Title: A Phase 1b/2a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Escalation Study With an Open-Label Part to Examine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-935 as an Adjunctive Therapy in Subjects With Developmental and/or Epileptic Encephalopathies

NCT Number: NCT03166215

SAP Approve Date: 26 October 2018

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-935-2001

A Phase 1b/2a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Escalation Study With an Open-Label Part to Examine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-935 as an Adjunctive Therapy in Subjects With Developmental and/or Epileptic Encephalopathies

Study of TAK-935 as an Adjunctive Therapy in Subjects With Developmental and/or Epileptic Encephalopathies

PHASE 1b/2a

Version**:** Final

Date**:** 26 October 2018

Prepared by:
PPD

Based on:

Protocol Version: Amendment 03

Protocol Date: 21 March 2018

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

Study Title: Study of TAK-935 as an Adjunctive Therapy in Subjects With Developmental and/or Epileptic Encephalopathies

Approvals:

PPD

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

24HC	24S-hydroxycholesterol
ABC-C	Aberrant Behavior Checklist-Community Edition
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BA	bioavailability
BID	twice daily
BMI	body mass index
$C_{av,ss}$	average concentration during a dosing interval at steady-state
CFR	Code of Federal Regulations
CH24H	24S-hydroxylase
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
EO	enzyme occupancy
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
M-I	metabolite of TAK-935

MRD	multiple-rising dose
PD	pharmacodynamic(s)
PDR	posterior dominant rhythm
PEG	Percutaneous endoscopic gastrostomy
PET	positron emission tomography
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PPS	per-protocol set
PTZ	pentylenetetrazol
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4.0 OBJECTIVES

4.1 Primary Objective

- To characterize the multiple-dose safety and tolerability profile of TAK-935 in adult subjects with developmental and/or epileptic encephalopathies.

4.2 Secondary Objective

- To characterize the multiple-dose PK profile of TAK-935 in adult subjects with developmental and/or epileptic encephalopathies on concomitant antiepileptic drugs (AEDs).

4.3 Exploratory Objectives

CCI

[redacted]

4.4 Study Design

This phase 1b/2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study with an open-label part is designed to examine the safety, tolerability, PK, and PD of TAK-935 as adjunctive therapy in adult subjects with a diagnosis of developmental and/or epileptic encephalopathies. This study will be conducted at approximately 11 sites in North America with experience in conducting clinical studies in patients with rare epilepsies.

Adult subjects (aged ≥18 and ≤65 years) with a diagnosis of developmental and/or epileptic encephalopathies demonstrating bilateral motor seizures (ie, drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, focal seizures with bilateral hyperkinetic motor features) (average of ≥2 per month during the past 3 months) based on the investigator's assessment will be enrolled. The study will screen a sufficient number of subjects to ensure approximately 20 randomized subjects.

At the Screening Visit (Visit 1), informed consent and/or assent (if applicable) is obtained from the subjects and/or subjects' legally acceptable representative. Subjects will then undergo screening procedures to assess study eligibility in accordance with the study entry criteria (see Appendix A and Sections 71 and 7.2**.** in the Protocol). At this Screening Visit and at subsequent visits, subjects and/or subjects' caregivers will be provided with a seizure diary and will be instructed to record seizure data on a daily basis starting at Baseline and throughout the study.

CCI [redacted] The 4-week Baseline Period CCI [redacted] can begin as soon as informed consent has been signed. At the end of the 4-week Baseline Period and after confirmation of eligibility, subjects will return to the clinic on Day 1 in Part 1 (Visit 2) for randomization. If a subject does not meet the eligibility criteria during the Screening/Baseline Period, the subject will be discontinued from the study (screen failure).

The study will consist of 2 parts:

Part 1 is a randomized double-blind part consisting of 3 periods: a screening/baseline period (4-6 weeks), titration period (20 days), and maintenance period (10 days). The target final dose of 300 mg BID will be reached after a 20-day titration period.

Part 2 is an open-label continuation part consisting of 4 periods: a titration period (10 days), maintenance period (44 days), de-escalation period (3-6 days) and follow-up period (30 days).

Part 1 of the study is designed to investigate the safety, tolerability, PK, and PD in adult subjects with developmental and/or epileptic encephalopathies in a double-blind manner. CCI [redacted] will be investigated in an exploratory manner. Approximately 20 adult subjects who CCI [redacted] during the 4-week Baseline Period will be randomly assigned on Day 1 (Visit 2) to receive TAK-935 (n=16) or matching placebo (n=4) twice daily (BID) orally or via stable gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube for 30 days during the Double-Blind Treatment Period. Subjects will initiate IP (investigational product; TAK-935 or placebo) at 100 mg BID from Days 1 through 10. Subjects who cannot tolerate the 100 mg BID dosing will be withdrawn from the study. On Day 11 (Visit 3), subjects will return to the clinic and the IP dose will be increased to 200 mg BID; this dose level will be maintained from Days 11 through 20 but may be reduced to 100 mg BID in subjects who cannot tolerate the 200 mg BID dose or demonstrate safety concerns, based on the investigator's judgment and in consultation with the subject's caregiver, when applicable. On Day 21 (Visit 4), subjects will return to the clinic; at this visit, the investigator will review the subject's safety data and will discuss the benefit-risk with the subject or subject's legally acceptable representative before proceeding to increase the dose from 200 mg BID to 300 mg BID, and this dose level will be maintained from Days 21 through 30. The dose may be reduced to 200 mg BID in subjects who cannot tolerate the 300 mg BID dose or demonstrate safety concerns, as described above. Subjects for whom the dose was reduced to a lower dose level will stay on that dose level until the end of the Double-Blind Treatment Period. Three days after each dose up-titration or de-escalation, subjects will be contacted by phone to monitor study drug compliance, concomitant medication use, and AEs. Any change in dose will be documented in the subject's clinic chart and the subject's caregiver will be advised to note the same in the dosing card.

