.** The following ILAE seizure subtypes associated with LGS, DS, or TSC will be collected in the ePRO diary (Specchio 2022, Zuberi 2022):

- Focal seizures
  - Focal motor seizures (with or without impairment of consciousness or awareness)
  - Focal seizures which evolve to bilateral convulsive seizures
- Generalised seizures:
  - Tonic
  - Clonic
  - Tonic-clonic
  - Atonic
- Other generalised or focal seizures:
  - Myoclonic
  - Absence
  - Focal non-motor (with or without impairment of consciousness or awareness)
  - Infantile/epileptic spasms
  - Other

Details of the composition and standard operating procedures of ESCI will be provided in a separate charter.

#### 9.1.12.2. Participant Diaries

At Visit 1 and throughout the study, caregivers will complete the ePRO diary to record information daily. During the screening/baseline period only, caregivers will also use a paper diary for tracking seizures to supplement the ePRO seizure diary (refer to Section 9.1.12.1). Caregiver training on diary completion will be provided at as outlined in APPENDIX 1. Caregivers will be asked to record the following information in the ePRO diary:

- Seizures
- Changes in participant's health (e.g., possible AEs)
- Study intervention usage, including dose time and volume
- Changes in concomitant medications, including rescue medication usage
- Details of each meal consumed by the participant within 24 hours prior to PK collection, including the start time, end time and meal type:

- High fat meal (breast milk, formula milk, or meat)
- Standard meal (fruit or vegetable)
- Other (if not fitting into one of the categories above)

Caregivers should be instructed to immediately contact the investigator by phone to discuss any AEs (including worsening of seizures as described in Section 12.1) or changes in concomitant ASMs (including use of rescue medication).

All diary entries will be reviewed and discussed with caregivers for verification, and where necessary, recorded within the applicable sections of the eCRF by site staff. Any changes in concomitant ASMs should be discussed with and approved by the medical monitor. Any entries of AEs should be reported according to AE reporting procedures outlined in Section 12.

#### 9.1.12.3. Infant and Toddler Quality of Life Questionnaire Short Form 47

Caregivers will be instructed on how to record and complete the ITQOL-SF47. Raw scores obtained in the questionnaire will be transformed to a value from 0 (worst health) to 100 (best health). The ITQOL-SF47 will be completed at the site by the caregiver on an electronic clinical outcomes assessment device (HealthActCHQ 2017).

#### 9.1.12.4. Neurodevelopmental Scale – Clinician Global Impression of Change/Severity

Clinicians will be instructed on how to record and complete the Clinician Global Impression of Change/Severity (CGIC/S) covering critical neurodevelopmental domains. This is a 2-question survey for each domain and will be completed by the clinician as part of the comprehensive neurodevelopmental assessment at Visits 3, 13, and EOT. Each participant should have their CGIC/S performed by the same clinician throughout the study and reported into EDC.

The CGIC/S domains include the following:

- Sensory (e.g., vision, touch, hearing, taste, smell)
- Motor (e.g., fine and gross motor)
- Cognition (e.g., understanding, reacting, reasoning, problems solving)
- Emotional/behavioural health (e.g., emotional regulation, self-soothing)
- Communication (e.g., receptive and expressive skills)
- Social (e.g., social interactions, responding)
- Adaptive functioning (e.g., self-help skills such as feeding self, aiding in dressing, etc.)

### 9.1.13. Study Intervention Accountability

Records of study intervention accountability will be maintained according to Section 5.1.4.

### 9.1.14. Adverse Events

All AEs and serious adverse events (SAEs) will be collected from the start of intervention until the safety follow-up visit, as specified in APPENDIX 1.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history not as AEs.

Note: All SAEs that occur after the consent form is signed but before study intervention is initiated must be reported by the investigator if they cause the participant to be excluded from the study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

All SAEs must be reported to the sponsor or designee immediately and within 24 hours of first knowledge of the event, as indicated in Section 12. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

Refer to Section 12 for definitions, procedures and further information on AE reporting.

### 9.1.15. Special Circumstances

During special circumstances (e.g., Coronavirus disease 2019 [COVID-19] pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. In cases where participants are not able to perform all protocol-defined assessments due to special circumstances, the investigator must discuss with the medical monitor potential mitigation approaches.

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

- Safety follow-up may be done by a telephone call, other means of virtual contact or home visit, if appropriate.
- Participant and/or clinician-rated outcomes assessments may be done by videoconference, telephone call, other means of virtual contact, if possible.
- An alternative approach for study intervention dispensing, secure delivery, and collection may be sought.
- Visits may take place in a different location than defined in the protocol. If this is not feasible, then the visit may take place virtually with the means of communication documented (e.g., phone call or videoconference).
- Biological samples may be collected and analysed at a different location than defined in the protocol. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until shipping/processing.

- If despite best efforts it is not possible to collect the biological samples or safety assessments (e.g., ECG, vital signs) within the interval predefined in the protocol (see APPENDIX 1), then the interval may be extended up to a maximum length of ± 7 days.
- If despite best efforts a safety assessment cannot be performed, the investigator must review the benefit-risk for participant continuation in the study and record this in the medical records.

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

# 10. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The participants' parent(s)/LAR have the right to withdraw the participant from study intervention and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to the participant's future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a participant(s) from study intervention, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 10.1 and Section 10.2.

## 10.1. Discontinuation of Study Intervention

- Parent(s)/LAR may decline to continue participating in study intervention and/or other protocol-required therapies or procedures at any time during the study.
- Parent(s)/LAR who choose to discontinue participating in study intervention and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, and in agreement with the sponsor, the participants should remain in the study to ensure safety surveillance and/or collection of outcome data.
- The investigator is to discuss with the participant's parent(s)/LAR the appropriate processes for discontinuation from study intervention or other protocol-required therapies. The investigator must discuss with the participant's parent(s)/LAR the possibilities for continuation of activities described in the SoA (APPENDIX 1) and must document this decision in the eCRF.
- These participants should complete an ET visit followed by 10-day taper period if clinically indicated (i.e., if no safety reasons prohibit continued treatment; refer to Section 8.1.2). A safety follow-up visit should be conducted 4 weeks after the participant's last dose of GWP42003-P. Remaining assessment visits and activities as determined by the investigator can still proceed as planned.

Reasons for removal from study intervention or procedural assessments include any of the following:

- Decision by the investigator.
- Decision by sponsor.
- Decision by regulatory authority.
- Withdrawal of parent(s)/LAR consent.
- Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects participant safety, as determined by the investigator (or designee).
- Protocol deviation that is considered to potentially compromise the safety of the participant.

- Noncompliance with study intervention.
- Noncompliance with any of the study assessments.
- Any clinically relevant sign or symptom that in the opinion of the investigator (or designee) warrants participant removal from study intervention.
- Liver Chemistry – Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the following conditions outlined or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
  - ALT or AST > 8 × ULN.
  - ALT or AST > 5 × ULN for more than 2 weeks.
  - ALT **or** AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5).

  Note: Prior to treatment discontinuation for the transaminase elevations noted above, the investigator may choose to confirm the transaminase elevations by repeating the following laboratory tests, tests within 24 to 48 hours: ALT, AST, TBL, INR, % eosinophils, gamma-glutamyl transferase (GGT), and alkaline phosphatase (also refer to Section 12.7). **Should the above transaminase elevation criteria be confirmed, the participant must permanently discontinue the study intervention. In cases where transaminase elevation withdrawal criteria are not met or confirmed, the dose of study intervention or a concomitant medication with known hepatotoxicity may be reduced following discussion with the medical monitor. The final decision regarding dose adjustments should be taken by the investigator.**
- Disease progression that compromises the ability of the participant to safely continue study intervention to the participant in the study.
- Participants who are withdrawn for nondrug related reasons may be replaced following discussion between the investigator and the sponsor. Participants withdrawn as a result of AEs thought to be related to study intervention, as determined by the investigator, will generally not be replaced. The decision regarding the replacement of participants will be documented.

