



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

Protocol Approve Date: 21 March 2018

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TAKEDA PHARMACEUTICALS
PROTOCOL

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

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015

Study Number: TAK-935-2001

IND Number: 121234 **EudraCT Number:** Not applicable

Compound: TAK-935

Date: 21 March 2018 **Amendment Number:** 03

Amendment History:

Date	Amendment Number	Region
05 April 2017	Initial version	North America
24 August 2017	01	North America
16 January 2018	02	North America
21 March 2018	03	North America

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	PPD
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reason for this amendment is to allow administration of TAK-935 or placebo via stable gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube after finalization of chemistry, manufacturing, and controls (CMC) in vitro studies demonstrating 100% drug delivery through a G-tube when crushed and suspended in water.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes and where the changes are located, see [Appendix E](#).

Changes in Amendment 03:

1. Clarified that TAK-935 or placebo can be administered either orally or via stable G-tube/ PEG tube.
2. Clarified that a separate consent form will be obtained for subjects with G-tube/PEG tubes.
3. Added inclusion criteria related to subjects with G-tube/PEG tubes.
4. Modified exclusion criteria to allow the use of medical marijuana.
5. Modified secondary endpoints to remove estimation of additional parameters.
6. Removed body weight/body mass index (BMI) from secondary and exploratory endpoints.
7. Modified study drug dosing and regimen sections to clarify how study drug will be administered via G-tube/ PEG tube.
8. Modified study drug dispensing procedures to clarify how the investigative product (IP) will be prepared for administration via G-tube/PEG tube.
9. Clarified when open-label extension study is expected to be initiated.
10. Updated the medical monitor contact information.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator ([Appendix B](#)).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix D](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

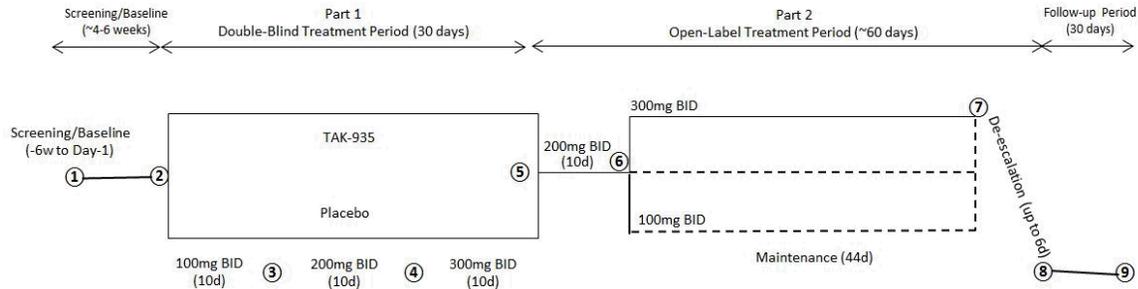
Name of Sponsor: Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015	Compound: TAK-935	
Title of Protocol: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Escalation Study With an Open-Label Part to Examine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-935 as an Adjunctive Therapy in Subjects With Developmental and/or Epileptic Encephalopathies	IND No.: 121234	EudraCT No.: Not applicable.
Study Number: TAK-935-2001	Phase: 1b/2a	
<p>Study Design:</p> <p>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. Drop seizures are defined as a seizure involving the entire body, trunk or head that leads to a fall, injury, slumping in a chair, or head hitting the surface, or could have led to a fall or injury, depending on the position of the subject at the time of the attack or spell. Drop seizures will be captured separately (eg, tonic seizures leading to a drop will be captured as a drop). The study will screen a sufficient number of subjects to ensure approximately 20 randomized subjects.</p> <p>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. 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]</p> <p>[REDACTED]. The 4-week Baseline Period CCI [REDACTED] can begin as soon as informed consent is 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).</p> <p>The study will consist of 2 parts:</p> <p>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 twice daily (BID) will be reached after a 20-day titration period.</p> <p>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).</p> <p>Part 1 of the study is designed to investigate the safety, tolerability, pharmacokinetics (PK), and PD in adult subjects with developmental and/or epileptic encephalopathies in a double-blind manner. CCI [REDACTED] exploratory manner.</p> <p>Approximately 20 adult subjects who demonstrate ≥ 1 bilateral motor seizure 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 BID orally or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube for 30 days during the Double-Blind Treatment Period. Subjects will initiate the investigative product (IP) (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</p>		

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 and will discuss the benefit-risk with the subject or the subject's legally acceptable representative before increasing 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 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 adverse events (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.

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. Efficacy of TAK-935 on CCI [REDACTED] exploratory 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 on TAK-935 up to 300 mg BID, 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 and will discuss the benefit-risk with the subject or the subject's legally acceptable representative before increasing 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 85 (Visit 7), subjects will return to the clinic for the Final Visit and enter the 3- or 6-day de-escalation phase. 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 antiepileptic drug (AED) blood sample collection.

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.

Study Schematic:



Primary Objective:

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

Secondary Objective:

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

Subject Population: Adult subjects aged ≥ 18 and ≤ 65 years with developmental and/or epileptic encephalopathies and on background AED therapy and continued seizure activity.