On Day 1 (Visit 2), PK, PD, AED, and optional PGx blood samples will be collected before the morning dose of study drug. PK and PD blood samples also will be collected at 1, 3, and 5 hours

after the morning dose on Day 1. On Day 11 (Visit 3) and Day 21 (Visit 4), PK and PD blood samples (before and approximately 1 hour after morning dose), an AED blood sample (before morning dose), and seizure diary data will be collected.

Subjects who are unwilling to continue into Part 2 of the study will proceed directly to the Final Visit (at Day 31), including dose de-escalation, as appropriate, followed by the 30-day Follow-up Period.

Part 2 of the study is designed to investigate the safety, tolerability, PK, and PD of TAK-935 in adult subjects with developmental and/or epileptic encephalopathies in an open-label manner. All subjects who complete the Double-Blind Treatment Period in Part 1 will have the option to continue directly into the Open-Label Treatment Period in Part 2. Because some subjects may enter Part 2 after receiving placebo and others TAK-935 up to 300 mg BID and to maintain the study blind, all subjects will start on TAK-935 200 mg BID at the start of Part 2. On Day 31 (Visit 5), subjects will return to the clinic and receive TAK-935 200 mg BID from Days 31 to 40 but may be reduced to 100 mg BID in subjects who cannot tolerate the 200 mg BID dose or demonstrate safety concerns, based on the investigator's judgment and in consultation with the subject's caregiver, when applicable. Subjects who cannot tolerate the 100 mg BID dose or demonstrate safety concerns, based on the investigator's judgment and in consultation with the subject's caregiver, will be discontinued from the study. On Day 41 (Visit 6), subjects will return to the clinic; at this visit, the investigator will review the subject's safety data and will discuss the benefit-risk with the subject or subject's legally acceptable representative before proceeding to increase the dose from 200 mg BID to 300 mg BID, and this dose level will be maintained until the Final Visit (Visit 7) for the dose de-escalation phase. Subjects' dose may be increased or decreased before Day 41 (Visit 6) based on clinical condition (ie, increasing seizures) and investigator judgment. This dose may be reduced to 200 mg BID in subjects who cannot tolerate the 300 mg BID dose or demonstrate safety concerns, as described above. Subjects for whom the dose was reduced to a lower dose level will stay on that dose level until the Final Visit (Visit 7) for the dose de-escalation phase. Three days after each dose up-titration or de-escalation, subjects will be contacted by phone to monitor study drug compliance, concomitant medication use, and AEs. Any change in dose will be documented in the subject's clinic chart and the subject's caregiver will be advised to note the same in the dosing card.

On Day 31 (Visit 5), PK, PD, AED, and PGx (if collected on Day 1) blood samples will be collected before the morning dose of study drug and seizure data will also be collected. On Day 41 (Visit 6), PK, PD, and AED blood samples will be collected before the morning dose of study drug and seizure data will also be collected.

On Day 85 (Visit 7), subjects will return to the clinic for the Final Visit and enter the 3- or 6-day de-escalation phase. At this visit, PK, PD, and AED blood samples will be collected before the morning dose of study drug and seizure data will also be collected. Subjects will then enter the dose de-escalation phase and will be instructed to follow the applicable de-escalation dosing schedule outlined below:

For subjects on 300 mg BID during the maintenance phase, the dose will be de-escalated to 200 mg BID for 3 days (Days 85-87) and subsequently to 100 mg BID for 3 days (Days 88-90).

For subjects on 200 mg BID during the maintenance phase, the dose will be de-escalated to 100 mg BID for 3 days (Days 85-87).

For subjects on 100 mg BID during the maintenance phase, there is no de-escalation and the dose is discontinued on Day 85.

Immediately after the last dose is the 30-day Follow-up Period comprised of a Follow-up Phone Call (Visit 8) on Day 91 and a Follow-up Visit (Visit 9) on Day 121. At the Follow-up Visit, subjects will return to the clinic for study procedures including PD and AED blood sample collection.