The participant may also be permanently discontinued from treatment for any of the following:

- Participant or parent(s)/LAR noncompliance.
- AE (including clinically significant laboratory result) which, in the opinion of the investigator, would compromise the continued safe participation of the participant in the study.
- Did not meet eligibility criteria.

- Any evidence of drug abuse or drug diversion.
- Disease progression that compromises the ability of the participant to safely continue participating in the study.

## 10.2. Participant Discontinuation/Withdrawal from the Study

- A participant's parent(s)/LAR may decide to withdraw the participant from the study at any time at their own request, or the participant may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or compliance reasons.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If a participant is withdrawn from the study, the study monitor will be informed immediately. If there is a medical reason for withdrawal, the participant will be followed up by the investigator until satisfactory health has returned.
- At the time of discontinuing from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, an ET visit should be conducted, followed by a 10-day taper period if clinically indicated (refer to Section 8.1.2). A safety follow-up visit should be completed 4 weeks after the participant's last dose of GWP42003-P. See the SoA (APPENDIX 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant's parent(s)/LAR withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant is withdrawn from the study, her/his parent(s)/LAR may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Reasons for removal of a participant from the study are:

- Decision by the investigator.
- Decision by sponsor.
- Decision by regulatory authority.
- Withdrawal of parent(s)/LAR consent.
- Death.
- Lost to follow-up.
- Parent(s)/LAR noncompliance with study schedule.
- Parent(s)/LAR noncompliance with study intervention administration.

### 10.2.1. Lost to Follow-up

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

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

- The site must attempt to contact the participant's parent(s)/LAR and reschedule the missed visit as soon as possible and counsel the parent(s)/LAR on the importance of maintaining the assigned visit schedule and ascertain whether or not the parent(s)/LAR wishes to and/or should have the participant continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant's parent(s)/LAR (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant's parent(s)/LAR continue to be unreachable, then the participant will be considered to have withdrawn from the study.

Site personnel, or an independent third party, may attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

# 11. URGENT SAFETY MEASURES

The sponsor and investigator may take appropriate urgent safety measures in order to protect the participants of a clinical study against any immediate hazard to their health or safety. If such measures are taken by the investigator, they must notify the sponsor immediately or at least within 24 hours of awareness (sponsor contact details are provided in the trial centre file [APPENDIX 2]). The sponsor will report urgent safety measures to regulatory authorities by telephone within 24 hours of awareness, wherever possible, and will provide a written report to the regulatory authorities and IRB/IEC within 3 days.

# 12. ADVERSE EVENT REPORTING

## 12.1. Adverse Event Definition

For the purposes of this study, an AE is defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

The participant's expected seizure types do not routinely require documentation as AEs. However, any worsening, including new seizure types and change in the pattern or severity of existing seizure types, should be documented in the eCRF if deemed to meet the definition of an AE, in the investigator's opinion.

As part of the ongoing safety review, an independent Safety Monitoring Committee (SMC) will monitor any worsening of seizures, including emergence of new seizure types or change in the pattern or severity of existing seizure types. New seizure types should be discussed with the medical monitor and the ESCI, and a New Seizure Form should be submitted to the ESCI For review and approval (refer to Section 9.1.12.1).

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

The number of inpatient hospitalisations that are, in the investigator's opinion, due to epilepsy will be recorded in the participant's eCRF and through the SAE reporting process.

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

## 12.2. Serious Adverse Events

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

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

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

- Is a congenital anomaly/birth defect.
- Is medically significant**.

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

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

**The sponsor considers all convulsive and non-convulsive SE events to be medically significant events that should be reported to the sponsor as medically significant SAEs. Status epilepticus is defined as any seizure lasting 30 minutes or longer.**

## 12.3. Reporting Procedures for Serious Adverse Events

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

**All SAEs must be recorded in the eCRF immediately and within 24 hours of discovery or notification of the event.** The sponsor will be automatically notified that an SAE has been recorded. Any additional information required for a case (follow-up or corrections to the original case) will be requested by the sponsor through eCRF queries. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The investigator is not obliged to actively monitor for any new SAEs that occurred after the safety follow-up visit. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator should promptly notify the sponsor.

After the participant completes the safety follow-up visit, any other problem discovered that is deemed to be an unexpected safety issue and likely to have an impact on other study participants must be treated as an SAE and reported to the sponsor. Such poststudy SAEs do not need to be recorded on the participant's eCRF if editing rights to the eCRF have been removed due to final study data lock. The sponsor may request safety follow-up information after the safety follow-up visit in order to investigate a potential safety issue.

Contact details for SAE reporting are provided in the trial centre file.

## 12.4. Causality Assessment

Causality assessment is required for all AEs and SAEs. Causality assessment must only be assigned by the investigator. All cases judged as having a reasonable suspected causal relationship to the study intervention must be reported as such. The expression *"reasonable causal relationship"* is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

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

*"In your opinion is there a plausible relationship to the study intervention?"* The answer is either "yes" or "no".

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

Considering the explanation given above, investigators are strongly encouraged to express their opinion on what the cause of an AE might be. For individual participants, the investigator is usually in the best position to assess the underlying suspected cause of an AE. For all AEs and especially SAEs, it is important that the investigator assess not only the possible role of the study intervention but also other potential contributing factors. Factors for consideration of the underlying cause may include:

- Medical and disease history.
- Lack of efficacy/worsening of treated condition.
- Concomitant or previous treatment.
- Study intervention discontinuation.
- Protocol-related procedure.

## 12.5. Reporting Procedures for All Adverse Events

All AEs (including SAEs) occurring during the study will be reported on the running logs in the AE section of the eCRF. This includes all events from the time following the initiation of study intervention (Visit 3) up to and including the safety follow-up visit, whether or not attributed to study intervention and observed by the investigator or participant's caregiver.

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

**A. Adverse Event (Diagnosis or Syndrome if Known, or Signs and Symptoms)**

Where the investigator cannot determine a diagnosis, signs or symptoms should be recorded in the AE section of the eCRF. Once a diagnosis has been determined the AE section of eCRF must be updated to reflect the diagnosis in replacement of the original symptoms. In circumstances where only a provisional diagnosis is possible (working diagnosis), the eCRF must be updated to reflect the provisional diagnosis in replacement of the original symptoms. In some circumstances it may be relevant for the investigator to include the symptoms alongside the diagnosis in the verbatim event

description. However, the diagnosis (full or provisional) should be clearly stated, (e.g., headache and fever due to pneumonia).

**B. Adverse Event Start Date and Stop Date**

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

**C. Outcome**

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

- Recovered/Resolved.
- Recovered/Resolved with sequelae.
- Recovering/Resolving.
- Not recovered/Not resolved.
- Fatal.

**D. Severity**

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

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

A severe AE is not the same as a SAE. For example, a participant 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.

The severity of an AE will be recorded as one of the following:

- **Mild:** easily tolerated, does not interfere with normal daily activities, does not require intervention
- **Moderate:** causes some interference with daily activities; minimal, local, or noninvasive intervention indicated
- **Severe:** daily activities limited or completely halted; intervention indicated.

**E. Causality**

See Section 12.4 above.

**F. Action Taken with Study Medication**

This question refers to the action taken with the study intervention due to an AE. The action with the study intervention must be classed as:

- Dose Increased.
- Dose Not Changed.
- Dose reduced.
- Drug interrupted.
- Drug Withdrawn.
- Not Applicable.

## 12.6. Follow-up Procedures for Adverse Events

The investigator may be asked to provide follow-up information to the sponsor for any reported AEs or during the investigation of potential safety issues. Such requests for additional safety information may occur after the safety follow-up visit (i.e., after the study).

Adverse events considered related to the study intervention by the investigator or the sponsor should be followed up until resolution or the event is considered stable.

