Sponsor	Jazz Pharmaceuticals Research UK Limited
Protocol Title:	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
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Approvals

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Document History

Version	Date	Section	Description of Change/Purpose
1.0	30-Jul-2021	See description of changes	Original issue
2.0	24-Jul-2024	See description of changes	Updated following Protocol Amendment 6
3.0	04-Mar-2025	See description of changes	Updated to support production of synoptic CSR, following study termination by sponsor

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Jazz Pharmaceuticals Research UK Limited "Jazz" protocol number GWEP17005 (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), dated 24-Jan-2024 version 6.0. Reference materials for this SAP include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. [redacted]

The SAP described hereafter is an*a priori* plan. It will be submitted to file prior to any descriptive analysis of data pertaining to the Jazz Pharmaceuticals Research UK Limited "Jazz" (formerly GW) study GWEP17005.

In view of poor recruitment and retention, and the low likelihood of meeting planned enrollment, a decision was reached to terminate the study on 28 January 2025. Following database lock, an abbreviated CSR will be produced. This abbreviated SAP describes the analyses that will be undertaken to support CSR production.

2. Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objectives

2.1.1.1 Safety: To evaluate the safety and tolerability of adjunctive GWP42003-P assessed during the 52-week treatment period.

2.1.1.2 Exposure: To investigate the exposure of GWP42003-P and its major metabolites following multiple doses of GWP42003-P.

2.1.1.3 Efficacy: To evaluate the efficacy of GWP42003-P in reducing the frequency of indication-specific countable seizures.

Primary clinical hypothesis: GWP42003-P has a positive risk/benefit outcome in the adjunctive treatment of seizures in participants with TSC, LGS, or DS.

2.1.2 Secondary Objectives

2.1.2.1 To evaluate the efficacy of GWP42003-P in reducing the frequency of total countable seizures.

2.1.2.2 To assess the retention of participants receiving GWP42003-P.

[redacted]

2.2 Study Endpoints

2.2.1 Primary Endpoints – Safety

The safety profile of adjunctive GWP42003-P will be assessed by measuring:

- Adverse events (AEs) (frequency, type, and severity)
- Vital signs
- Physical examination
- 12-lead electrocardiogram (ECG)
- Clinically significant changes in laboratory parameters
- Emergence of new seizure types as recorded by AE reporting
- Comprehensive neurodevelopmental assessment

2.2.2 Primary Endpoints - Exposure

- Trough, 3-hour, and 6-hour post dose plasma concentrations of GWP42003-P and its major metabolites following multiple doses of GWP42003-P.

2.2.3 Primary Endpoints – Efficacy

- 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).

*Focal/generalized seizures – Tuberous Sclerosis Complex (TSC)
Drop seizures – Lennox–Gastaut Syndrome (LGS)
Convulsive seizures – Dravet Syndrome (DS)

2.2.4 Secondary endpoints –Efficacy

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:

- Number and percentage of participants considered treatment responders, defined as those with a $\geq$ 50% reduction from baseline in total countable seizures.
- Categorical percentage change from baseline to EOT in total countable seizures 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.

2.2.5 Secondary endpoints – Retention

- Percentage of participants still taking GWP42003-P at Week 12 and every 4 weeks thereafter.

[redacted]

[redacted]

3. Overall Study Design and Plan

3.1 Overall Design

This is a Phase 3, multicentre, open-label, single-arm study that will evaluate the safety, tolerability, PK, efficacy[redacted] of adjunctive GWP42003-P in participants < 2 years of age with TSC, DS, or LGS. The study duration will be up to approximately 62 weeks, which includes a 4-week screening/baseline period, a 52-week dose optimization period (including a fixed 2-week titration period followed by flexible dose optimization), a 10-day taper period, and a safety follow-up period (4 weeks after the end-of-taper visit).

After signing the informed consent form (ICF), participants will be considered enrolled and will 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.

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 antiseizure medication (ASM) regimen). GWP42003-P will be taken orally or with G-or NG-tube b.i.d (e.g., morning and evening) at about the same time each day, consistently with or without food. 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).