In Parts 1 and 2, subjects will be instructed to not take their morning dose of study drug or concomitant AEDs on the days of scheduled study visits to facilitate collection of the predose PK, PD, AED, and optional PGx blood samples. The morning dose of study drug and concomitant AEDs will be administered in the clinic on these study days after laboratory samples are collected. For subjects who are not able to come for the visit during the morning hours, they should be instructed to take their morning dose, as usual, and come to the study site during the afternoon hours, as feasible for the subject. While in the clinic, the site should attempt to obtain 2 PK samples, separated by 1-2 hours, if possible. Hours since the last dose of the study medication must be recorded in the eCRF upon collection of the PK sample(s).

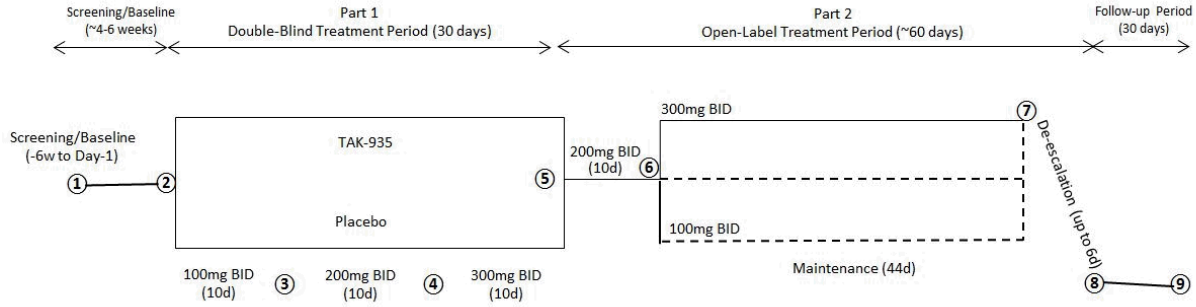
Seizure data will be recorded daily in the seizure diary by each subject and/or subjects' caregiver throughout the Screening/Baseline Period up until the Follow-up Visit (Visit 9) on Day 121 and will be collected from the diary at each visit.

The investigator, in consultation with the sponsor, may decide to reduce the TAK-935 dose at any time during the study in the event of any safety or tolerability concerns.

Any subject who prematurely withdraws from the study should proceed directly to the Final Visit (at time of withdrawal), including dose de-escalation, as appropriate, followed by the 30-day Follow-up Period.

A schematic of the study design is shown in Figure 4.a. Refer to Appendix A in the Protocol for a schedule of study procedures.

Figure 4.a Schematic of Study Design



Note 1: Circled numbers denote study visits.
Note 2: Subjects will remain on stable background AED therapy throughout the study.
Note 3: Starting doses for Parts 1 and 2 are shown; individual subject doses may be reduced to the previous dose level if there are safety and tolerability concerns at new dose level.
Note 4: Maintenance dose levels (ie, 100, 200, or 300 mg BID) will be de-escalated at the end of the maintenance phase of Part 2, depending on the dose subjects are taking at that time (ie, if at TAK-935 300 mg BID level, reduce to 200 mg BID for 3 days followed by 100 mg BID for 3 days; if at the 200 mg BID level, reduce to 100 mg BID for 3 days; if at the 100 mg BID level, there is no de-escalation).

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

Percentage of subjects with at least 1 treatment-emergent adverse event (TEAE), as reported by the subjects or subjects' caregivers or observed by the investigator, after TAK-935 treatment.

5.2 Secondary Endpoints

- Population mean estimates of drug clearance (CL), volume of distribution of the central compartment (V_c), absorption rate constant (K_a), volume of distribution of the peripheral compartment (V_p), intercompartmental clearance (Q), the maximum plasma concentration (C_{max}), the area under the plasma concentration-time curve over a dosing interval ($AUC_{0\text{-}tau}$), the average concentration during a dosing interval at steady-state ($C_{av,ss}$), and the plasma concentration immediately prior to dosing (C_{trough}) for TAK-935.
- Percentage of subjects with at least 1 markedly abnormal value for clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters after TAK-935 treatment.

5.3 Exploratory Endpoints

CCI

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 20 adult subjects are planned to be randomized. A formal sample size calculation was not performed for this study. The current sample size is deemed appropriate to evaluate the safety and tolerability of TAK-935 before dosing in pediatric subjects <18 years of age. Subjects who fail to complete Part 1 may be replaced and will receive the same treatment as the replaced subject.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All confidence intervals (CI), statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the counts and percentages of subjects will be tabulated. The denominator for the percentages will be based on the number of subjects who provide non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

All data analyses and figures will be generated using SAS System® Version 9.2 or higher.

7.1.1 Definition of Study Day and Baseline

Study day will be calculated relative to the date of the first dosing. Study day prior to the first dose of treatment will be calculated as: date of assessment/event – date of treatment; study day on or after the date of first dose of treatment will be calculated as: date of assessment/event – date of treatment + 1.

Baseline for Part 1 is defined as the last non-missing measurement prior to first dose of study drug in Part 1. Baseline for Part 2 is defined as the last non-missing measurement prior to first dose of study drug.