It will be left to the investigator's clinical judgment whether an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. Further details of withdrawal are presented in Section 10. If either of these occurs, the participant should proceed to an ET visit and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If a safety concern is identified following withdrawal of a participant, the sponsor may contact the investigator for additional follow-up information.

## 12.7. Potential Cases of Drug-Induced Liver Injury

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

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

These reports must be sent to the sponsor via email for SAE reporting within 24 hours of becoming aware of the results. In addition, please send a copy of the participant's baseline laboratory results with all reports to the sponsor. Sponsor contact details are provided in the trial centre file (APPENDIX 2).

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

important medical events. The investigator will arrange for the participant to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, TBL, INR, % eosinophils, alkaline phosphatase, and GGT levels, detailed history, and physical examination. Participants should be followed in this way until all abnormalities have normalised (in the investigator's opinion) or returned to the baseline state. However, if the above transaminase elevation criteria are confirmed by the first set of follow-up laboratory tests, the participant must permanently discontinue the study intervention.

Elevations in ALT **or** AST > 3 × ULN **or** TBL > 2 × ULN alone are not considered potential cases of drug-induced liver injury, but will be followed as detailed above, within 72 hours' notice of abnormal results. If the participant cannot return to the investigational site, repeat assessments may be done at a local laboratory and the results sent to the sponsor.

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

In accordance with the Regulation (EU) 536/2014, relevant parts of the FDA Code of Federal Regulations and any national regulations, the sponsor will inform investigators, regulatory authorities, and relevant IRBs/IECs of all relevant safety information. This will include the reporting of relevant SAEs and all Suspected Unexpected Serious Adverse Reactions (SUSARs). In the EU, submission of expedited safety reports to Eudravigilance will be performed via E2B.

This information will be provided through 2 sources:

1. Investigator's Brochure: a compilation of the clinical and non-clinical safety data available on the study intervention that is relevant to the trial. The Investigator's Brochure is updated annually or when important new safety information becomes available.
2. Council for International Organizations of Medical Sciences (CIOMS) reports: these reports are issued every time a SUSAR is reported to the sponsor. They provide information on individual case reports and are sent to all the regulatory authorities, the relevant central IRB/IEC that have approved the trial and investigators. As required, the investigator should notify their regional IRBs/IECs of SAEs or SUSARs occurring at their site and other AE reports, i.e., CIOMS reports and any additional safety documentation received from the sponsor, in accordance with local procedures.

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

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

The FDA guidance states that, accordingly, to satisfy the investigator's obligation to notify the IRB/IEC of unanticipated problems, any investigators participating in a multicentre study may rely on the sponsor's assessment and provide to the IRB/IEC a report of the unanticipated problem prepared by the sponsor.

The sponsor will inform investigators, regulatory authorities and relevant IRBs/IECs of any safety issues or case reports that are considered to be unanticipated and provide such reports as mentioned above. It should be noted that a single SUSAR report notified to investigators in the study does not necessarily constitute an unanticipated problem unless identified by the sponsor in the submission cover letter.

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

# 13. STATISTICAL CONSIDERATIONS

Further details of the proposed statistical analysis will be documented in the Statistical Analysis Plan (SAP), which will be finalised prior to any descriptive analysis of data pertaining to Study GWEP17005. Any deviations from the SAP will be described in the final clinical study report.

## 13.1. Sample Size, Power and Significance Levels

Up to 27 participants will be assigned to receive the study intervention in order to achieve 18 evaluable participants, which the Paediatric Investigational Plan for GWP42003-P considers sufficient to characterize PK in children < 2 years of age. Enrolment will be stratified to ensure that at least 5 participants each with LGS and DS (1 to < 2 years of age) and 8 participants with TSC (4 participants < 1 year of age and 4 participants aged 1 to < 2 years) are included in this study. The SAP will describe the definition of an evaluable participant in greater detail.

There will be no formal testing of statistical hypotheses in this study.

**Note**: Participants are considered "enrolled" when their parent(s)/LAR has/have signed the ICF (refer to Section 9.1.1).

## 13.2. Intermediate Analysis

Exploratory intermediate analyses may be conducted during the study to examine, for example, baseline data distribution, participant disposition, treatment exposure, or a subset of efficacy and safety outcomes, upon specific request. Results from these analyses may also support publication objectives (described elsewhere) or internal evaluation of trends. The justification and the details of any intermediate analysis will be documented in a separate SAP covering intermediate reporting.

## 13.3. Analysis Sets

**Screening Analysis Set**

All participants who are enrolled will be included. This analysis set will be used to describe administrative aspects of study enrolment, including reasons for screening failure.

**Safety Analysis Set**

All enrolled participants who receive at least 1 dose of GWP42003-P will be included. This analysis set will be used to estimate retention and all safety-related endpoints.

**Efficacy Analysis Set**

All enrolled participants who receive at least 1 dose of GWP42003-P and at least 1 post-baseline efficacy measurement (seizure diary or ITQOL-SF47). This analysis set will be used to estimate all efficacy-related endpoints.

- If warranted, a **Per-Protocol Analysis Set** may be additionally defined, in which participants with important protocol deviations that compromise efficacy assessments are excluded.

**PK Analysis Set**

All enrolled participants who receive at least 1 dose of GWP42003-P, have at least 1 postdose PK measurement on Visit 9 or the EOT/ET visit, and have not experienced any intercurrent events that could impact exposure. Intercurrent events include an AE of vomiting that occurs within 2 times the median time to maximum plasma concentration ($T_{max}$). This analysis set will be used for all PK-related endpoints.

## 13.4. Protocol Deviations

All protocol deviations will be listed.

## 13.5. General Considerations

Unless stated otherwise, continuous variables will be summarised showing the number of non-missing values (n), mean, standard deviation or standard error, median, interquartile range, minimum and maximum. Categorical variables will be summarised showing the number and percentage of participants in each category.

Summaries will be presented by indication and overall, unless otherwise specified.

For clinic visit-based endpoints (unless otherwise specified), baseline is defined as the last record or measure collected prior to the first dose of GWP42003-P.

## 13.6. Accountability and Background Characteristics

### 13.6.1. Enrolment and Disposition

All enrolled participants (screened, prematurely terminated study intervention, etc.) will be accounted for in the enrolment and disposition summary tables.

### 13.6.2. Baseline and Demographic Characteristics

Age, sex, race (as per local data protection laws in each specific country) and any other demographic or baseline characteristics will be summarised using appropriate summary statistics.

### 13.6.3. Medical History

Previous and current medical conditions (including details of TSC, LGS, or DS and other comorbid disorders) will be summarised by System Organ Class (SOC).

### 13.6.4. Concomitant Medication

Concomitant medications (including ASMs and antiseizure therapies) taken prior to and during the study will be summarised separately; details will be specified in the SAP.

### 13.6.5. Treatment Compliance and Extent of Treatment Exposure

Exposure to the study intervention overall and at each dose level, expressed in dosing days, in addition to treatment compliance will be summarised.

## 13.7. Endpoints and Statistical Methods

### 13.7.1. Primary Safety and Pharmacokinetic Endpoints

Analysis and reporting of the primary safety and PK endpoint parameters will include descriptive statistical summaries of each element at baseline and follow-up study visits where collection was performed.

#### 13.7.1.1. Adverse Events

Adverse events will be collected as specified in Section 9.1.1414, are defined in Section 12.1, and will be coded according to the Medical Dictionary for Regulatory Activities dictionary.

Descriptive presentations of AEs will be given by preferred term and SOC for the safety analysis set. The number of participants reporting at least 1 AE will be provided. Adverse events will be summarised in terms of the number of participants with at least 1 event (N) and the percentage of participants with at least 1 event (%).