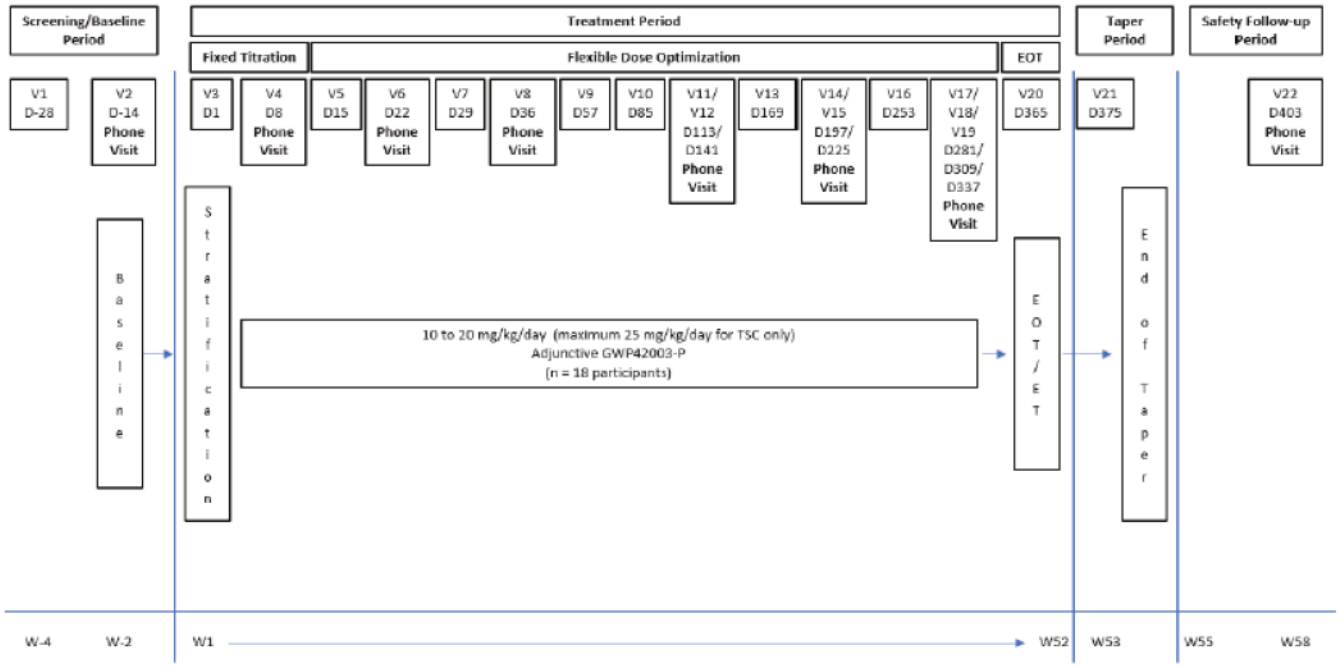
Starting at Visit 5, after titrating to the target dose level, investigators will have the option to titrate a participant's dose no more rapidly than 5 mg/kg every 7 days, up to a maximum dose of 20 mg/kg/day (for LGS and DS) or 25 mg/kg/day (for TSC), as recommended and based on the participant's individual 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 current dosage, following discussion with the medical monitor. Doses may be decreased below the target dose level based on safety and tolerability. Where possible, participants should be encouraged to return to the target dose level. Investigators should regularly monitor a participant's response to treatment and re-evaluate the need for adjustments to dosage at the next study visit, if applicable.

In general, doses should not be adjusted within the 3 days prior to PK study visits, 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.

Figure 1 Study Schema



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).

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.

3.2 Sample Size and Power

Up to 27 participants will be assigned to receive the study intervention in order to achieve 18 evaluable participants, which the Pediatric 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, in order to achieve 18 evaluable participants. There will be no formal hypothesis testing and as such no formal sample size calculation has been performed. Evaluability is defined in Section 5.0 Analysis Populations.

3.3 Study Population

Male or female 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 may enter the study.

Participants with TSC must have a diagnosis per the 2012 International Tuberous Sclerosis Complex Consensus Conference. 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). VEEG shall be available for confirmation of diagnosis.

Participants to be enrolled are 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.

Participants must have seizures which are not adequately controlled through their current ASMs, defined as ≥ 1 seizure reported on the seizure diary during the screening/baseline period.

The entire list of inclusion/exclusion criteria can be found in Clinical Study Protocol.

3.4 Method of Assigning Participants to Treatment Groups

Enrolment will be stratified via the Randomisation and Trial Supply Management (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 GWP42003-P in this nonrandomised study.

The RTSM will be used to manage study intervention supply. The RTSM system will be used at each clinic visit in order to:

- Obtain a participant's number.
- Obtain dispensing information.
- Provide completion/taper/premature termination information.

3.5 Treatments Administered

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 flavoring).

On Day 1 of treatment with GWP42003-P, participants will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg BID). On Day 8 (±3 days), the dose will be increased to 10 mg/kg/day (5 mg/kg BID). 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 GWP42003-P (10 mg/kg BID) for LGS and DS, or 25 mg/kg/day GWP42003-P (12.5 mg/kg BID) for TSC. If clinically indicated for safety, participants may decrease their dose at any time. 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). If a provider chooses to transfer the participant to a commercially available product above the 25mg/kg/day amount, then the participant must be terminated from the study and complete an EOT/ET visit.

3.6 Blinding and Unblinding

No blinding is applied, being an open-label study.

3.7 Schedule of Events

Visit schedule for the study is provided in the study protocol.

3.8 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. 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.

4. Statistical Analysis and Reporting

By-subject listings and descriptive summaries, if any, will be performed using SAS (release 9.4 or higher) after the database is locked.

4.1 Introduction

Continuous (quantitative) variable summaries will include the number of participants (n) with non-missing values, the number of missing values, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum, unless otherwise specified.

Categorical (qualitative) variable summaries will include the frequency and percentage of patients who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of participants in the study population with the non-missing value of the categorical variable, unless otherwise specified.