Number of Subjects:

- Approximately 20 subjects (n=16 for TAK-935 and n=4 for placebo) for Part 1.
- Up to 20 subjects (all TAK-935) for Part 2.

Number of Sites:

~11 sites in North America

Dose Levels:

- TAK-935 100, 200, and 300 mg BID.
- Matching placebo BID.

Route of Administration:

Oral or via G-tube/PEG-tube

Duration of Treatment:

Part 1: 30 days
 Part 2: ~60 days

Period of Evaluation:

~20 weeks (includes 4 to 6-week Screening/Baseline and 30-day Follow-up Periods)

Main Criteria for Inclusion:

- The subject is a male or female aged ≥ 18 and ≤ 65 years at the time of informed consent and the first dose of study drug.
- The subject has a documented clinical diagnosis of developmental and/or epileptic encephalopathies with bilateral motor seizures, defined as an average of ≥ 2 per month during the past 3 months, based on the investigator's assessment, and a monthly average of ≥ 1 per month during the 4-week Baseline Period based on the seizure diary record.
- The subject is taking 1 to 4 AEDs at a stable dose for ≥ 4 weeks before Screening (Visit 1), and the subject or subject's legally acceptable representative is willing to keep the regimen(s) stable throughout the study.
- The subject has an average of ≥ 1 bilateral motor seizure per month during the 4-week Baseline Period (ie, drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, focal seizures with bilateral hyperkinetic motor features). If the subject has < 1 bilateral motor seizure per month during the Baseline Period, the subject will be considered a screen failure.

Main Criteria for Exclusion:

- The subject was admitted to a medical facility for treatment of status epilepticus requiring mechanical respiration within 3 months before Screening (Visit 1).
- The subject had a vagal nerve stimulator implanted within 6 months before Screening (Visit 1) and settings have been changed within 1 month of the Screening Visit (Visit 1) and/or are anticipated to change during the study.
- The subject has unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, or endocrine disease or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted.
- The subject has a history of suicidal behavior or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening (Visit 1). If the subject is unable to comply with the C-SSRS due to developmental status, a parent proxy may be used for the completion of the C-SSRS. The Investigator may also use clinical judgment, which must then be documented in the source document.

Main Criteria for Evaluation and Analyses:

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.

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-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.

Statistical Considerations:

TEAEs will be a primary endpoint for each part of the study. TEAEs will be summarized using descriptive statistics (number and percentage of subjects) for the safety analysis set. No statistical testing will be performed or inferential statistics will be generated.

The PK of TAK-935 and other safety endpoints will be analyzed as the secondary endpoints in each part of the study. The number and percentage of subjects with clinical laboratory test, vital sign, weight/BMI, and ECG parameter values that meet Takeda's predefined criteria for markedly abnormal values at least once postdose will be summarized by treatment and part of the study. Plasma concentrations of TAK-935 will be listed for each subject and summarized by each time point for each dose and part of the study. A population PK/PD analysis approach will be used to determine the population estimates for TAK-935.

After all subjects have completed the Double-Blind Treatment Period or have discontinued from the study (and prior to completion of the Open-Label Period), an unblinded safety summary may be generated (Section 13.2).

Sample Size Justification: 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 epilepsy 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.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research, as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 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
G-tube	gastrostomy tube
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for 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	pentylentetrazol
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

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

TAK-935 is a potent and selective cholesterol 24S-hydroxylase (CH24H) inhibitor currently in development for adjunct treatment for epileptic disorders.

In the brain, cholesterol is metabolized by CH24H, which is specifically and constitutively expressed in neurons, to 24S-hydroxycholesterol (24HC). This cholesterol metabolite, 24HC, leaves the brain via lipoproteins and is excreted in bile. Aberrant cholesterol metabolism is implicated in epilepsy disorders/syndromes.

Under normal conditions, extracellular glutamate is sequestered by glutamate transporters on neighboring astrocytes that require adequate cholesterol levels to efficiently maintain lipid raft structures in the astrocyte plasma membrane. Upon central nervous system (CNS) injury, CH24H is induced in reactive astrocytes and microglia. This leads to disruption in astrocytic glutamate homeostasis and a large increase in extracellular glutamate levels. As the CH24H enzyme converts cholesterol essential for the integrity of plasma membrane lipid rafts to 24HC, the circulating levels of 24HC increase and may further contribute to underlying pathophysiological processes. Excessive extracellular glutamate and 24HC levels are thought to play major roles in excitotoxicity either through a sustained activation of the N-methyl-D-aspartate (NMDA) receptor channel or as a positive allosteric modulator of the receptor [1]. The processes may be equally important in contributing to the enhanced glutamatergic activity observed in epilepsy disorders.

To date, TAK-935 has been studied in 4 clinical studies including a single-rising dose (SRD) first-in-human study (TAK-935-101), a single-dose positron emission tomography (PET) target occupancy study (TAK-935-1003), a multiple-rising dose (MRD) study (TAK-935-1002), and a single-dose relative bioavailability (BA) and food-effect study (TAK-935-1005). The pharmacokinetics (PK) and pharmacodynamics (PD) of TAK-935 administered as an oral solution or tablet in healthy subjects were characterized in these studies. In addition, the PET study provided clinical evidence of dose-dependent decreases in plasma 24HC concentrations and PET occupancy measurements that were dose- and time-dependent and correlated with circulating levels of 24HC.