The following summaries will be produced as a minimum:

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

#### 13.7.1.2. Clinical Laboratory Data

Clinical laboratory data will be summarised at screening/baseline and at each time point during the treatment period using appropriate summary statistics. Categorical shift tables will be presented, showing the numbers of participants with values outside the normal range. Change from baseline will also be summarised by visit.

#### 13.7.1.3. Vital Signs, 12-Lead Electrocardiogram, Physical Examination and Other Safety Data

Vital signs, ECG, physical examination, and neurodevelopmental assessment data will be summarised, at screening/baseline and at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs from baseline will also be summarised.

#### 13.7.1.4. Pharmacokinetics

Plasma concentrations for CBD and its major metabolites (7-hydroxy-cannabidiol [7-OH-CBD] and 7-carboxy-cannabidiol [7-COOH-CBD]) will be summarised by nominal time, participant, and dose level. Pharmacokinetic data collected in this study will be combined with data from other studies to estimate PK parameters via a population PK analysis; results of this analysis will be reported separately.

### 13.7.2. Primary and Secondary Efficacy Endpoints

Analysis and reporting of the primary and secondary efficacy endpoints will include descriptive statistical summaries of seizure frequency, percent change from baseline, and percent change from baseline categories (i.e., increase or reduction, as specified in Section 2). Because GWP42003-P dose levels are not fixed during the study, summaries as well as 95% confidence intervals for percent change from baseline will be reported by indication and overall. Ancillary tables summarising efficacy endpoints by seizure type, based on indication, will also be provided.

#### 13.7.2.1. Total Countable Seizures

All measurements of total countable seizures (average per 28 days) will be determined as recorded by caregivers on seizure diaries at Week 12, every 4 weeks thereafter, and during the 4-week period prior to EOT.

**Primary Efficacy Endpoint**

The percentage change from baseline in indication-specific countable seizures* will be summarised using descriptive statistics and including the lower and upper quartiles.

*Indication-specific seizures are defined as follows:

- DS: Convulsive seizures, defined as tonic-clonic, tonic, clonic, or atonic.
- LGS: Drop seizures, defined as an attack or spell (atonic, tonic, or tonic-clonic) involving the entire body, trunk, or head that led or could have led to a fall, injury, slumping in a chair, or hitting the participant's head on a surface.
- TSC: Focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalised convulsive seizures and generalised seizures (tonic-clonic, tonic, clonic, or atonic) that are countable.

Additional seizure categories include other generalised or focal seizures (myoclonic, absence, focal non-motor, IS/ES, other) and SE (convulsive and non-convulsive seizures lasting 30 minutes or longer) that are **recognisable and countable**.

**Secondary Efficacy Endpoints**

- The number and percentage of participants considered treatment responders (i.e., with a $\geq$ 50% reduction in total countable seizures) will be summarised using descriptive statistics and including the lower and upper quartiles.
- The categorical percentage change from baseline to EOT in total countable seizures will be summarised, with categories defined as follows:
  - $>$ 25% (increase)
  - $\geq$ 0% to $\leq$ 25% (increase)
  - $>$ –25% to $<$ 0% (reduction)
  - $>$ –50% to $\leq$ –25% (reduction)

- $> -75\%$ to $\leq -50\%$ (reduction)
- $\leq -75\%$ (reduction)

- Seizure freedom, defined as 100% reduction from baseline in total countable seizures, will be summarised.

### 13.7.3. Other Secondary and Exploratory Endpoints

To assess treatment retention, the percentage of participants still taking GWP42003-P at Week 12 and every 4 weeks thereafter will be estimated using the Kaplan-Meier method. Time at risk will begin on the date of first dose. Participants discontinuing study treatment for any reason will be classified as a failure as of their last known treatment date. Participants who withdraw from the study or are lost to follow-up for non-treatment-related reasons will be considered censored as of their last known treatment date.

Endpoints related to VEEG-recorded seizures (listed in Section 2) will be summarised in a manner similar to those related to seizures recorded in ePRO diaries. Where possible, multichannel VEEG-recorded seizures will be correlated with the seizure frequency recorded by investigators and caregivers in ePRO diaries.

Results of the ITQOL-SF47 and change from baseline will be summarised for each study time point.

[redacted]

# 14. SAFETY MONITORING COMMITTEE

An independent SMC will be used in this study to evaluate participant safety. Details of the composition and standard operating procedures of the SMC will be detailed in a separate charter.

# 15. REGULATORY AND ETHICAL OBLIGATIONS

## 15.1. Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the current version and subsequent amendments of the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite Guideline for GCP Topic E6(R2), Regulation (EU) 536/2014, the EU GCP Directive and the clinical trial regulations adopting European Commission Directives into national legislation.

## 15.2. Informed Consent

- The investigator or their representative will explain the nature of the study to the participant's parent(s) or LAR and answer all questions regarding the study.

Participant's parent(s) or LAR must be informed that their participation is voluntary. Participant's parent(s) or LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Regulation (EU) 536/2014, the Health Insurance Portability and Accountability Act of 1996 requirements (where applicable), Regulation (EU) 2016/679 General Data Protection Regulation requirements (where applicable), and the IRB/IEC or trial centre' existing population database, and/or through referrals, and/or other materials (e.g., flyers, patient advocacy group newsletters, social media etc.) which would be approved by the IRB/IEC.

## 15.3. Institutional Review Board

A copy of the protocol, proposed ICF, master ICF, other participant information material, any proposed advertising material and any further documentation requested must be submitted to the IRB/IEC for written approval. The sponsor must receive a copy of the written approval of the appropriate version of the protocol and ICF before recruitment of participants into the study and shipment of the study intervention.

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

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

The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, Regulation (EU) 536/2014, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

## 15.4. Recruitment Strategy

The study will utilize various tools for recruitment, including but not limited to flyers, patient advocacy outreach, website, and social media.

## 15.5. Financial Disclosure

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

## 15.6. Pre-study Documentation Requirements

The investigator is responsible for forwarding the following documents to the sponsor for review before allowing any participants to consent for entry into the study:

- Signed and dated protocol signature page.
- Copy of IRB/IEC approved ICF (including version number and date) and other participant information material.
- Copy of the IRB/IEC approval of the protocol, ICF forms (including version number and date) and other participant information material.
- Up to date curricula vitae and medical licenses (as per local regulations) of the principal investigator (PI) and all sub-investigators.
- The IRB/IEC composition and/or written statement of the IRB/IEC in compliance with the FDA regulations relating to GCP and clinical studies, Regulation (EU) 536/2014, the EU GCP Directive, or the ICH Tripartite Guidelines for GCP Topic E6(R2) where the Regulation (EU) 536/2014and EU GCP Directive do not apply.
- Signed and dated laboratory normal ranges and documentation of laboratory certification (or equivalent) unless using central laboratory arranged by the sponsor.
- Signed and dated clinical study agreement (including participant/investigator indemnity insurance and financial agreement).
- Form FDA 1572, if required.
- Drug Enforcement Administration Registration (as required).
- Completed financial disclosure statements for the PI and all sub-investigators, if relevant.

The sponsor will ensure that the site is informed of when screening of participants can commence.

## 15.7. Participant Confidentiality

The investigator must ensure that the participant's anonymity is maintained. In the eCRFs and within databases used to collect the study data or other documents submitted to the sponsor, participants should be identified by their study participant number only. Documents that are not for submission to the sponsor (e.g., signed ICF) should be kept in strict confidence by the investigator.

In compliance with the FDA regulations relating to GCP and clinical studies, and the EU CTR/ICH Tripartite Integrated Addendum to ICH E6(R1): Guideline for GCP

E6(R2), it is required that the investigator and institution permit authorised representatives of the company, the regulatory authorities and the IRB/IEC have direct access to review the participant's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the participant that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the participant.