The number of missing values will be calculated as difference of the total number of participants in the study population minus the number of non-missing values.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean, median, Q1, and Q3) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented with one decimal place, unless otherwise specified.

4.2 Intermediate Analysis, Data Review

4.2.1 Safety data review

An independent safety monitoring committee (SMC) will be constituted to evaluate participant safety. Details of the composition and standard operating procedures of the SMC will be detailed in a separate charter.

5. Analysis Sets

Screening Analysis Set

- All participants who signed the ICF, are enrolled, and enter the screening/baseline period 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 assess retention and all safety-related endpoints.
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PK Analysis Set

- 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 events that could impact exposure such as (1) an AE of vomiting that occurs within 4 hours of dosing or (2) dose adjustment within 3 days of PK sampling, will be included in the PK analysis set. This analysis set will be used for all PK-related endpoints. A subset analysis may be conducted to evaluate participants who have experienced the events noted above.

A participant is evaluable for Safety or PK if the participant satisfies or meets the definition of the corresponding analysis set. A participant is evaluable for the study if he or she is evaluable for at least 1 of the analysis sets.

6. General Issues for Statistical Analysis

A pre-specified subset of the data collected will be listed, ordered by site, indication, participant number and, where applicable, chronological order of the assessment.

6.1 Statistical Definitions and Algorithms

6.1.1 Conventions for treatment/visit naming

In all tables and listings, the study visits will be referred to and labelled as per Table 1.

Table 1 Study Visits

Actual Visit	Visit Label	Phone Visit
Visit 1	Screening	
Visit 2: Baseline	Baseline	X
Visit 3: Day 1	Day 1§	
Visit 4: Day 8	Day 8	X
Visit 5: Day 15	Day 15	
Visit 6: Day 22	Day 22	X
Visit 7: Day 29	Day 29	
Visit 8: Day 36	Day 36	X
Visit 9: Day 57	Day 57	
Visit 10: Day 85	Day 85	
Visit 11: Day 113	Day 113	X
Visit 12: Day 141	Day 141	X
Visit 13: Day 169	Day 169	
Visit 14: Day 197	Day 197	X
Visit 15: Day 225	Day 225	X
Visit 16: Day 253	Day 253	
Visit 17: Day 281	Day 281	X
Visit 18: Day 309	Day 309	X
Visit 19: Day 337	Day 337	X

Visit 20: Day 365	EOT/ET	
Visit 21: Day 375	End of Taper	
Visit 22: Day 403	Safety Follow-up ʃ	X

§ occurs 14 days (+ 3 days) after Visit 2, but not <28 days after Visit 1
ʃ Phone or clinic visit

6.1.2 Baseline

For participants who meet the eligibility criteria, the baseline is defined as follows:

For ITQOL-SF47, the baseline is based on the assessment at Visit 3.

For all safety endpoints (e.g., vital signs, physical examination, 12-lead electrocardiogram, laboratory parameters), the last non-missing observation recorded before the first study intervention administration will be used as the baseline observation for all calculations, if required.

For safety endpoints, if no observation is available before administration of the study intervention, then the first non-missing observation during the same day of study intervention administration will be used as the baseline observation.

6.1.3 Last Visit

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

6.1.4 Study Periods

The four study periods are the following:

- Screening/Baseline, defined as Day -28 to Day -1
- Treatment period, defined as Day 1 to Day 365
- Taper Period, defined as Day 366 to Day 375
- Safety Follow-up Period, defined as Day 376 to Day 403.

6.1.5 Day Numbering

The first day of treatment (Day 1) will be the date on the 'Enrolment Verification' eCRF, under Visit 3, RTSM Enrolment date.

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

Date − (Date of Day 1), to give Day −1, −2, −3 etc.

Any day post Day 1 will be calculated as:

1 + Date − (Date of Day 1), to give Day 1, 2, 3 etc.

6.1.6 Analysis Visit Windows

If applicable for summarizing or listing safety endpoints (Biochemistry, Hematology, Urinalysis. Vital Signs, ECG, Physical Examination), the following analysis visits are defined:

Table 2. Analysis Visits

Actual Visit	Visit Label	Analysis Visit	Target Study Day (AWTARGET)	Window Days	Analysis Window Study Day	
					Low (AWLO)	High (AWHI)
Visit 2: Baseline	Baseline	Baseline	-14	±3	-17	-11
Visit 3: Day 1	Day 1§	Day 1	1	±3	-3	4
Visit 4: Day 8	Day 8	Week 1	8	±3	5	11
Visit 5: Day 15	Day 15	Week 2	15	±3	12	18
Visit 6: Day 22	Day 22	Week 3	22	±3	19	25
Visit 7: Day 29	Day 29	Week 4	29	±3	26	32
Visit 8: Day 36	Day 36	Week 6	36	±3	33	39
Visit 9: Day 57	Day 57	Week 8	57	±7	50	64
Visit 10: Day 85	Day 85	Week 12	85	±7	78	92
Visit 11: Day 113	Day 113	Week 16	113	±7	106	120
Visit 12: Day 141	Day 141	Week 20	141	±7	134	148
Visit 13: Day 169	Day 169	Week 24	169	±7	162	176
Visit 14: Day 197	Day 197	Week 28	197	±7	190	204
Visit 15: Day 225	Day 225	Week 32	225	±7	218	232
Visit 16: Day 253	Day 253	Week 36	253	±7	246	260
Visit 17: Day 281	Day 281	Week 40	281	±7	274	288
Visit 18: Day 309	Day 309	Week 44	309	±7	302	316
Visit 19: Day 337	Day 337	Week 48	337	±7	330	344
Visit 20: Day 365	EOT/ET	Week 52	365	±7	258	372
Visit 21: Day 375	End of Taper	End of Taper	375	±3	372	378
Visit 22: Day 403	Safety Follow-up	Safety Follow-up	403	±3	400	406

§ occurs 14 days (+ 3 days) after Visit 2, but not <28 days after Visit 1

A visit is mapped to an analysis visit which is closest to the target day. If 2 or more assessments are equidistant from the target day for a given analysis window, the later (latest) assessment is chosen for analysis. Scheduled and early termination visits will be eligible for analysis.

Unscheduled visits will not be eligible for analysis but will be listed.

6.1.7 Handling of Dropouts or Missing Data

Every effort will be made to minimize missing data for this study. The participant reported outcomes will be completed by the participant's primary caregiver on electronic devices. These assessments have been set up in such a way that the caregiver cannot proceed to the next question if they have not entered a response for the current question. In addition, on the off chance that the device does not function correctly, wherever possible, alternative data collection methods will be

utilized.

6.1.8 Pooling of Sites

As there are expected to be relatively few participants per centre, the centre will not be taken into account in the analyses. Therefore the question of pooling of centres does not arise.

6.1.9 Derived Variables

6.1.9.1 Adverse events

All AEs and serious adverse events (SAEs) will be collected from the start of intervention until the safety follow-up visit, with the following exception: 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.

An AE will be considered treatment-related if the plausibility relationship to study intervention is recorded on the CRF as 'yes'. If the data on plausibility relationship to study intervention is missing, then the relationship will be set to missing, i.e., no imputation will be made. Events that start before the first dose of study intervention (pre-treatment) should be considered as not causally related unless the pre-treatment AE is reported to worsen post-treatment, in which case causality should not be ruled out.

An AE will be considered leading to permanent discontinuation of IMP if the action taken with study intervention is recorded on the CRF as 'DRUG WITHDRAWN' or the outcome is recorded on the CRF as 'FATAL'.

An AE will be considered leading to study intervention temporary discontinuation if the action taken with IMP is recorded on the CRF as 'DRUG INTERRUPTED'.

An AE will be considered leading to temporary or permanent study intervention dose reduction if the action taken with IMP is recorded on the CRF as 'DOSE REDUCED'.

An AE will be considered fatal if the outcome is recorded on the CRF as 'FATAL'.

The time to first onset of AE will be calculated as:

Start date of AE – Date of first dose of study intervention + 1

The time to AE resolution will be calculated for as:

Stop date of AE – Start date of AE + 1

6.1.9.2 Prior and concomitant medications

Medications that started and stopped prior to Day 1 will be considered prior medications. A concomitant medication is defined as any medication that was administered during the treatment period. This includes medications that started before the treatment period and continued while on treatment and medications that started during the treatment period.

There will be no imputation of partially or completely missing start/stop dates.

6.1.9.3 Age

Age will be recorded in months in the eCRF.

6.1.9.4 Exposure

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

- (Date of last dose in the treatment phase from eCRF study outcome – Date of Day 1) + 1

The number of days in which study intervention was taken at least once (AM or PM) will be summarized and calculated as:

- Total number of dosing days – the number of days where study intervention was not taken in the AM nor PM (from morning/evening diary)

The number of days in which study intervention was taken both AM and PM will be summarized and calculated as:

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

Compliance is calculated based on diary data, and recorded in eCRF:

- 100 × [(Number of days study intervention taken at least once + number of days study intervention taken both AM and PM) ÷ (2 × study day of completion or withdrawal during the treatment period)]

6.1.9.5 Data Adjustments/Handling/Conventions

A pre-specified subset of collected data will be listed to support production of the synoptic CSR.

7. Study Participants and Demographics

7.1 Disposition of Participants and Withdrawals

Participants who failed screening and reasons for screen failure will be listed.

Among participants in the safety analysis set, participant disposition through the safety follow-up will be listed, indicating

- participant status - completed or withdrew, and date of completion or withdrawal, if withdrew, primary reason for withdrawal. The date of the last dose will also be listed
- whether participant continued to the taper period (Yes/No) and if not, reason for not continuing; if the participant entered the taper period, whether the participant completed or not, and if not, the reason for not completing.
- whether the participant entered the safety follow-up (Yes/No).

Among participants in the safety analysis set, participants who permanently discontinued treatment will be listed along with the date of and reason for permanent treatment discontinuation.