For further information, refer to the TAK-935 Investigator's Brochure.

4.2 Rationale for the Proposed Study

The term epileptic encephalopathies describes a heterogeneous group of epilepsy syndromes in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (eg, cortical malformation) and that can worsen over time [2]. These disorders are generally diagnosed in childhood and adolescence, varying in their etiologies, seizure types, electroencephalographic patterns, cognitive deficits, and prognosis, while sharing a consistent and significant impact on neurological development.

The International League against Epilepsy (ILAE) recently expanded this definition to include disorders that may result in developmental delay before epilepsy onset and used the term of Developmental and/or Epileptic Encephalopathy to encompass this broader population [3].

The current study is designed to further characterize the safety, tolerability, PK, and PD of multiple-dose TAK-935 administration in adult subjects with developmental and/or epileptic encephalopathies. An additional aim is to explore the effects of TAK-935 on seizure frequency using a seizure diary. In addition, this study will use a dose-escalation design, which will help guide dosing recommendations for future studies.

Pharmacogenomic (PGx) analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. As PGx is an evolving science, currently many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response and safety that may lead to additional hypothesis-generating exploratory research on stored samples. Participation of study subjects in PGx sample collection is optional.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 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).

5.1.3 Exploratory Objectives

CCI



5.2 Endpoints

5.2.1 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.

5.2.2 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-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.

CONFIDENTIAL

5.2.3 Exploratory Endpoints

CCI



6.0 STUDY DESIGN AND DESCRIPTION

6.1 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 7.1 and 7.2). CCI

The 4-week Baseline Period CCI 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. Efficacy CCI

CCI 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).

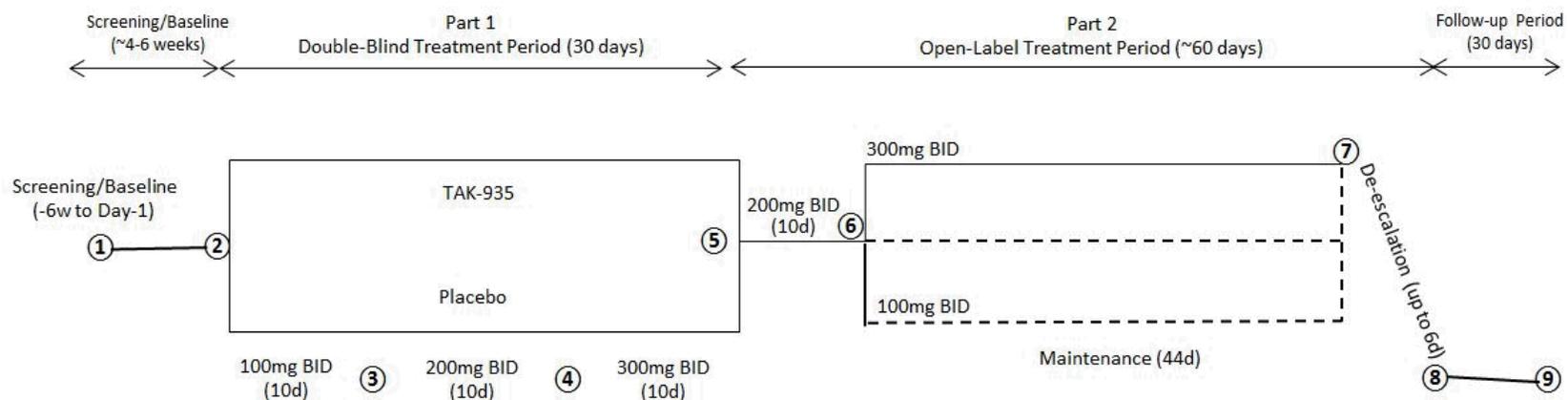
Seizure data will be recorded daily in the seizure diary by each subject and/or subjects' caregiver throughout the Screening/Baseline Period up until the Follow-up Visit (Visit 9) on Day 121 and will be collected from the diary at each visit.

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 6.a](#). A schedule of study procedures is listed in [Appendix A](#).

Figure 6.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).

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study with an open-label part to examine the safety, tolerability, PK and PD, and preliminary efficacy of TAK-935 as adjunctive therapy in the treatment of subjects 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.

The safety, tolerability, PK, and CCI of TAK-935 after multiple-dose administration either orally or via G-Tube/PEG tube is first assessed (in Part 1), and then the longer-term safety, tolerability, and PK/PD of TAK-935 is assessed (in Part 2), with a seamless transition between Parts 1 and 2. The main goal of this study is to identify the safe and tolerable dose of TAK-935 to assess the efficacy of TAK-935 in subjects with developmental and/or epileptic encephalopathies.

6.2.2 Dose

6.2.2.1 Dose Selection Rationale

In the current study, dose selection was mainly based on the safety and tolerability data from the single- and multiple-dose phase 1 studies in healthy subjects administered TAK-935 as an oral solution. The selection of BID doses was also supported by the PK/PD/enzyme occupancy (EO) modeling and simulations using available phase 1 data. In addition, nonclinical data from rodent epilepsy models were used to define efficacious doses.