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

The contract between the sponsor and trial centres specifies the responsibilities of the parties' related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

# 16. ADMINISTRATIVE AND LEGAL OBLIGATIONS

## 16.1. Protocol Amendments and End of Study or Termination

Protocol amendments must be made only with the prior approval of sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB/IEC and regulatory authorities must be informed of all amendments and give approval for any substantial amendments. Amendments for administrational changes can be submitted to the IRB/IEC for information only. The investigator must send a copy of the approval letter from the IRB/IEC to the sponsor.

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

## 16.2. Study Documentation and Storage

The investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties.

Source documents are original documents, data and records containing all protocol-specified information from which the participant's eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, electronic data captured by ePRO, microfiches, VEEG recordings, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralised filing system of all study-related, essential documentation (as outlined in the ICH Tripartite Guidelines for GCP Topic E6[R2], Section 8.2), suitable for inspection at any time by sponsor representatives and/or applicable regulatory authorities. Elements should include:

- Participant files containing completed eCRFs, ICF forms and supporting copies of source documentation.
- Study files containing the protocol with all amendments, IB, copies of pre-study documentation (see Section 15.6) and all correspondence to and from the IRB/IEC and the sponsor.
- Enrolment log of all participants who consented to take part in the study.
- Screening and recruitment log of all participants screened and whether or not they were recruited into the study (i.e., dosed with GWP42003-P).
- Proof of receipt, study intervention accountability record, return of study intervention for destruction, final study intervention reconciliation statement and all drug related correspondence.

In addition, all original source documents supporting entries in the eCRFs, diary data and electronic data captured by ePRO must be maintained and be readily available.

Following completion or termination of a clinical study, the sponsor will initiate proper archive of clinical study-related documentation and electronic records

generated by the investigator and/or the sponsor. Unless local requirements require archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. However, the medical files of participants shall be archived in accordance with national law. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by the sponsor.

The sponsor will inform the investigators for each site in writing of the need for record retention. No study document may be destroyed without prior written agreement between the sponsor 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 the sponsor in writing of the new responsible person and/or the new location.

## 16.3. Study Monitoring and Data Collection

The sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs and other pertinent data) provided that participant confidentiality is respected.

The sponsor study monitor, or designee, is responsible for inspecting (on-site or remotely) the eCRFs and available ePRO/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 must have (direct or remote) access to participant medical records and other study-related records needed to verify the entries on the eCRFs.

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

To ensure the quality of clinical data across all participants and sites, a clinical data management review will be performed on participant data received at the sponsor or a Clinical Research Organisation (CRO). During this review, participant 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, ICH Tripartite Guidelines for GCP Topic E6(R2) and all other applicable regulatory requirements. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and then returned to the sponsor or the CRO, as applicable.

## 16.4. Electronic Data Collected by Electronic Patient Reported Outcomes and Video Electroencephalogram

Source data for the assessments collected via ePRO and VEEG will be managed by the service providers in accordance with ICH Tripartite Guidelines for GCP Topic E6(R2) and in adherence to a quality management system. All data will be stored in a secure (e.g., redundant hardware, password control, limited physical access to servers), fully audit-trailed environment with appropriate industry standard backup and offsite storage practices.

Where applicable, access for participants providing assessments and investigators will be authenticated and meet industry standards and comply with the requirements

outlined in the FDA Code of Federal Regulations Title 21, Part 11, Subpart B (Electronic Records).

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

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

## 16.5. Quality Assurance

In accordance with the FDA regulations EU CTR/ICH Tripartite Guidelines for GCP the sponsor's audit plans, representatives from the sponsor's Clinical Quality Assurance Department may select this study for audit. Inspection of site facilities, e.g., pharmacy, drug storage areas, laboratories, and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, the EU CTR (when applicable)/ICH Tripartite Guidelines for GCP Topic E6(R2) and applicable regulatory requirements.

The sponsor study monitor, or designee, is responsible for inspecting (on-site or remotely) the eCRFs and available electronic 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 must have (direct or remote) access to participant medical records and other study-related records needed to verify the entries on the eCRFs.

## 16.6. Compensation

The sponsor will indemnify the investigator and the trial centre in the event of any claim in respect of personal injury arising due to a participant's involvement in the study, providing that the study protocol has been adhered to. This would include claims arising out of or relating to the administration of the study intervention or any clinical intervention or procedure provided for or required by the protocol to which the clinical study participant would not otherwise have been exposed, providing there is no evidence of negligence on behalf of the investigator or their team. The sponsor will not be liable for any claims arising from negligence on the part of the investigator or their team.

## 16.7. Publication Policy

As the sponsor of the study, Jazz Pharmaceuticals. is solely responsible for disclosing results on ClinicalTrials.gov, EU CTR, and other public registries in accordance with applicable global laws and regulations. By signing this protocol, the investigator acknowledges that all posting requirements are solely the responsibility of the sponsor and agrees not to submit any information about the study or its results.

The sponsor recognises that there is a responsibility under the regulatory guidelines to ensure that results of scientific interest arising from this clinical study are appropriately published and disseminated. They will coordinate this dissemination and may solicit input and assistance from the chief/PIs.

A summary of the results of this study will be made available on http://www.clinicaltrials.gov and https://euclinicaltrials.eu/(as applicable), as required by US and EU law.

Any publication of the study data will be made in accordance with the terms of the Clinical Trial Agreement.

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

The sponsor also reserves the right to delay the submission of such information by a period of up to 6 months from the date of first submission to them in order to allow them to take steps to protect proprietary information where applicable.

## 16.8. Intellectual Property Rights

All intellectual property rights owned by or licensed to either the sponsor 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 the sponsor and, as such, the PI must promptly disclose all knowledge to the sponsor and refrain from using such knowledge without the prior written consent of the sponsor.

## 16.9. Confidential Information

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

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# APPENDIX 1 SCHEDULE OF ACTIVITIES

**Schedule of Activities**

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| **General Study Activities** | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | ICF must be signed prior to any study-related activities, including the collection of a suitable VEEG from the participant's medical records. |
| I/E Criteria | X | | X | | | | | | | | | | | | | | | | Recheck eligibility before first dose of GWP42003-P. |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| Demography | X | | | | | | | | | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | | | | | | | | | • Clinical condition: Complete seizure, epilepsy (lifetime), Status Epilepticus, hospital-isations; diagnosis per investigator and as defined by ILAE/TSC Consensus Conference (2012).<br>• Diagnostic: 1) TSC: Imaging (e.g., |

**Schedule of Activities**

| Study Period Visit | Screening/ Baseline Period (4 weeks) | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| Visit Number | 1 | 2[d] | 3[e] | 4[d] | 5 | 6[d] | 7 | 8[d] | 9 | 10 | 11[d], 12[d] | 13 | 14[d], 15[d] | 16 | 17[d], 18[d], 19[d] | 20 | 21 | 22[d] | |
| Day | −28 | −14 | 1 | 8 | 15 | 22 | 29 | 36 | 57 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309, 337 | 365 | 375 | 403 | |
| Window (days) | ±3 | | +3 | | | ±3 | | | ±7 | | | | | | | | +3 | ±3 | |
| | | | | | | | | | | | | | | | | | | | ultrasound, MRI, CT scan);<br>2) LGS/DS: EEG<br>• Genetic: *TSC1/TSC2* genetic mutation status for TSC; *SCN1A* for DS (where known) |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| Prior Medications | X | X | | | | | | | | | | | | | | | | | Any medications taken in 3 months prior to Visit 3. Additionally, all prior/current ASMs, rescue medications, and vaccinations (from birth to present) (Section 9.1.4). |
| **Study Intervention** | | | | | | | | | | | | | | | | | | | |
| Stratification | | | X | | | | | | | | | | | | | | | | |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| Dispense Study Intervention | | | X | | X | | X | | X | X | | X | | X | | X | | | • Sufficient GWP42003-P will be dispensed to last until the next dispensing visit.<br>• At Visit 3, participants will take their first dose of GWP42003-P in the clinic.<br>• GWP42003-P will be administered in the clinic on days where PK |