Membership to the analysis sets – Screening, Safety, and PK, will be shown in listings of disposition.

7.2 Protocol Deviations

Protocol deviations will be categorized into the type of deviation and whether important or non-important before database lock. All protocol deviations will be listed for the screening analysis set.

7.3 Demographics and Baseline Characteristics

7.3.1 Demographics

The following data will be listed for the for the safety analysis set, and the efficacy analysis set only if different from the safety analysis set:

- Age (months)
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White, Unknown or Not Reported)
- Weight at baseline (kg)
- Height at baseline (cm)
- Body mass index at baseline (kg/m^2)
- Previous use of cannabis

7.3.2 Seizure History – Current and Past

Seizure history will include seizures no longer occurring and current seizures. The following data will be listed for participants in the safety analysis set:

- For seizures no longer occurring,
  - Type of seizure (Focal motor, Focal non-motor, Tonic-clonic, Tonic, Clonic, Atonic, Absence, Myoclonic, Infantile/Epileptic seizures, Focal seizures which evolve to bilateral generalized convulsive seizures, Other)
  - Onset date and Resolved date
  - Description
- For current seizures
  - Type of seizure (Focal motor, Focal non-motor, Tonic-clonic, Tonic, Clonic, Atonic, Absence, Myoclonic, Infantile/Epileptic seizures, Focal seizures which evolve to bilateral generalized convulsive seizures, Other)
  - Onset date and Resolved date
  - Description
  - Seizure duration (2 mins, 2-10 mins, 10+ mins, unknown)
  - Seizure frequency (integer-valued) and duration. Duration, with possible values of 'per hour', 'per day', 'per week', 'per month', 'lifetime'.
  - Triggers (Fever, Water, Excitement, Tiredness, Other).

7.3.3 Neuroimaging History

The following data will be listed for participants in the safety analysis set:

- Neuroimaging type (MRI, CT Scan, Ultrasound, Other:specifics)
- Date of most recent neuroimaging
- Result (Normal/Abnormal)
- Details of findings if partial, diffuse or non-specific/incidental

7.3.4 EEG history (Non-video and Video)

The EEG history data will be listed for participants in the the safety analysis set:

- Type of EEG (Non-video or Video)
- Date Performed and duration
- EEG result (Normal, Abnormal (Epileptiform), Abnormal (Non-epileptiform only), or report not available)
- If Abnormal, additional features as captured in the CRF (e.g., focal spikes)
- Whether seizures were observed, and if yes, type of Seizure (Focal motor seizures, Focal Non-Motor Seizures, Tonic-Clonic, Tonic, Clonic, Atonic, Absence Seizures, Myoclonic, Infantile/epileptic spasms, Focal Seizures which evolve to Bilateral Generalized Convulsive, Other)

In addition to above, for video EEG (VEEG) the following will be listed:

- EEG Recording Time (Start and Stop Date, Start and Stop Time), included only in listings
- Total Number of Focal Motor Seizures: Awake with Impairment, Awake without Impairment, Asleep with Impairment, Asleep without Impairment
- Total Number of Focal to Bilateral Generalized Convulsive Seizures: Awake, Asleep
- Total Number of Tonic Seizures: Awake, Asleep
- Total Number of Clonic Seizures: Awake, Asleep
- Total Number of Tonic-Clonic Seizures: Awake, Asleep
- Total Number of Atonic Seizures: Awake, Asleep
- Total Number of Myoclonic Seizures: Awake, Asleep
- Total Number of Absence Seizures: Awake, Asleep
- Total Number of Focal Non-Motor Seizures: Awake with Impairment of Consciousness or Awareness, Awake without Impairment of Consciousness or Awareness, Asleep with Impairment of Consciousness or Awareness, Asleep without Impairment of Consciousness or Awareness
- Total Number of Infantile Spasms: Awake, Asleep
- Total Number of Other Seizures: Awake, Asleep
- Total Unevaluable Hours of EEG recording (Hours)
- Total Evaluable Hours of EEG recording (Hours)
- Total Awake Duration (Hours)
- Total Asleep Duration (Hours)
- Interictal epileptiform activity: Yes or No
- Slowing: Yes or No
- Sleep Spindles: Yes or No
- Vertex Waves: Yes or No
- PDR (in hertz)

7.3.5 Medical History

The medical and surgical history and current medical condition data will be listed for participants in the safety analysis set. All conditions and diagnoses on the 'medical history' CRF page will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA v24 or later).

7.4 Exposure and Compliance

Study intervention is to be administered twice daily (morning and evening). The first dose will be taken on Day 1. The date of final dose in the treatment phase will be recorded on the CRF. The date of final dose, for participants who enter the taper period, will be recorded on the CRF at the end of taper visit. The date of last dose in the treatment phase will be obtained from the CRF at the end of treatment visit. Any doses of study intervention that were not taken according to the dosing schedule will be captured in the daily dosing diary, together with the amount of study intervention that was administered.