The safety results from the phase 1 studies show that TAK 935 (up to a single dose of 1350 mg) is generally safe and well tolerated in healthy male and female subjects. TAK-935 has been evaluated at doses up to 600 mg once daily (QD) as well as 300 mg BID in healthy adult subjects in the MRD study. Multiple rising doses of TAK-935 up to 400 mg QD for 14 days without up-titration was generally safe and well tolerated in healthy subjects. When administered in a nontitrating fashion, AEs considered by the investigator to be nonserious were seen in individual subjects at 300 mg BID (mental confusion of mild intensity) and 600 mg QD (acute psychosis of severe intensity) dose levels. This TAK-935-2001 study will continue to investigate safety, tolerability, PK, and PD of TAK-935 by studying a dose range of 100 mg BID to 300 mg BID in an epilepsy adult patient population. In this study, a titration scheme will be used to ensure safety and tolerability before moving to higher doses.

In pentylenetetrazol (PTZ)-induced kindling in mice, TAK-935 at a dose of 1 mg/kg resulted in a statistically significant reduction in seizure counts. This dose also resulted in an approximately 60% reduction in mean brain 24HC levels, which translated to an average EO of approximately

65%. At higher doses, TAK-935 exerted stronger effects on generalized seizures. The 1 mg/kg dose was determined to be the minimum effective dose of TAK-935.

A selective PET ligand was developed and used to assess the CNS target engagement of TAK-935 in healthy adult subjects, and a preliminary PK/PD/EO model was developed. Firstly, an empirical PK model was developed to characterize complex and nonlinear PK data in healthy adult subjects from the SRD and MRD studies as well as the relative BA study comparing the exposure between oral dosing with solution and tablet formulations. Subsequently, the predicted TAK-935 plasma concentrations were modeled with PD (24HC and PET occupancy) data to assess target engagement. The relationship between TAK-935 plasma concentrations and the observed brain occupancy values was characterized by a sigmoidal maximum effect model using an effect-site compartment to account for the temporal lag observed between PK and PD measurements. The relationship between TAK-935 plasma concentrations and plasma 24HC levels was characterized by an inhibitory indirect response model. This PK/PD/EO model was used to select the doses for the current study. The model-based simulations were performed for both QD and BID dosing regimens with the same daily dose in adult subjects, and the BID regimen was selected over QD regimen due to its lower variability on the expected EO, PK, and PD parameters and a more sustained period during a dosing interval with EO above 65%.

6.2.2.2 Dose Selection Procedures

The planned doses are based on predictions from the available PK/PD/EO model. A TAK-935 100 mg tablet, administered as 1, 2, or 3 tablets corresponding to the different dose levels, will be used for dosing in adult subjects.

The EO levels and planned TAK-935 doses are shown for each part of the study in [Table 6.a](#).

Table 6.a Planned TAK-935 BID Doses and Associated Estimated EO Levels

TAK-935 BID Dose (mg)	Average EO Level (%) (a)
300	85-95
200	80-90
100	70-80

(a) Average EO% at steady state during a dosing interval.

The investigator, in consultation with the sponsor, may decide to reduce the IP (TAK-935 or placebo) during Part 1 and TAK-935 during Part 2 dose at any time during the study, in the event of any safety or tolerability concerns. In Part 1, the planned starting dose of TAK-935 for adult subjects is 100 mg BID to achieve an average steady-state EO of approximately 70% to 80%. If well tolerated, this dose will be increased to 200 mg BID on Day 11 and subsequently to 300 mg BID on Day 21; the average steady-state EO at these doses are expected to be approximately 80% to 90% and 85% to 95%, respectively ([Table 6.a](#)).

In Part 2, the planned starting dose of TAK-935 for all subjects, including those who received placebo in Part 1, is 200 mg BID to be increased to 300 mg BID. The dose may be decreased at any time due to safety or tolerability concerns.

6.2.3 Endpoints

6.2.3.1 Safety Endpoints

The safety-related endpoints of TEAEs, clinical laboratory test results, vital sign measurements, C-SSRS, and ECG parameters selected for this study are standard methods for assessing safety and tolerability in clinical studies. The ABC-C is a standard tool for measuring the severity of a range of problem behaviors commonly observed in individuals with intellectual and developmental disabilities.

6.2.3.2 PK Endpoints

The secondary PK endpoints selected for this study, C_{max} , AUC_{0-tau} , $C_{av,ss}$, and C_{trough} are common PK parameters used to describe the steady-state exposure of a study drug following multiple doses in clinical studies. Additional population PK parameters will be included in the population PK model used to characterize the TAK-935 concentration-time profile and will be reported in the population PK report.