Baselines for Part 1 and Part 2 (when needed for the analysis) are defined as the last observation prior to the first dose in Part 1 and 2, respectively. Both date and time of the measurement and the dosing date and time should be used when determining the baseline if possible. For Part 1, in the case where the last non-missing measurement (except AE and concomitant medications) and the first dose on Day 1 coincide at the same time, or the same date if time of the measurement is not collected, that measurement will be considered as baseline value for Part 1. For Part 2, in the case where the last non-missing measurement (except AE and concomitant medications) and the first dose on Day 31 coincide at the same time, or the same date if time of the measurement is not collected, that measurement will be considered as baseline value for Part 2.

7.1.2 Definitions of Study Visit Windows

For each visit, a window will be defined; this window will establish a time interval around which data will be considered for the analysis of the scheduled visit pertaining to that window. The lower and upper bounds of each window are the approximate midpoints between the scheduled days for the current visit and its adjacent scheduled visits. The value used in analysis for by-visit

summaries is the value within the specified window that is closest to the scheduled study day. If two observations are equidistant from the scheduled visit date, the observation with a later date will be used. The visit windows and applicable study day ranges are presented below in Table 7.a and Table 7.b. Cut-off days for inclusion in the window (number of days following the date of the last dose of open-label study drug) are provided.

Table 7.a Visit Analysis Windows for Part 1

		Visit Window (Days)				
Visit	**Scheduled Visit Day**	**Vital Signs, CCI, PK, CCI Plasma Sample for AED, Concomitant Medications**	**CCI**	**ECG, Clinical Laboratory Tests**	**CCI, Serum/urine Pregnancy Test**	**Physical Exam, Neurological Exam**
Baseline I	1	≤1	≤1	≤1	≤1	≤1
Visit 3	11	2-16	2-16	2-16	2-43	
Visit 4	21	17-26	17-26			2-33
Visit 5	31	27-36	27-36	17-58		
Visit 6	41	37-53	37-53			
Visit 7	85	54-Last Dose+7	54-Last Dose+7	59-Last Dose+7	44-Last Dose+7	34-Last Dose+7

Note: Any value collected after the administration of first dose on Day 1 will be grouped under Day 2, except for PK, CCI and plasma sample for AED.

Table 7.b Visit Analysis Windows for Part 2

		Visit Window (Days)				
Visit	**Scheduled Visit Day**	**Vital Signs, CCI PK, C CI, Plasma Sample for AED, Concomitant Medications**	**CCI**	**ECG, Clinical Laboratory Tests**	**CCI, Serum/urine Pregnancy Test**	**Physical Exam, Neurological Exam**
Baseline II		≤First Dose in Part 2	≤First Dose in Part 2	≤First Dose in Part 2	≤First Dose in Part 2	≤First Dose in Part 2
Visit 6	41	Day after First Dose in Part 2-53	Day after First Dose in Part 2-53			
Visit 7	85	54-Last Dose+7	54-Last Dose+7	Day after First Dose in Part 2-Last Dose+7	Day after First Dose in Part 2-Last Dose+7	Day after First Dose in Part 2-Last Dose+7

Note: Any value collected after the administration of first dose in Part 2 will be grouped under day after first dose in Part 2, except for PK, C CI and plasma sample for AED.

7.1.3 Conventions for Missing Adverse Event Dates

Adverse events with completely or partially missing dates will be imputed as follows.

7.1.3.1 Imputation of missing or partial dates of AE start dates

- Month/year available and day missing:
  - If the month and year are the same as those in the first dose date in Part 1 and the event is not indicated as a pre-treatment event, the first dose date in Part 1 is to be used to impute the start date.
  - If the month and year are the same as those in the first dose date in Part 1 and the event is indicated as a pre-treatment event, the date prior to the first dose date in Part 1 is to be used to impute the AE start date. If the date prior to the first dose date in Part 1 is in previous month/year, set the start month/year to the previous month/year.
  - If the month and year are after the first dose date in Part 1 and the same as or before the last dose date in Part 1 plus 30 days for patients who do not continue to Part 2 or before the first dose date in Part 2, the first day of the month will be used for the start date.
  - If the month and year are the same as the first dose date in Part 2 and the same as the last dose date in Part 1, the first day of the month will be used for the start date.
  - If the month and year are the same as the first dose date in Part 2 and after the last dose date in Part 1, then the event is considered as a treatment emergent for Part 2 and the first dose date in Part 2 is to be used to impute the start date.

  - If the month and year are after the first dose date in Part 2, the first day of the month will be used for the start date.

- Year available and month/day missing:
  - If the year is the same as the year of the first dose in Part 1 and same as or before the first dose in Part 2 and the event is not indicated as a pre-treatment event, the first dose date in Part 1 is to be used to impute the AE start date.
  - If the year is the same as the year of the first dose date in Part 1 and same as or before the first dose in Part 2 and the event is indicated as a pre-treatment event, the date prior to the first dose date in Part 1 is to be used to impute the AE start date. If the date prior to the first dose date in Part 1 is in previous month/year, set the start month/year to the previous month/year.
  - If the year is the same as the first dose date in Part 2 and after the last dose date in Part 1, the first dose date in Part 2 is to be used to impute the AE start date.
  - If the year is not the same as the year of the first dose date in Part 1 or the year of first dose date in Part 2, set the start date as January 1.
- Year/month/day all missing:
  - If the event is not indicated as a pre-treatment event, the first dose date in Part 1 is to be used to impute the AE start date.
  - If the event is indicated as a pre-treatment event, the date prior to the first dose date in Part 1 is to be used to impute the AE start date.