Total number of dosing days in the treatment phase, and the number of days in which study intervention was taken at least once (AM or PM), and both AM and PM will be listed for all participants in the safety analysis set.

In addition, the amount of study intervention dispensed, and the amount of study intervention returned as recorded on the participant supply accountability log, and the % of the overall compliance calculated according to the Section 6.1.9.4 will be listed for all participants in the safety analysis set.

8. Efficacy Analysis

Efficacy will not be evaluated for the synoptic CSR.

8.1 Efficacy Endpoints

Seizure-related endpoints from either seizure diary data or VEEG will neither be listed nor summarized. These include indication-specific seizure frequency, seizure types, total countable seizures, percent reduction in total countable seizures from baseline to post-baseline, number of seizure-free days, treatment responder status

8.2 Infant Toddler Quality of Life Questionnaire

Caregivers will be instructed on how to record and complete the ITQOL-SF47 scale by recording from 0 (worst health) to 100 (best health). The ITQOL-SF47 will be completed at the site by the caregiver on an iPAD.

ITQOL-SF47 questionnaire items will be listed at baseline and end of treatment. See APPENDIX 4 for details.

ITQOL-SF47 scale scores are assessed on a validated, age appropriate QoL scale. Scale scores will also be listed.

9. Safety and Tolerability Analysis

Unless specified otherwise, safety data will be listed for participants in the safety analysis set.

9.1 Adverse Events

All reported AEs will be classified by system organ class (SOC), preferred term, and lower-level term using MedDRA Version 23.1 or later.

All reported AEs with start date on or after the first exposure to IMP until the end of the study (including Taper and Follow-up period) will be analyzed.

All AEs will be listed. Listings will include the start and stop day of the AE, severity (Mild, Moderate, Severe) relationship to IMP (Yes, No), whether serious (Yes/No) and if serious, SAE

criteria, Action Taken with respect to IMP (Not Applicable, Dose Not Changed, Dose Reduced, Drug Interrupted, Drug Withdrawn, Dose Increased, or Unknown), whether participant received Treatment and if yes, treatment received, AE Outcome (Fatal, Not Recovered/Not Resolved, Resolved/Recovered, Recovered/Resolved with Sequalae, Recovering/Resolving), and whether AE caused participant to discontinue from study (Yes/No). Partially or completely missing AE start and end dates will not be imputed.

9.2 Clinical Laboratory Evaluation

9.2.1 Hematology and Biochemistry

Hematology and Biochemistry results will be listed for all participants in the safety analysis set.

If values for any of the parameters are below or above the limit of quantification of the assay (BLQ or ALQ), then these will be displayed in the listings as '< xx' or '> yy', where xx and yy are the lower and upper limits respectively of detection or quantitation.

For estimated creatinine clearance, results > 60 will be displayed as '> 60'. Hence, estimated glomerular filtration rate (eGFR) will be calculated as:

The revised Schwartz estimate will be used:

$$\text{eGFR (mL/min)} = (36.2 \times \text{height}) / \text{serum creatinine},$$

where height is measured in cm and serum creatinine is measured in µmol/L.

eGFR will be indexed to body surface area (BSA) using the following formula:

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

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

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

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

When available, enzymatic serum creatinine will be used. Otherwise, the Jaffe serum creatinine will be used. If height or weight is missing at the collection date, then the closest value to the sample date will be used. If there is more than one height or weight value on the same day, or 2 height or weight values equally distant from the collection date, then the mean will be used.

Values will be categorized as 'Normal', 'Low' or 'High' based on normal range.

For serum creatinine values that are reported as BLQ, eGFR will be set to missing.

Treatment emergent ALT or AST is defined as criteria not met at baseline but met at any time post-baseline:

- Alanine aminotransferase (ALT) > 1×ULN at baseline
- Aspartate aminotransferase (AST) > 1×ULN at baseline
- ALT or AST > 1×ULN at baseline
- Treatment emergent ALT > 3×ULN, > 5×ULN and > 8×ULN

- Treatment emergent AST > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent ALT or AST > 3×ULN, > 5×ULN and > 8×ULN
- Treatment emergent ALT or AST > 3×ULN and either bilirubin > 2×ULN or INR > 1.5

Participants who meet treatment-emergent ALT or AST criteria will be listed.

9.2.2 Urinalysis

Urinalysis results will be listed.

9.3 Vital Signs, Other Physical Findings and Other Safety Data

9.3.1 Vital Signs

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

Vital signs data will be listed for all participants in the safety analysis set. Vital signs data include blood pressure, body temperature, pulse rate, respiratory rate, head circumference and whether potentially clinically significant based on criteria presented APPENDIX 2.

9.3.2 Physical Examination

Physical examination data will be listed for all participants in the safety analysis set. Physical examination data include weight and height.

9.3.3 Electrocardiogram

ECG data will be listed for all participants in the safety analysis set. ECG data include mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB and QTcF and whether potentially clinically significant based on criteria given in APPENDIX 3.