6.2.3.3 CCI

CCI

6.2.3.4 CCI

CCI

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for TAK-935, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an Institutional Review Board (IRB), or a regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before the first dose of study drug.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the subject or subject's legally acceptable representative is capable of understanding and complying with protocol requirements.
2. The subject or the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization before the initiation of any study procedures, including requesting that a subject fast for any clinical laboratory evaluations. An assent should be obtained from the subject, if possible. If the subject cannot provide assent (ie, due to developmental status), the investigator should document why assent was not obtained. For subjects with G-tube/PEG tube, a separate supplemental consent form will be signed by the subject/caregiver and attached to the general consent.
3. The subject is a male or female aged ≥ 18 and ≤ 65 years at the time of informed consent and the first dose of study drug.
4. The subject has a documented clinical diagnosis of developmental and/or epileptic encephalopathies with bilateral motor seizures, defined as an average of ≥ 2 per month during the past 3 months, based on the investigator's assessment, and a monthly average of ≥ 1 per month during the 4-week Baseline Period, based on the seizure diary record.

Developmental and/or epileptic encephalopathy will be defined as:

- Subjects with an established diagnosis of the following: for example, Lennox-Gastaut Syndrome, Dravet Syndrome, Tuberous Sclerosis Complex, OR
- Retrospectively including:
 - History of special education classes, OR
 - Formal IQ < 70 , OR
 - Generalized background slowing (posterior dominant rhythm [PDR] persistently < 8 Hz) on interictal EEG,

AND

- Epilepsy not due to a brain injury acquired after age 3 years.
5. The subject is taking 1 to 4 AEDs at a stable dose for ≥ 4 weeks before Screening (Visit 1), and the subject or subject's legally acceptable representative is willing to keep the regimen(s) stable throughout the study. For the purposes of this study ketogenic diet and vagus nerve stimulation will not be considered AEDs.

6. The subject has an average of ≥ 1 bilateral motor seizure per month during the 4-week Baseline Period (ie, drop seizures, tonic-clonic, tonic, bilateral clonic, atonic, myoclonic-atonic, myoclonic-tonic-clonic, focal seizures with bilateral hyperkinetic motor features). Drop seizures are defined as a seizure involving the entire body, trunk or head that leads to a fall, injury, slumping in a chair, or head hitting the surface, or could have led to a fall or injury, depending on the position of the subject at the time of the attack or spell. Drop seizures will be captured separately (eg, tonic seizures leading to a drop will be captured as a drop). If the subject has < 1 bilateral motor seizure per month during the Baseline Period, the subject will be considered a screen failure.
7. A female subject of childbearing potential* must have a negative serum pregnancy (human chorionic gonadotropin [hCG]) test at Screening (Visit 1) and a negative urine pregnancy test before Randomization (Visit 2). If urine cannot be collected, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the investigator prior to randomization.
8. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely an adequate method of contraception* from signing of informed consent throughout the duration of the study and for 30 days after last dose.
9. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 30 days after last dose.

*Definitions and acceptable methods of contraception are defined in Section 9.1.12 and reporting responsibilities are defined in Section 9.1.13.

10. Subjects and/or subjects' caregivers must agree to not post any subject's personal medical data related to the study or information related to the study on any web site or social media site (eg, Facebook, Twitter) until the study has been completed.
11. For subjects with G-tube/PEG tube, G-tubes/PEG tubes should have been placed and been functioning for at least 3 months prior to screening. Naso-gastric tubes are not allowed.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has been part of a clinical study involving another investigational product in the previous 3 months or subject is currently receiving an investigational product.
2. The subject has received TAK-935 in a previous clinical study or as a therapeutic agent.
3. The subject was admitted to a medical facility for treatment of status epilepticus requiring mechanical respiration within 3 months before Screening (Visit 1).
4. The subject had a vagal nerve stimulator implanted within 6 months before Screening (Visit 1) and settings have been changed within 1 month of the Screening Visit (Visit 1) and/or are anticipated to change during the study.

5. The subject is on a ketogenic diet that has been started within 6 months of the Screening Visit (Visit1), has been changed within 1 month of the Screening Visit (Visit 1), or is anticipated to change during the study.
6. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
7. The subject has unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, or endocrine disease or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the Medical Monitor may be warranted.
8. The subject has degenerative eye disease.
9. The subject has a history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS at Screening (Visit 1). If the subject is unable to comply with the C-SSRS due to developmental status, a parent proxy may be used for the completion of the C-SSRS. The Investigator may also use clinical judgment, which must then be documented in the source document.
10. Positive for human immunodeficiency virus, hepatitis B, or hepatitis C infections. (Note that subjects who have been vaccinated against hepatitis B [hepatitis B surface antibody {Ab}-positive] who are negative for other markers of prior hepatitis B infection [eg, negative for hepatitis B core Ab] are eligible. Also note that subjects who are positive for hepatitis C Ab are eligible as long as they have a negative hepatitis C viral load by quantitative polymerase chain reaction [qPCR]).
11. The subject has an abnormal and clinically significant ECG at Screening (Visit 1), in the opinion of the investigator, for example, second or third-degree heart block or a corrected QT interval (QTc) >450 msec. Entry of any subject with an abnormal but not clinically significant ECG must be approved and documented by signature by the principal investigator or appropriately qualified delegate.
12. The subject has abnormal clinical laboratory test results at Screening (Visit 1) that suggest a clinically significant underlying disease. If the subject has alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2.5 × the upper limit of normal (ULN), the Medical Monitor should be consulted.
13. The subject has a known hypersensitivity to any component of the formulation of TAK-935.
14. The subject has received any excluded medications, procedures, or treatments during the time periods listed in Section 7.3.