7.1.3.2 Imputation of missing or partial dates of AE end dates

If the event is indicated as ongoing at the end of the study, no imputation is needed.

If the event is not indicated as ongoing:

- Month/year available and day missing:
  - Use the last day of the month to impute the AE end date. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.
- Year available and month/day missing:
  - If the year is the same as or before the year of the last dose in Part 2, set the end date as December 31.
  - If the year is after the year of the last dose in Part 2, set the end date as January 1.

- Year/month/day all missing:
  - Impute the end date as December 31 of the Part 2 last dose year. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.

7.1.4 Conventions for Missing Concomitant Medication Dates

Concomitant medications with completely or partially missing will be imputed as follows.

7.1.4.1 Imputation of missing or partial dates of concomitant medication start dates

- Month/year available and day missing:
  - The first day of the month will be used for the start date.
- Year available and month/day missing:
  - Set the start date as January 1.
- Year/month/day all missing:
  - If date of birth is available, use the date of birth as the start date.
  - If date of birth is not available, estimate date of birth using the screening date and age, and use the estimated date of birth as the start date.

7.1.4.2 Imputation of missing or partial dates of concomitant medication end dates

If the concomitant medication is indicated as ongoing, no imputation is needed.

If the concomitant medication is not indicated as ongoing, use the same algorithm in Section 7.1.3.2 to impute.

7.1.5 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarization of concentration values. These values will be flagged in the data listings and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

7.2 Analysis Sets

The randomized set will include all subjects who were randomly assigned to planned treatment through the IVRS/IWRS.

The PK analysis set for Parts 1 and 2 will include all subjects who received at least 1 dose of study drug and have at least 1 post-dose measurable TAK-935 or M-I plasma concentration.

CCI [redacted]

The full analysis set (FAS) for Parts 1 and 2 will include all subjects who were randomized, received at least 1 dose of study drug, and have at least 1 valid post-baseline value for assessment of the efficacy endpoint(s) in Part 1 or Part 2. In FAS efficacy summaries, subjects will be analyzed according to the treatment to which they were randomized.

The safety analysis set for Parts 1 and 2 will include all subjects who received at least 1 dose of study drug. In safety summaries, subjects will be analyzed according to the actual treatment they received.

7.3 Disposition of Subjects

Study information will be presented, including date first subject signed the Informed Consent Form, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Regulatory Activities (MedDRA) Version, World Health Organization Drug Dictionary Version (WHODRUG), and SAS Version.

Disposition of all screened subjects (denominator) will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

The number and percentage of subjects who complete study drug and all study visits in Part 1 of the study, prematurely discontinue study drug and study visits in Part 1 will be summarized by treatment group and overall for all randomized subjects in the double-blind period. For all the subjects who continue in Part 2 of the study, the number and percentage of subjects who complete study drug and all study visits in Part 2, prematurely discontinue study drug and study visits in Part 2 will be summarized. For each of Part 1 and Part 2, the primary reason for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings. Disposition of screen failure subjects in Part 1 will be summarized descriptively. Primary reasons for failure will be summarized and will be presented in a data listing

The number and percentage of subjects who comprised each analysis set will be summarized by treatment group and overall in Part 1, and overall in Part 2, respectively.

Disposition of the study drug dose combination for subjects in Part 1 and 2 will also be summarized by sequence of dose. For example, for subjects taking TAK-935 in Part 1, the number and percentage of subjects with dose combination of 100 to 200mg BID will be summarized. This summary will be based on safety analysis set. Details for important (significant) protocol deviations will be provided in a data listing.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics (e.g., date of birth, sex, Hispanic ethnicity, race as described by the subject, epilepsy diagnosis) will be summarized and listed for subjects by treatment group and overall using the safety analysis set in Part 1. Summary statistics (number of

subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables (e.g., age, and weight), and the number and percentage of subjects within each category will be presented for categorical variables (e.g., sex, ethnicity, race). No inferential statistics will be presented. Individual subject demographic and baseline characteristic data will be listed.

Demographic variables of screen failure subjects and reasons for screen failure will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, any available safety data and reason for screen failure will also be presented in the data listing.

7.5 Medical History and Concurrent Medical Conditions

Medical history refers to the significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases present at signing of informed consent.

Medical history, epilepsy diagnosis, and concurrent medical conditions will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA, version 19.0) and will be summarized by treatment group and overall in Part 1, using System Organ Class (SOC) and MedDRA preferred term. The table will include number and percentages of subjects and will be sorted in alphabetical order by system organ class and preferred term. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms. Summaries will be presented for Part 1 only, and will be based on the safety analysis set for Part 1.

All medical history, epilepsy diagnosis, and concurrent medical condition data will be presented in listing.