9.4 Comprehensive Neurodevelopmental Assessments

Neurodevelopmental assessments will be performed at Visits 3, 13, and EOT and will include recording of the following aspects:

- Paediatric neurological examination
- Developmental milestones assessment
- Recording of ongoing health conditions such as seizures, changes in participant's health (e.g., AEs), changes in concomitant medications, including use of rescue medications
- Longitudinal monitoring of neurodevelopment via Clinician Global Impression of Change/Severity (CGIC/CGIS) for sensory, motor, cognition, emotional/behavioral health, communication, social, and adaptive functioning

- Quality of life assessments via Infant and Toddler Quality of Life Questionnaire Short Form 47 (ITQOL-47)

CGIC/CGIS will be listed for all participants in the safety analysis set, which will include assessments at the following domains: sensory, motor, cognition, emotional/behavioral health, communication, social and adaptive functioning.

Comprehensive neurodevelopmental exam will be listed for all participants in the safety analysis set.

9.5 Other Measures

9.5.1 Concomitant Medication

Medications will be coded using the WHO-DD Enhanced (v. WHO Drug Global B3 – Sep 2020 or later).

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

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

- If coded to level 4 then the level 4 coded term will be presented.
- If coding is not performed at level 4 but level 3 coding is present, then level 3 coded term will be presented.
- If coding is not performed at level 3 but level 2 coding is present, then the level 2 coded term will be presented.
- If coding is not performed at level 2 but level 1 coding is present, then the level 1 coded term will be presented.

The ATC term, preferred term, reported generic name and reported brand name will be listed for participants in the safety analysis set.

The start day and stop day will be included in the listing. In the case of partial dates, the missing components will be left blank. Completely missing start/stop dates will not be imputed.

9.5.2 Antiseizure medications, therapies and rescue medications

Prior and concomitant antiseizure medications will be listed separately by ATC term and preferred term.

The start day and stop day will be included in the listing. In the case of partial dates, the missing

components will be left blank. Completely missing start/stop dates will not be imputed.

The ATC term, preferred term, reported generic name or reported brand name will be listed.

9.5.3 Procedures and Non-Drug Therapies

Prior and concomitant procedures and non-drug therapies will be listed for all participants in the safety analysis set.

9.5.4 Plasma Concentrations of CBD and its Major Metabolites

At the indicated PK visits, a pre-dose sample will be collected within 60 minutes prior to the morning dose of the study intervention (*i.e.*, trough collection). The study intervention can then be administered during the visit once the pre-dose PK sample has been collected. At Visit 9 and Visit 20, additional PK samples will be collected at 3 and 6 hours after administration of the study intervention (each PK sampling time point will be separated by at least 2 hours).

Plasma concentrations of CBD and its major metabolites, 7-hydroxy-CBD (7-OH-CBD) and 7-carboxy-CBD (7-COOH-CBD), will be listed for all participants in the PK analysis set. Concentrations for each analyte will be summarized by the sample collection nominal timepoints for all participants in the PK analysis set.

9.5.5 Dosing and food intake

Morning and evening dosing from the eDiary will be listed for all participants in the screening analysis set.

Mealtime and food diary data will be listed for all participants in the screening analysis set.

9.6 Changes in the Conduct of the Trial or Planned Analysis

Due to poor recruitment and retention, a decision was made to administratively discontinue the study on 28 January 2025. To support the production of a synoptic CSR, a pre-specified set of collected data will be listed.

10. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.

4. HealthActCHQ. (2018). ITQOL: Infant Toddler Quality of Life Questionnaire
5. QualityMetric Incorporated, LLC. (2011-2023). ITQOL: Infant and Toddler Quality of Life Questionnaire (ITQOL-SF47™) Parent Short Form – 47 Italy (Italian)

11. Tables, Listings and Figures

All outputs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

There are no planned figures for the abbreviated CSR.

11.1 Planned Table Descriptions

Planned summary tables for protocol GWEP17005 are described in separate shells documentation. Tables are numbered according to the nomenclature used to support the CSR and according to Jazz standards.

11.2 Planned Listing Descriptions

Planned listings for protocol GWEP17005 are described in separate shells documentation. Listings are numbered according to the nomenclature used to support the CSR.

All listings will be sorted by site and participant number.

In all listings a blank line will be placed between each participant. Within a data listing, if an item appears line after line (e.g., repetition of participant number), then only the first occurrence will be displayed.

In data listings, the information for one participant will be kept on one page, if at all possible, rather than splitting a participant's information across pages.

Tables, Listings, and Listing Shells

11.3 Standard Layout for all Tables and Listings

Table and listing shells are provided as a separate document. The final statistical tables will be produced in the format of the shells and will additionally include "double" page numbering in the format "page xx of yy". Note that programming notes may be added or modified if appropriate after each shell.

The final statistical output will be provided as fully bookmarked pdf file including a table of contents.