15. The subject has a history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, within the previous 2 years before Screening (Visit 1). Medical marijuana use is allowed.
16. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study; or intending to donate ova during such time period.
17. If male, the subject intends to donate sperm during the course of this study or within 30 days after the last dose of study drug.

7.3 Excluded Medications, Procedures, and Treatments

The following medications and products are excluded from the Screening Visit (Visit 1) until the end of the Follow-up Visit (Visit 9):

- Intermittent use of benzodiazepines as rescue medication ≥ 3 times a week. Chronic benzodiazepine use is not exclusionary.
- Stiripentol

Subjects should be advised to not consume alcohol or drugs such as cannabis (medical marijuana is allowed) during the study. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

7.4 Diet, Fluid, and Activity Control

TAK-935 tablets should be administered at approximately the same time on each dosing day with or without food. The time of the last meal relative to dosing must be recorded in the electronic case report form (eCRF) at each PK/PD sampling visit. Subjects and/or subjects' caregivers should be instructed to maintain the same dose administration time for the concomitant AEDs throughout the study, if possible. It is recommended that subjects remain upright (seated, standing, or ambulatory) for approximately 1 hour after study drug dosing on the PK sampling days, if possible. For subjects receiving study drug via G-tube/PEG tube, other medications or enteral feeds should not be given concurrently.

Subjects who are on a ketogenic diet must maintain stable dietary habits throughout the study. The ketogenic diet should not be altered during the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

Subjects who cannot tolerate the 100 mg BID dosing will be withdrawn from the study and should undergo all procedures scheduled for the Final Visit at the time of withdrawal.

The primary reason for discontinuation or withdrawal of the subject from the study or of study drug should be recorded in the eCRF using the categories listed below. For screen failure subjects, refer to Section 9.1.21.

1. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
 - Liver Function Test (LFT) Abnormalities

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.11), if the following circumstances occur at any time during study drug treatment:

 - ALT or AST $>8 \times$ ULN, or
 - ALT or AST $>5 \times$ ULN and persists for >2 weeks, or
 - ALT or AST $>3 \times$ ULN in conjunction with elevated total bilirubin $>2 \times$ ULN or international normalized ratio (INR) >1.5 , or
 - ALT or AST $>3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
2. Significant Protocol Deviation. The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to Follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Withdrawal by Subject. The subject wishes to withdraw (or subject's legally acceptable representative wishes to withdraw the subject) from the study.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. Withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category.
5. Progressive Disease. Clinically significant worsening in seizure frequency as judged by the investigator in either Part 1 or Part 2.
6. Symptomatic Deterioration. The subject has an episode of clinically symptomatic status epilepticus that requires mechanical respiration.
7. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
8. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.13.
9. Other.

Note: The specific reasons should be recorded in the “specify” field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject’s study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject’s participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Final Visit (at time of withdrawal), including dose de-escalation, as appropriate, followed by the 30-day Follow-up Period. Up to 6 discontinued or withdrawn subjects may be replaced at the discretion of the sponsor. For the subjects who discontinue or are withdrawn from the study, whenever possible, the seizure activity monitoring will continue for 30 days following study exit to assess possible rebound in seizure activity.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

The sponsor will supply the study sites with TAK-935 100 mg tablets and matching placebo tablets. TAK-935 100 mg tablets and matching placebo tablets are manufactured by Spera Pharm Inc, Osaka Japan. Study drug will be supplied in high-density polyethylene bottles with induction seal and child-resistant caps. Each bottle will contain a label that includes pertinent study information and caution statements. The label text will be in English. The bottles to be used will be identifiable by a unique identification number and managed by the interactive voice response system (IVRS)/interactive web response system (IWRS).

For subjects receiving study drug via G-tube/PEG tube, tablets will be crushed, suspended in water, and the suspension will be administered via the G-tube/PEG tube using a syringe. Complete instructions will be provided to subjects/caregivers in a document provided outside of the protocol.

8.1.1.2 Rescue Medication

Rescue medication will be used in case of major seizures, according with the judgment of the investigator and based on evidence of prior positive responses of each subject. Rescue medication will not be supplied by the sponsor.

8.1.1.3 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol are the following:

- TAK-935 100 mg tablets.
- Matching placebo tablets.

8.1.2 Storage

TAK-935 100 mg tablets and matching placebo tablets must be stored at 20°C to 25°C (68°F-77°F). Excursions are permitted between 15°C and 30°C (59°F-86°F).

Study drug, must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

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8.1.3 Dose and Regimen

Each subject and/or subject's caregiver will be instructed to administer study drug, orally or via G-tube/PEG tube, at the same time each day with or without food. The study site personnel will indicate how many tablets should be taken per day on the bottle label, per information provided by the IVRS/IWRS. For each visit with scheduled PK blood sampling, the morning dose of study drug will be administered in the clinic. The time of the last meal relative to dosing must be recorded in the eCRF at each PK/PD sampling visit.