7.6 Medication History and Concomitant Medications

Medication history information to be obtained includes any medication relevant to eligibility criteria and the efficacy or safety evaluations stopped at or within 28 days before signing of informed consent. AED history will be collected as part of the medication history information. Medications used from signing of informed consent through the end of each study part will be considered as concomitant medications for each study part, respectively.

Summaries of medication history will be presented for Part 1 and Part 2, separately, and will be based on the safety analysis set for Part 1. Concomitant medications that started and stopped prior to baseline, started prior to baseline and ongoing at baseline, started after baseline, and ongoing at baseline and started after baseline will be summarized using the safety analysis set in Part 1. Concomitant medication for Part 1 is defined as the medication that the patient started taking before first dose in Part 1 and ongoing in Part 1 of the study, and concomitant for Part 2 is defined as the medication that the patient started taking before first dose in Part 2 and ongoing in Part 2. No inferential statistics will be presented.

All prior and concomitant medications data will be presented in listing.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in a data listing based on the safety analysis set. Summaries of study drug concentration and exposure data will be provided by dose using the safety analysis set in Parts 1 and 2 separately. No inferential statistics will be presented.

The duration of exposure (days) to the double-blind study medication in Part 1 is defined as (date of last dose of double-blind study drug - date of first dose double-blind study drug + 1). The duration of exposure to the open-label study medication in Part 2 is defined as (date of last dose of open-label study drug – date of first dose of open-label study drug + 1). For patients who have been treated in both Parts 1 and 2 with active drug (TAK-935), the duration of exposure to the TAK-935 overall is defined as (date of last dose of open-label study drug – date of first dose of double-blind study drug +1).

The date of last dose of study drug will be obtained from the eCRF. In the event that the date of last dose is missing, then for analysis and summary purpose, the last dose date will be estimated as the later date between the last drug dispense date plus the number of days in the dosing interval (dispense date + (next visit day – last visit day) + 1) and the last study visit day.

The duration of double-blind treatment in Part 1 will be summarized by treatment group using the following categories: 1 to 11 days and 12 to 21 days, 22 to 31 days. The duration of open-label treatment in Part 2 will be summarized using the following categories: 32 to 41 days, 42 to 85 days, and 85 days or more. The intervals are calculated using the actual study days according to the visit window definitions in Table 7.a and Table 7.b.

In Part 1 of the study, subjects are to take 1-3 tablets for TAK-935 (100mg/200mg/300mg) or matching placebo twice each day. In Part 2, subjects are to take 1-3 tablets for TAK-935 (100mg/200mg/300mg) twice daily. Overall percent study drug compliance for each period (Part 1 and Part 2) will be calculated as:

Overall compliance (%) = 100 ×{(number of tablets dispensed – number of tablets returned) / (expected number of tablets to be taken)},

where expected number of tablets to be taken = [number of tablets to be taken daily*(date of last dose of medication – date of first dose of medication + 1)].

Compliance will be presented to 1 decimal place in the derived dataset and Table, Figures, and Listings (TFLs) outputs.

Overall study drug compliance in Part 1 and Part 2 will each be summarized using descriptive statistics and by the number of subjects in each of the following compliance categories: <70%, >=70 to <=130%, >130%, and missing, if applicable.

All study drug administration (double-blind placebo in Part 1, double-blind active (TAK-935) drug in Part 1, and open-label study drug in Part 2) and accountability data will be listed by site and subject number. The following variables will be listed: subject identifier, treatment, first and last double-blind dose dates, first and last open-label dose dates, number of tablets dispensed and

returned, overall double-blind percent compliance in Part 1, and overall open-label study drug percent compliance in Part 2.

7.8 Efficacy Analysis

Efficacy analysis will be performed using FAS in Parts 1 and 2 separately.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Exploratory Efficacy Endpoint(s)

CCI

CCI

[redacted]

CCI

[redacted]

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Pharmacokinetic Concentrations

Blood samples (one 4-mL sample per scheduled time) for the measurement of plasma concentrations of TAK-935 and its metabolite M-I will be collected according to Table 7.c.

Table 7.c Collection of Plasma Samples for Measurement of TAK-935 and M-I in Plasma

Study Part	Study Day/Visit	Scheduled Time
Part 1	Day 1	Before and 1, 3, 5 hours after morning dose
	Days 11 and 21	Before and ~1 hour after morning dose
Part 2	Days 31, 41 and 85	Before morning dose

The plasma concentration of TAK-935 and its metabolite M-I will be listed for each subject and summarized by each time point for each dose and part of the study (N, mean, SD, median, minimum, and maximum).

7.9.1.2 Pharmacokinetic Parameters (Secondary Endpoints)

A population PK analysis approach will be used to determine the population estimates for TAK-935. The PK analysis will be described in a separate analysis plan, and the PK parameters for TAK-935 will be summarized in a separate population PK/PD report.