APPENDIX 1 Abbreviations

Abbreviation	Definition
AE	Adverse Event
ALQ	Above the Limit of Quantification
ASM	Antiseizure Medication
BLQ	Below the Limit of Quantification
CBD	Cannabidiol
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CSR	Clinical Study Report
D	Day
DS	Dravet Syndrome
ECG	Electrocardiogram
eCRF	Electronical Case Report Form
EDRS	Epilepsy Diary Reference Sheet
EEG	Electroencephalogram
ePRO	Electronic Participant Reported Outcome
EMA	European Medicines Agency
EOT	End of Treatment
ESCI	The Epilepsy Study Consortium
ET	Early Termination
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ILAE	International League Against Epilepsy
IMP	Investigational Medicinal Product
ITQOL-SF47	Infant Toddler Quality of Life Questionnaire – Short Form 47
LGS	Lennox-Gastaut Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
QTcB	QT-interval for ECG Corrected for Heart Rate Using Bazette's Formula
QTcB	QT-interval for ECG Corrected for Heart Rate Using Fridericia's Formula
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIF	Seizure Identification Form
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TSC	Tuberous Sclerosis Complex
VEEG	Video Electroencephalogram
WHO	World Health Organization

APPENDIX 2 Ranges for Clinically Significant Changes and Other Defined Flagged Values in Vital Signs

The range of values that will be used to identify clinically significant changes in vital signs parameters (See Section 9.3.1) are presented in Table 3. Ranges for Potentially Clinically Significant Changes in Vital Signs.

Table 3. Ranges for Potentially Clinically Significant Changes in Vital Signs

Vital Sign	Range
Supine Systolic BP (mmHg)	Change: < -20, > 20
Supine Diastolic BP (mmHg)	Change: < -10, > 10
Pulse Rate (beats/min)	Change: < -10, > 10

Defined flagged values that will be used to identify low or high vital signs parameters (See Section 9.3.1) are presented in Table 4. Other Defined Flagged Values for Vital Signs

Table 4. Other Defined Flagged Values for Vital Signs

Vital Sign	Flag
Supine Systolic BP (mmHg)	< 70, > 121
Supine Diastolic BP (mmHg)	< 32, > 76
Pulse Rate (beats/min)	< 95, > 210
Temperature (°C)	> 38.0, < 35.5
Respiratory Rate (breath/min)	< 15, > 53

APPENDIX 3 Defined Flagged Values in ECG Parameters

Defined flagged values that will be used to identify low or high ECG parameters (See Section 9.3.2) are presented in Table 5. Defined Flagged Values for ECG Parameters

Table 5. Defined Flagged Values for ECG Parameters

ECG Parameter	Flag
QTcB (msec)	> 460

APPENDIX 4 Scoring the ITQOL-SF47 Questionnaire

Infant Toddler Quality of Life Questionnaire - 47 Items

Response options for both lengths of the ITQOL scales are five levels, with the exception of Parent-Time Limitations which is 4 levels.

Scores will be converted to a 0-100 scale by Medidata according to the age specific validated scale.

Infant/toddler focused concepts:

- How would you rate your child's health?
- Considering your child's age and abilities, has he/she been limited in any of the following because of health or learning problems?
    - Feeding/nursing/eating
    - Sleeping
    - Grasping
    - Rolling over
    - Playing
    - Taking steps or walking
    - How satisfied are you with your child's:
- Physical growth and development?
- Motor development?
- Responsiveness to others?
- Language development?
- Learning abilities or cognitive development?
- How much bodily pain or discomfort (due to gas, teething, injury, illness) has your child had anywhere in his/her body?
- How often has your child had discomfort or pain anywhere in his/her body?
- How much of the time did your child seem: Less active than usual? Bothered or upset? "Just not him/herself"?; Cheerful?; Easily upset?; Alert?
- How much do you agree/disagree with each statement for your child? My child's behavior is sometimes difficult to manage; My child seems to misbehave more often than other children I know; People have complimented me on my child's behavior. Others have complained about my child's behavior.
- Compared to children of the same age, how would you rate your child's behavior overall?
- How often did your child:
    - Have behavior that was difficult to manage?
    - Get along with other children?
    - Throw tantrums?
    - Respond positively to affection?
    - Act withdrawn?
    - Act his/her age?
    - Listen to or follow directions?
- How true or false is each statement for your child?
    - My child seems to be less healthy than other children I know.

    - My child has never been seriously ill.
    - When there is something going around my child usually catches it.
    - I expect my child will have a very healthy life.
    - I worry about my child's health more than other people worry about their children's health.
- Compared to one year ago, how would you rate your child's health now?

Parent-focused concepts:

- How much anxiety or worry did each of the following cause you? Your child's physical health; emotional well-being/behavior/temperament; learning abilities or cognitive development; ability to interact with others
- Were you limited in the amount of time you had for your own personal needs due to problems with your child's:
    - Physical health
    - Emotional well-being/behavior/temperament
    - Learning abilities or cognitive development
    - Ability to interact with others
- How would you rate your family's ability to get along with one another?

APPENDIX 5 Clinical Global Impression Questionnaire

1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

1 = Normal, not at all ill
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill patients

2. Global improvement:

Compared to the patient's condition at time of first assessment, how much has he/she changed?

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

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Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

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