**Schedule of Activities**

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| Visit Number | 1 | 2[d] | 3[e] | 4[d] | 5 | 6[d] | 7 | 8[d] | 9 | 10 | 11[d], 12[d] | 13 | 14[d], 15[d] | 16 | 17[d], 18[d], 19[d] | 20 | 21 | 22[d] | |
| Day | −28 | −14 | 1 | 8 | 15 | 22 | 29 | 36 | 57 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309, 337 | 365 | 375 | 403 | |
| Window (days) | ±3 | | +3 | | | ±3 | | | ±7 | | | | | | | | +3 | ±3 | |
| | | | | | | | | | | | | | | | | | | | samples are collected.<br>• In cases where participants are not able to attend study visits due to special circumstances (e.g., COVID-19 pandemic), the investigator will discuss with the sponsor potential mitigation approaches for |

**Schedule of Activities**

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | | **±3** | | | **±7** | | | | | | | | **+3** | **±3** | |
| | | | | | | | | | | | | | | | | | | | GWP42003-P dispensing, secure delivery, and collection. |
| Collect Study Intervention/ Compliance Review | | | | | X | | X | | X | X | | X | | X | | X | X | | |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| **Safety and Tolerability** | | | | | | | | | | | | | | | | | | | |
| Physical Examination | X | | X | | X | | X | | X | X | | X | | X | | X | X | | • Each visit: Height/ length, weight, and head circum-ference<br>• Visit 1: full physical examination<br>• Subsequent clinic visits: abbreviated physical examination (as needed/ clinically indicated) |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | | **±3** | | | **±7** | | | | | | | | **+3** | **±3** | |
| Comprehensive neurodevelopmental assessment | | | X | | | | | | | | | X | | | | X | | | Section 9.1.6 |
| CGIC/S | | | X | | | | | | | | | X | | | | X | | | Section 9.1.12.4 |
| Vital Signs | X | | X | | X | | X | | X | X | | X | | X | | X | X | | Section 9.1.77 |
| ECG | X | | X | | | | X | | X | | | X | | X | | X | | | |
| Haematology | X | | X | | | | X | | X | | | X | | X | | X | | | Baseline results to be reviewed by a physician prior to Visit 3 (Section 9.1.1010). |
| Chemistry | X | | X | | X | | X | | X | X | | X | | X | | X | | | |

## Schedule of Activities

| Study Period Visit | Screening/ Baseline Period (4 weeks) | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | | **±3** | | | **±7** | | | | | | | | **+3** | **±3** | |
| Urinalysis | X | | | | | | X | | | X | | X | | X | | X | | | • Complete when possible.<br>• Baseline results to be reviewed by a physician prior to Visit 3.<br>• Urine samples will be sent for further analysis only if the local labs identify relevant findings. |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| Optional Blood Sample | | | X | | | | | | | | | | | | | | | | Complete when possible; refer to Section 9.1.10.3 |
| Optional Plasma Sample | | | X | | | | | | | | | | | | | X | | | |
| Adverse Event | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | • AEs will be collected from the start of study intervention until the safety follow-up visit, whether or not attributed to study intervention and observed by the |

**Schedule of Activities**

| Study Period Visit | Screening/ Baseline Period (4 weeks) | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| Visit Number | 1 | 2[d] | 3[e] | 4[d] | 5 | 6[d] | 7 | 8[d] | 9 | 10 | 11[d], 12[d] | 13 | 14[d], 15[d] | 16 | 17[d], 18[d], 19[d] | 20 | 21 | 22[d] | |
| Day | −28 | −14 | 1 | 8 | 15 | 22 | 29 | 36 | 57 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309, 337 | 365 | 375 | 403 | |
| Window (days) | ±3 | | +3 | | | ±3 | | | ±7 | | | | | | | | +3 | ±3 | |
| | | | | | | | | | | | | | | | | | | | investigator or caregiver.<br>• Includes worsening of seizures.<br>• Refer to Section 9.1.1414 (for AEs) and Section 9.1.12.1 (for seizure class-ification). |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | | **±3** | | | **±7** | | | | | | | | **+3** | **±3** | |
| Concomitant Medications | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Any medications (or changes thereof) on or after Visit 3 and throughout study participation, including ASMs, rescue medications, and vaccinations (Section 9.1.4). |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| Visit Number | 1 | 2[d] | 3[e] | 4[d] | 5 | 6[d] | 7 | 8[d] | 9 | 10 | 11[d], 12[d] | 13 | 14[d], 15[d] | 16 | 17[d], 18[d], 19[d] | 20 | 21 | 22[d] | |
| Day | −28 | −14 | 1 | 8 | 15 | 22 | 29 | 36 | 57 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309, 337 | 365 | 375 | 403 | |
| Window (days) | ±3 | | +3 | | ±3 | | | | ±7 | | | | | | | | +3 | ±3 | |
| **Pharmacokinetics** | | | | | | | | | | | | | | | | | | | |
| PK | | | X | | X | | X | | X | | | | | | | X | | | • At all indicated PK visits, samples are to be collected within 60 minutes prior to morning GWP42003-P dose (i.e., trough collection)<br>• At Visit 9 and Visit 20, 3-hour and 6-hour postdose samples (≥ 2 hours between |

## Schedule of Activities

| Study Period Visit | Screening/ Baseline Period (4 weeks) | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| Visit Number | 1 | 2[d] | 3[e] | 4[d] | 5 | 6[d] | 7 | 8[d] | 9 | 10 | 11[d], 12[d] | 13 | 14[d], 15[d] | 16 | 17[d], 18[d], 19[d] | 20 | 21 | 22[d] | |
| Day | −28 | −14 | 1 | 8 | 15 | 22 | 29 | 36 | 57 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309, 337 | 365 | 375 | 403 | |
| Window (days) | ±3 | | +3 | | | ±3 | | | ±7 | | | | | | | | +3 | ±3 | |
| | | | | | | | | | | | | | | | | | | | each sampling time point) are also to be collected.<br>• Caregivers must record the participant's meals (timing and content) during the 24 hours prior to sample collection (Section 9.1.12.2).<br>• Doses adjustments should be avoided |

**Schedule of Activities**

| Study Period Visit | Screening/ Baseline Period (4 weeks) | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| Visit Number | 1 | 2[d] | 3[e] | 4[d] | 5 | 6[d] | 7 | 8[d] | 9 | 10 | 11[d], 12[d] | 13 | 14[d], 15[d] | 16 | 17[d], 18[d], 19[d] | 20 | 21 | 22[d] | |
| Day | −28 | −14 | 1 | 8 | 15 | 22 | 29 | 36 | 57 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309, 337 | 365 | 375 | 403 | |
| Window (days) | ±3 | | +3 | | | ±3 | | | ±7 | | | | | | | | +3 | ±3 | |
| | | | | | | | | | | | | | | | | | | | within the 3 days prior to PK visits. PK sample collection should not occur until > 3 days following any dose adjustment. Doses may be adjusted on PK visits after all PK samples have been collected (Section 9.1.10.2). |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| **Efficacy** | | | | | | | | | | | | | | | | | | | |
| Send Information to ESCI | X | | | | | | | | | | | | | | | | | | • Complete and submit provided forms (SIF for TSC, SIF/DRF for DS and LGS, and EDRS for all participants) and supporting information within 24 hours of Visit 1.<br>• Any new seizure types after initial ESCI approval must be |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | | **±3** | | | **±7** | | | | | | | | **+3** | **±3** | |
| | | | | | | | | | | | | | | | | | | | reported via the New Seizure Form for ESCI review and approval.<br>• Refer to Section 9.1.12.1. |
| Seizure Classification | X | X | | | | | | | | | | | | | | | | | Caregivers must be contacted immediately for retraining if the ESCI identifies any misclassified seizures (Section 9.1.12.1). |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| ePRO/Paper Seizure Diary Training | X | X | | | | | | | | | | | | | | | | | • The paper seizure diary is only required during the screening/baseline period.<br>• Caregivers must be contacted immediately for retraining if the ESCI identifies any misclassified seizures before Visit 3.<br>• Refer to Section 9.1.12.1. |
| ePRO/Paper Seizure Diary Completion | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| ePRO/Paper Seizure Diary Review | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | | **±3** | | | **±7** | | | | | | | | **+3** | **±3** | |
| VEEG | X | | | | | | | | | | | | | | | X | | | • Baseline VEEG will be obtained from the medical records (if available and taken within 1 year of Visit 1); otherwise, must be completed and read by an investigator and independent reviewer prior to Visit 3.<br>• Additional VEEG |