7.9.2 Pharmacodynamic Analysis

7.9.2.1 Pharmacodynamic Concentrations

CCI

[redacted]

CCI

[redacted]

7.9.3 Concomitant AEDs Analysis

CCI

[redacted]

7.9.3.2 Parameter and Analysis

CCI

[redacted]

CCI

[redacted]

7.11 Safety Analysis

Safety analyses include AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters. The safety analysis set will be used for all summaries of safety parameters. The safety endpoints will be presented by placebo TAK-935, and overall in Part 1, by placebo, TAK-935 received in Part 1 and overall in Part 2 of the study, and by placebo, TAK-935 received in Part 1 and overall for Part 1 and 2 combined.

7.11.1 Adverse Events

A Pre-Treatment Event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study, but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. PTE and AE verbatim terms will be coded by SOC and PT using MedDRA (version 19 or later).

TEAEs for Part 1 will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occur after the first dose of study drug received in Part 1 and up to 30 days (onset date – last date of dose + 1 ≤ 30) after the last dose of study drug in Part 1 or

early termination. AEs that occur on the same day as the first dose of study drug in Part 1 but with missing time will be considered as TEAEs for Part 1.

TEAEs for Part 2 will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occur after the first dose of study drug received in Part 2 and up to 30 days (onset date – last date of dose + 1 ≤ 30) after the last dose of study drug in Part 2 or early termination. AEs that occur on the same day as the first dose of study drug in Part 2 but with missing time will be considered as TEAEs for Part 2.

TEAEs for Part 1 and 2 combined will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occur after the first dose of study drug received in Part 1 and up to 30 days (onset date – last date of dose + 1 ≤ 30) after the last dose of study drug in Part 2 or early termination. AEs that occur on the same day as the first dose of study drug in Part 1 but with missing time will be considered as TEAEs for Part 1 and 2.

TEAEs will be presented by severity (mild, moderate, and severe). Serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death will also be summarized using SOC and PT.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary.

AEs with missing severity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. Similarly, if the relationship of an event is missing, the event will be considered as related but in listings it will be presented as missing.

In general, AEs will be tabulated at the following levels: overall summary (subjects with at least 1 AE in any dose or treatment), the MedDRA SOC, and the MedDRA PT. The tables will include the number and percentage (N[%]) of subjects. The following summary tables will be generated for each study part (Part 1 and Part 2):

- Overview of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events by Preferred Term
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Most Frequent (>5% or N>2) Non-Serious Adverse Events by Preferred Term
- Most Frequent (>5% or N>2) Non-Serious Adverse Events by System Organ Class and Preferred Term
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term

- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Drug-Related Treatment-Emergent Adverse Events by Preferred Term
- Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Pretreatment Adverse Events by System Organ Class and Preferred Term

In addition, subject mappings for the TEAEs by SOC and PT will be generated.

Data listings will be provided for PTEs, TEAEs, TEAEs leading to study drug discontinuation, SAEs, and AEs that resulted in death.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be assessed using the safety analysis set and will be evaluated and presented using International System of Units (SI) unless otherwise stated. Table 7.f shows a list of all clinical laboratory tests.

Table 7.f Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (a)	Study Specific
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets PT/INR aPTT	ALT Albumin Alpha-1-acid glycoprotein Alkaline phosphatase AST Total bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium Total cholesterol HDL cholesterol LDL cholesterol Triglycerides FSH (c) Estradiol (d)	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis: (b) RBC/high power field WBC/high power field Epithelial cells, casts etc	**Plasma** CCI **Plasma (Concomitant AEDs)** Carbamazepine Clobazam Valproic acid Phenytoin Topiramate Lamotrigine Rufinamide Zonisamide Phenobarbital Levetiracetam Lacosamide 10-hydroxycabazepine (metabolite of oxcarbazepine) Felbamate

Diagnostic Screening

Serum	Urine (a)
HIV HBsAg and anti-HCV HCV RNA detection by qPCR (e) hCG (for pregnancy) (f)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine hCG (for pregnancy) (f)

aPTT= activated partial thromboplastin time, FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, HDL=high-density lipoprotein, LDL=low-density lipoprotein, PT=prothrombin time, RBC=red blood cell; WBC=white blood cell.
(a) If urine cannot be collected at the time of the Screening Visit or other Visits due to the subject's cooperation or because the subject is wearing a diaper, it is acceptable for the subject to continue in the study and the reason should be documented in the source document.
(b) Only if dipstick results are positive.
(c) For diagnostic purposes in female subjects only.
(d) In female patients only
(e) Subjects who are positive for hepatitis C Ab should return to the clinic for an unscheduled visit to provide a blood sample for HCV qPCR.
(f) Only for female subjects of childbearing potential. If urine cannot be collected at Visit 2, the reason should be documented in the source document and the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the investigator prior to randomization. An additional serum hCG pregnancy test will be performed at the Final Visit.

All laboratory test parameters will be displayed in individual subject data listings in both SI units and conventional (CV) units. For test results not in SI units, the conversion to SI units will be done in derived analysis data sets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived dataset. All summaries and analyses will be based on the values using these preferred SI units.

Only observations within 7 days of the last dose of study drug will be included in the tables. No inferential statistics will be presented unless otherwise stated.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed and change from baseline values will be presented for Parts 1 and 2 separately. Study baseline defined in Section 7.1.1 will be used for change from baseline in each part of the study. Note that character urinalysis tests will only be listed.