For G-tube/PEG-tube administration, the required number of tablets will be ground into a powder, suspended in water, and the suspension will be administered via G-tube/PEG-tube using a syringe. Complete instructions for administering the drug via G-tube/PEG-tube will be provided to subjects/caregivers in a document provided outside of the protocol.

The investigator or designee will instruct the subject and/or subject's caregiver on the dosing procedures and study drug storage requirements. Subjects and/or subjects' caregivers should return unused study drug at each study visit to allow the investigator or designee to evaluate subjects' compliance with the dosing instructions.

The planned daily dose and tablet count to be administered to subjects in each part of the study is shown in [Table 8.a](#).

Table 8.a Planned Dose and Regimen

Study Part	Planned Doses	Treatment Description
Part 1 (double-blind dose escalation)	TAK-935 200 mg/day (100 mg BID) Matching Placebo BID	1 TAK-935 100 mg tablet BID for 10 days 1 placebo tablet BID for 10 days
	TAK-935 400 mg/day (200 mg BID) Matching Placebo BID	2 TAK-935 100 mg tablets BID for 10 days 2 placebo tablets BID for 10 days
	TAK-935 600 mg/day (300 mg BID) Matching Placebo BID	3 TAK-935 100 mg tablets BID for 10 days 3 placebo tablets BID for 10 days
Part 2 (open-label dose escalation)	TAK-935 400 mg/day (200 mg BID)	2 TAK-935 100 mg tablets BID for 10 days
	TAK-935 600 mg/day (300 mg BID)	3 TAK-935 100 mg tablets BID for 44 days

Note 1: The dose of IP will be gradually escalated during Parts 1 and 2, provided there are no safety or tolerability concerns. At the end of Part 2, the dose of TAK-935 will be de-escalated before dosing is discontinued. See Section 6.1 for details of the dose escalation and de-escalation procedures.

Note 2: The investigator, in consultation with the sponsor, may reduce the IP (Part 1) or TAK-935 (Part 2) dose at any time in the event of any safety or tolerability concerns, including to the 100 mg BID dose in Part 2.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented in the eCRF. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on the AE eCRF page according to Section 10.2.1.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive their treatment according to the randomization schedule. The investigator or investigator's designee will access the IVRS/IWRS at the Screening Visit (Visit 1) to obtain the subject number. At Randomization (Visit 2), the investigator or the investigator's designee will use the IVRS/IWRS to randomize eligible subjects into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. The medication identification (ID) number of the study drug to be dispensed will then be provided by the IVRS/IWRS. At subsequent drug-dispensing visits, the investigator or designee will again contact the IVRS/IWRS to request additional study drug for a subject. The medication ID number of the study drug to be dispensed will again be provided by the IVRS/IWRS. The medication ID number will be entered onto the eCRF. If sponsor-supplied drug (TAK-935 100 mg or matching placebo tablets) is lost or damaged, the site can request a replacement from the IVRS/IWRS (refer to the IVRS/IWRS manual provided separately).

Each subject and/or subject's caregiver should be instructed as follows:

- Keep sponsor-supplied drugs in original containers until the time of dosing.
- Administer study drug as instructed. If the subject misses a dose, he or she should not be given twice the dose the next day.
- Store sponsor-supplied drugs according to the label and keep them out of the reach of children.
- Return sponsor-supplied drugs at each clinic visit.
- On the dosing card provided with each supply of drug, record the AM and PM daily doses and days/times the drug has been down-titrated, including during the de-escalation portion of the study.

In addition to the above, subjects/caregivers will be provided complete instructions on preparing the study drug for administration via G-tube/PEG-tube in a document provided outside of the protocol. They should follow these instructions carefully.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

Study drug will be administered in a double-blind manner in Part 1 and in an open-label manner in Part 2. The study drug blind will be maintained using the IVRS/IWRS. The principal investigator at each study site will receive instructions for obtaining the study drug assignment through the IWRS. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of assigned and unassigned bottles of study drug. All assigned/unassigned study drug bottles will be reconciled and returned to the sponsor or a designee before study closure.

8.4 Unblinding Procedure

The study drug blind in Part 1 shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the sponsor/designee should be notified before the study drug blind is broken. If a medical emergency requiring unblinding occurs, the investigator (or designee) at the site will contact the sponsor or designee (see Takeda Medical Monitor contact information listed in Section 1.1) to assess the necessity to break the study drug blind.

For unblinding a subject, the investigator can obtain the study drug blind information by accessing the IVRS/IWRS. The sponsor/designee must be notified immediately if the study drug blind is broken. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate eCRF.

If any site personnel is unblinded, study drug must be de-escalated in consultation with the Medical Monitor and the subject must be withdrawn from the study. The reason for withdrawal should be recorded as "Protocol Deviation." Subjects who are withdrawn early from the study should undergo all procedures scheduled for the Final Visit at the time of withdrawal.

8.5 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-935 100 mg and matching placebo tablets), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the study drug is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IVRS/IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to the following:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot (or medication ID number) used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IVRS/IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (TAK-935 100 mg and matching placebo tablets) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date, date and amount dispensed including initials or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures to be performed and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in [Appendix A](#).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

9.1.1.1 Study Informed Consent Procedure

Informed consent must be obtained before the subject enters into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for clinical laboratory evaluations.