## Schedule of Activities

| Study Period | Screening/ Baseline Period | | Treatment Period (52 weeks) | | | | | | | | | | | | | | End of Taper[b] | Safety Follow-up[c] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fixed | | Flexible Dose Optimisation | | | | | | | | | | | EOT /ET[a] | | | |
| **Visit Number** | **1** | **2[d]** | **3[e]** | **4[d]** | **5** | **6[d]** | **7** | **8[d]** | **9** | **10** | **11[d], 12[d]** | **13** | **14[d], 15[d]** | **16** | **17[d], 18[d], 19[d]** | **20** | **21** | **22[d]** | |
| **Day** | **−28** | **−14** | **1** | **8** | **15** | **22** | **29** | **36** | **57** | **85** | **113, 141** | **169** | **197, 225** | **253** | **281, 309, 337** | **365** | **375** | **403** | |
| **Window (days)** | **±3** | | **+3** | | **±3** | | | | **±7** | | | | | | | | **+3** | **±3** | |
| | | | | | | | | | | | | | | | | | | | criteria are provided in Section 6.1. |
| Quality of Life | | | X | | | | | | | | | | | | | X | | | Section 9.1.12.3 |

Abbreviations: AE = adverse event; ASM = antiseizure medication, CGIC/S = Clinician Global Impression of Change/Severity; COVID-19 = corona virus disease-19; CT = computerised tomography; DRF = Diagnostic Review Form; DS = Dravet syndrome; ECG = electrocardiogram; EDRS = Epilepsy Diary Reference Sheet; EEG = electroencephalogram; EOT = end of treatment; ePRO = electronic patient-reported outcome; ESCI = Epilepsy Study Consortium; ET = early termination; ICF = informed consent form; I/E = inclusion/exclusion; ILAE = International League Against Epilepsy; LGS = Lennox-Gastaut syndrome; MRI = magnetic resonance imaging; PK = pharmacokinetic; *SCN1A* = sodium voltage-gated channel alpha subunit 1; SIF = Seizure Identification Form; TSC = tuberous sclerosis complex; VEEG = video electroencephalogram.

[a] Participants who discontinue prior to Visit 20 should attend an ET visit as soon as possible (Section 10).

[b] A 10-day taper period follows the EOT/ET visit (unless not possible for safety reasons).

[c] Occurs 4 weeks after the end-of-taper visit or last dose (as applicable; see Section 10).

[d] Phone Visit

[e] Visit 3 occurs 14 days (+ 3 days) after Visit 2, but not < 28 days after Visit 1.

# APPENDIX 2 STUDY PERSONNEL

## Appendix 2.1 Investigator Details

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

## Appendix 2.2 Sponsor Contact Details

| | |
|---|---|
| Sponsor: | Jazz Pharmaceuticals Research UK Limited<br>Building 730, Kent Science Park<br>Sittingbourne, Kent<br>United Kingdom, ME9 8AG<br>Tel: +44 8081890387<br>Fax: +44 (0) 1223 235 667 |
| Medical Advisor, 24-hour Emergency Contact details, Pharmacovigilance Department (for SAE reporting), and Clinical Project Manager: | Please refer to the Sponsor and Related Contact Details form in the trial centre file. |
| Clinical Trial Supplies: | G-Pharm Ltd<br>Tel: +44 (0) 1795 435 029<br>Fax: +44 (0) 1795 475 439 |

## Appendix 2.3 Contract Research Organisations

Premier Research Europe

1st Floor, Rubra 2

Mulberry Business Park

Fishponds Road

Wokingham, RG41 2GY

United Kingdom

Tel: +44 118 936 4000

## Appendix 2.4 Bioanalytical Laboratory

Covance Laboratories Limited

Otley Road

Harrogate, North Yorkshire, HG3 1PY

United Kingdom

Tel: +44-142-350-0011

## Appendix 2.5 Video EEG Vendor

Lifelines Neuro Company, LLC

411 Edwardsville Road

Troy, IL 62294

United States

Tel: +1-866-889-6505

# APPENDIX 3 QUESTIONNAIRES/ASSESSMENTS

## Appendix 3.1 Diagnostic Criteria for Clinical Diagnosis of Tuberous Sclerosis

The following diagnostic criteria were adapted from the 2012 International TSC Consensus Conference (Northrup 2013).

**Genetic Diagnostic Criteria for *Definite* TSC**

The identification of either a *TSC1* or *TSC2* pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC.

A pathogenic mutation is defined as a mutation that clearly inactivates the function of the *TSC1* or *TSC2* proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment. Other *TSC1* or *TSC2* variants whose effect on function is less certain do not meet these criteria and are not sufficient to make a definite diagnosis of TSC.

**Note:** Ten percent to 25% of patients with TSC have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

**Clinical Diagnostic Criteria for TSC**

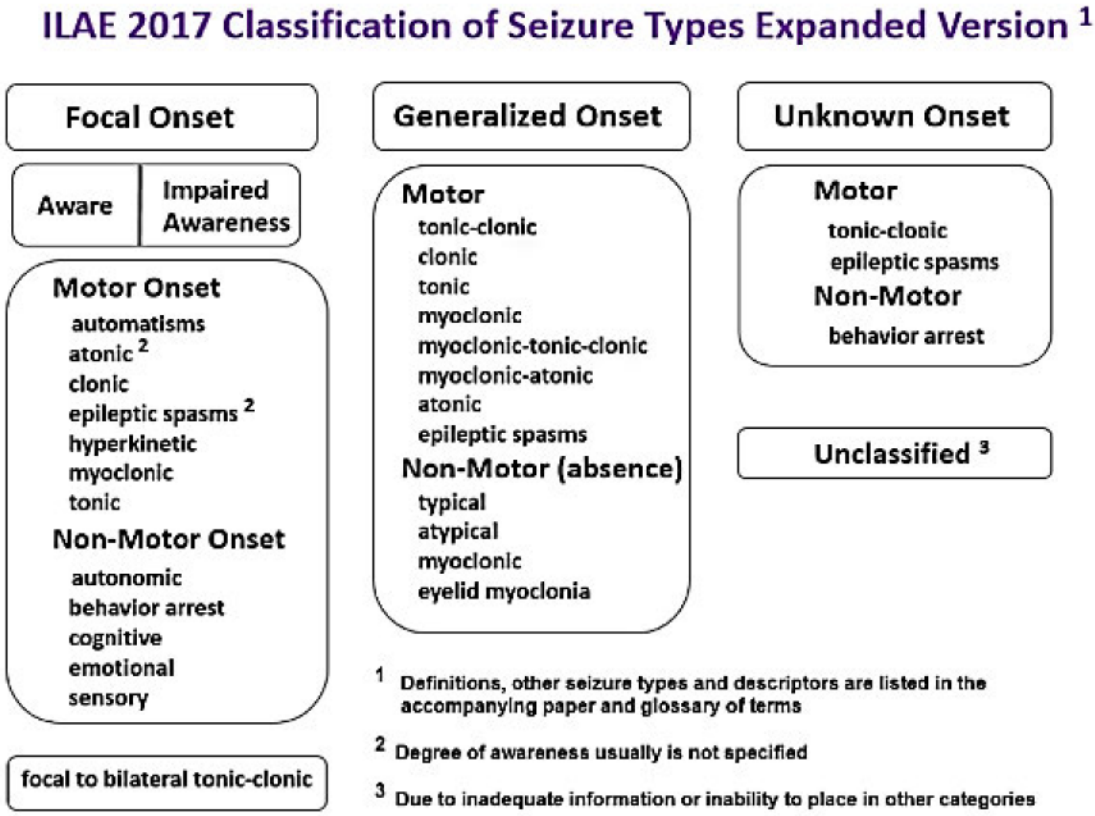
| Major Features | Minor Features |
|---|---|
| Hypomelanotic macules (≥ 3, at least 5-mm diameter) | "Confetti" skin lesions |
| Angiofibromas (≥ 3) or fibrous cephalic plaque | Dental enamel pits ( >3) |
| Ungual fibromas (≥ 2) | Intraoral fibromas (≥ 2) |
| Shagreen patch | Retinal achromic patch |
| Multiple retinal hamartomas | Multiple renal cysts |
| Cortical dysplasias* | Nonrenal hamartomas |
| Subependymal nodules | |
| Subependymal giant cell astrocytoma | |
| Cardiac rhabdomyoma | |
| Lymphangioleiomyomatosis (LAM)† | |
| Angiomyolipomas (≥ 2)† | |