Laboratory Markedly Abnormal Values (MAVs), identified by the criteria defined in Appendix A, will be tabulated. If a subject has a MAV for a particular laboratory test, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal laboratory test result will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries if MAV criteria are satisfied.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

7.11.3 Vital Signs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize vital sign parameters at baseline, each post-baseline visit, and change from baseline to each post-baseline visit for both Parts 1 and 2. Study baseline defined in Section 7.1.1 will be used. Only observations within 7 days of the study drug will be included in the tables.

Vital sign MAVs, identified by the criteria defined in Appendix B, will be tabulated. If a subject has a MAV for a particular vital signs parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal vital signs measurement will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries if MAV criteria are satisfied.

All vital signs will be listed in a data listing.

7.11.4 12-Lead ECGs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters, including heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (Fredericia's and Bazett's corrections), will be presented for baseline, each post-baseline visit, and change from baseline to each post-baseline visit for both Parts 1 and 2. Study baseline defined in Section 7.1.1 will be used. Only the scheduled measurements will be included in the

summary. Only observations within 7 days of the study drug will be included in the tables. No inferential statistics will be presented.

ECG MAVs, identified by the criteria defined in Appendix C, will be tabulated. If a subject has a MAV for a particular 12-lead ECG parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal 12-lead ECG measurement will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

Overall ECG interpretation category (normal, abnormal not clinically significant, abnormal clinically significant, not evaluable) is collected by eCRF at baseline and at each scheduled post-baseline visit. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations, not evaluable, with missing, if applicable, and total categories by each treatment (placebo, TAK-935).

All ECG parameters will be listed in a data listing.

7.12 Changes in the Statistical Analysis Plan

No additional/modified FAS or per-protocol populations will be defined. No interim analysis for Part 1 will be performed.

8.0 REFERENCES

1. A Phase 1b/2a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Escalation Study With an Open-Label Part to Examine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-935 as an Adjunctive Therapy in Subjects With Developmental and/or Epileptic Encephalopathies, Takeda, Protocol Amendment No.03 for TAK-935-2001, dated 21 March 2018.
2. Aman, M.; Singh, N. The Aberrant Behavior Checklist-Community. East Aurora, NY: Slosson Education Publications, Inc.; 1994.
3. Carpenter, JR, Kenward, MG, Vansteelandt, S.A comparison of multiple imputation and doubly robust estimation for analyses with missing data. Journal of the Royal Statistical Society: Series A (Statistics in Society) 2006: 169: 571–584.
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5. Schmidt JD, Huete JM, Fodstad JC, Chin MD, Kurtz PF. An evaluation of the aberrant behavior checklist for children under age 5. Res Dev Disabil 2013; 34: 1190–1197.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology – Criteria for Markedly Abnormal Values (SI units)

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 × LLN	>1.5 × ULN
Platelet count	Conventional	$<75 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$
	SI	$<75 \times 10^9/L$	$>600 \times 10^9/L$
Prothrombin time/international normalized ratio	Both	--	>1.5 × ULN
Activated partial thromboplastin time	Both	--	>1.5 × ULN

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry – Criteria for Markedly Abnormal Values (SI units)

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3 × ULN
AST	Both	--	>3 × ULN
GGT	Both	--	>3 × ULN
Alkaline phosphatase	Both	--	>3 × ULN
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8 × LLN	>1.2 × ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI	--	>177 μmol/L
Blood urea nitrogen	Conventional	--	>30 mg/dL
	SI	--	>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L

Serum Chemistry – Criteria for Markedly Abnormal Values (SI units)

Parameter	Unit	Low Abnormal	High Abnormal
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Bicarbonate	Conventional	<8.0 mEq/L	--
	SI	<8.0 mmol/L	--
Creatine kinase	Conventional	--	>5 × ULN
	SI	--	>5 × ULN
Total Cholesterol	Conventional	--	>300 mg/dL
	SI	--	>7.72 mmol/L
Triglycerides	Both	--	>2.5 × ULN
LDL Cholesterol	Conventional	< 50 mg/dL	>160 mg/dL
	SI	<1.30 mmol/L	>4.14 mmol/L
HDL Cholesterol	Conventional	<40 mg/DL	>60mg/DL
	SI	<1.04 mmol/L	>1.55 mmol/L
Alpha-1-Acid Glycoprotein	Conventional	<47mg/DL	>125 mg/DL

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	< 35.6	>37.7

Appendix C Criteria for Markedly Abnormal 12-Lead ECG Parameters

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	< 50	> 120
PR	msec	≤ 80	≥ 200
RR	msec	≤ 600	≥ 1440
QRS	msec	≤ 80	≥ 180
QT Interval	msec	≤ 50	≥ 460
QTcF Interval	msec	≤ 50	≥ 500 OR ≥ 30 change from baseline and ≥ 450

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	31-Oct-2018 13:35 UTC
	Clinical Approval	31-Oct-2018 13:51 UTC
	Biostatistics Approval	01-Nov-2018 15:55 UTC