*Includes tubers and cerebral white matter radial migration lines.
†A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

**Definite Diagnosis:** Two major features **or** 1 major feature with ≥ 2 minor features

**Possible Diagnosis:** Either 1 major feature **or** ≥ 2 minor features

# Appendix 3.2 International League Against Epilepsy Seizure Classification



# Appendix 3.3 Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors

Preterm and term neonates have very limited blood volume and, when sick, are often anaemic due to frequent routine sampling. Micro-methods on dry spots and scavenged blood remnants should be used whenever possible, since they reduce trial-related blood loss. Opportunistic, population, or sparse sampling, or other innovative methods could also reduce the frequency and volume of blood sampling. Although not evidence based, the following recommendations can be made: per individual, the research related blood loss (including any waste) as a general rule should not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time. This recommendation leads to the allowable sample volumes, indicated in the table below. Routine health care may require significant blood sampling (recorded in infants and neonates), and the indicated research related blood volumes may even be excessive, especially in (preterm newborn) infants. This means that in individual cases, acceptable research related blood loss may be lower than indicated in the table below. Research related blood sampling and volumes should always be justified in the protocol and explained in the patient information material. Blood transfusions (or iron or erythropoietin supplementation) should not be used as a convenience to justify increased volume or frequency of blood sampling as per relevant EU guidance on ethical considerations for clinical trials on medicinal products conducted with minors.

| **Body weight (kg)** | **Circulating total blood volume (ml)** | **Maximum allowable sample volume over 4 weeks (ml) - 3% of total blood volume** | **Maximum allowable sample volume at single time (ml) - 1% of total blood volume** |
|---|---|---|---|
| 0.5 - 1.5 | 50 - 150 | 1.5 -4.5 | 0.5 – 1.5 |
| 2.5 - 5 | 250 - 500 | 7.5 – 15 | 2.5 – 5 |
| 5 - 12 | 480 - 960 | 14.4 – 28.8 | 4.8 - 9.6 |
| 12 - 20 | 960 - 1600 | 28.8 – 48 | 9.6 -16 |
| 20 - 30 | 1600 - 2400 | 48 – 72 | 16 – 24 |
| 30 - 70 | 2400 - 5600 | 48 – 168 | 24 – 56 |

Table: Maximum allowable research-related blood sample volumes. Total blood volume is approximately 80-90 ml/kg body weight, in neonates approximately 100 ml/kg body weight. Of note: when routine health care requires significant blood sampling, these maximums may even be excessive.

Adapted from: Chapter V: Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (EudraLex – Volume 10).

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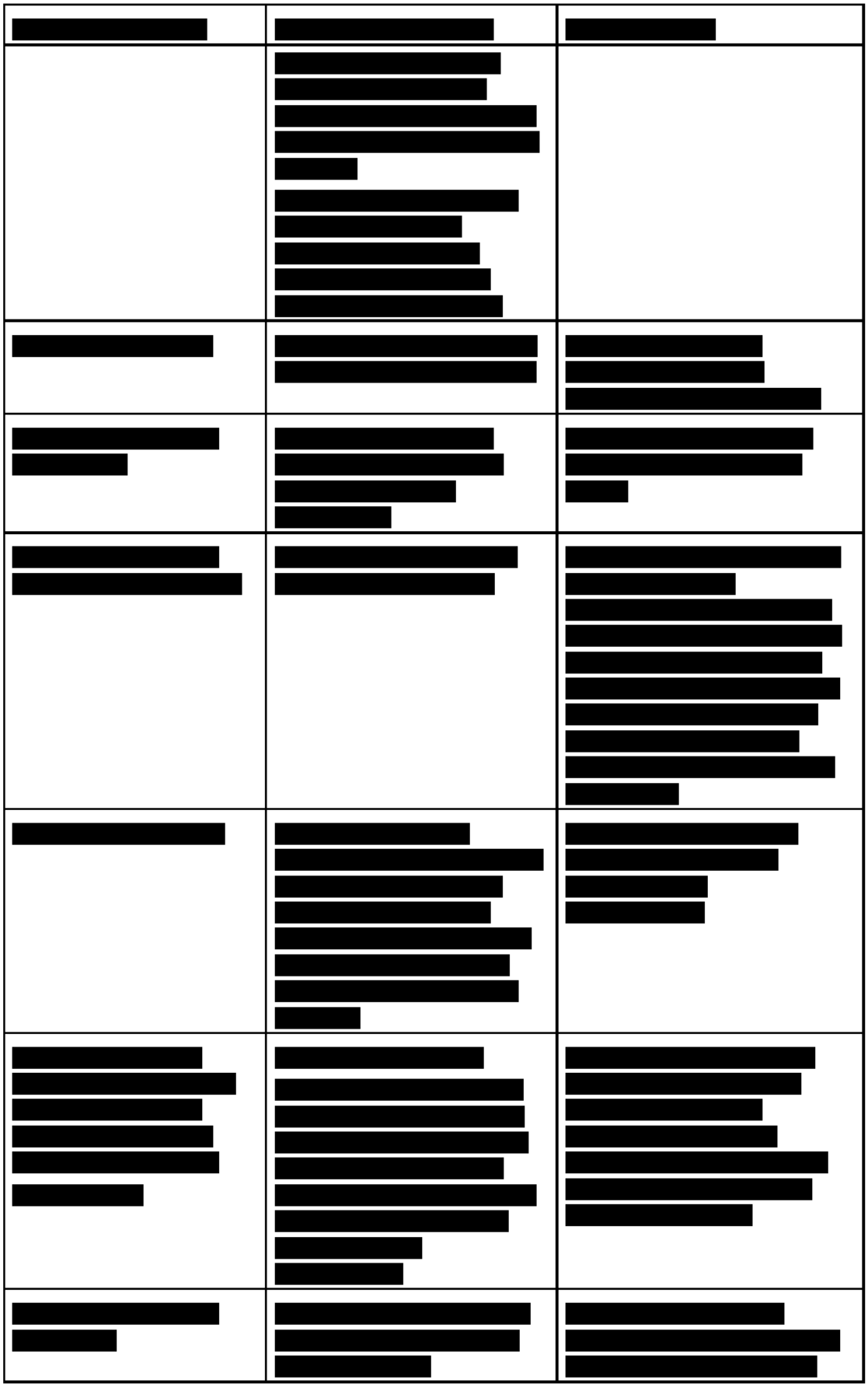

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