The informed consent form must be signed by the subject or the subject's legally acceptable representative. A verbal or written subject assent should be obtained from the subject in the event the subject is not capable of providing an informed consent. If the subject is not capable of providing an assent, the reason should be documented by the investigator.

In addition, a separate supplemental informed consent form (ICF) providing information on G-tube/PEG-tube administration of study drug will be signed.

A unique subject identification (ID) number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.1.2 PGx Informed Consent Procedure

A separate informed consent form pertaining to collection, storage, and analysis of the PGx blood samples must be obtained before collecting these samples in this study. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject. Height and weight will be collected at Screening (Visit 1).

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.10](#)).

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.

9.1.3 Physical Examination Procedure

The physical examination will consist of the following body systems: (1) ears, nose, throat; (2) cardiovascular system; (3) respiratory system; (4) gastrointestinal system; (5) dermatologic system; (6) extremities; (7) musculoskeletal system; (8) lymph nodes; (9) psychiatric status; and (10) other. All examinations are to be performed by the investigator. The physical examination must be captured in the source document and eCRF.

9.1.4 Neurological Examination Procedure

A separate neurological examination will be performed and collected in the eCRF. This will include testing mental status, gait, cerebellar function, cranial nerves, motor function (including strength and reflexes), and sensation.

As part of the neurological exam, vision testing is recommended to include fundoscopy and best corrected visual acuity using a pocket vision screening card, if possible.

9.1.5 Weight, Height, and BMI

Weight and height are to be measured while the subject is wearing indoor clothing and with shoes off. If unable to obtain height or weight, data may be collected from other sources (eg, medical records or the subject's caretaker). The investigator must document in the source document the reason for not obtaining height or weight (eg, the subject is in a wheelchair). The BMI is calculated using metric units with the formula provided below. The Takeda standard for collecting height is centimeters without decimal places and for weight is kilograms (kg) with 1 decimal place. BMI should be derived as follows:

$$\text{Metric: } BMI = \frac{\text{weight (kg)}}{\text{Height (m)}^2}$$

Note that although height is reported in centimeters, the formula uses meters, which can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818 \text{ kg/m}^2$.

9.1.6 Vital Sign Procedure

Vital signs to be measured are oral body temperature, sitting (after resting for 5 minutes) blood pressure, heart rate (beats per minute), and sitting respiratory rate. Heart rate and blood pressure will also be measured after 5 minutes supine and after 1 and 3 minutes standing, if possible. The investigator must document in the source document the reason for not obtaining a standing or supine blood pressure (eg, the subject is in a wheelchair).

Vital signs should be measured at the same time of day across visits, if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.25 hour before or after the scheduled blood draw, if possible.

All vital sign data collected at study visits will be recorded on the source documents and in the eCRF.

9.1.7 CCI [REDACTED]

CCI [REDACTED]

9.1.8 Documentation of Study Drug

A dosing card will be provided to the subject and/or caregiver at each clinic visit to record daily AM and PM study drug administration throughout the study, including changes in dosing regimen (de-escalation) that may occur between visits and during the de-escalation period of the study.

9.1.9 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the source document and eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.10 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. These include clinically significant laboratory, ECG, or physical examination abnormalities noted at Screening (Visit 1), according the judgment of the

investigator. The condition (ie, diagnosis) should be described and recorded on the Medical History form.

9.1.11 Procedures for Clinical Laboratory Samples

Blood and urine samples are to be collected at the time points stipulated in the Schedule of Study Procedures (Appendix A). Blood samples for hematology and serum chemistry tests are to be collected after an overnight fast of ≥ 8 hours, if possible. Samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

For an individual subject, the maximum volume of blood collected at any single visit will be approximately 71 mL, and the approximate total volume of blood collected over the course of the study will be 230 mL (Table 9.a).

Table 9.a Approximate Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples (a)			Total Volume (mL)
		Screening Visit	Part 1	Part 2	
HIV, HBsAg, HCV (b)	6	1	---	---	6
HCV RNA detection by qPCR (c)	6	1	---	---	6
FSH (d)	(d)	1		1	(d)
Estradiol (e)	2	1		1	4
Serum chemistry (f)	6	1	1	2	24
Hematology	2	1	1	2	8
Plasma sample for TAK-935 PK analysis	4	---	8	3	44
Plasma sample for AED analysis	4	---	3	3	28
Plasma sample for PD analysis (g)	4	2	16	6	104
Blood sample for DNA PGx	6	---	1	---	6
Blood sample for RNA PGx (g)	2.5	---	2	2	10
Total Blood Volume (mL)					240

--- =not applicable.

(a) Does not include blood draws at any unscheduled visits.

(b) One 2-mL blood sample for each test.

(c) 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.

(d) For diagnostic purposes in female subjects only; sample will be run from serum chemistry volume (no extra volume required).

(e) In female subjects only.

(f) Includes serum pregnancy test for female subjects of childbearing potential.

(g) Two blood samples per scheduled time.

The clinical laboratory tests to be performed are listed in [Table 9.b](#).

Table 9.b Clinical Laboratory Tests

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

Diagnostic Screening

Serum

HIV
 HBsAg and anti-HCV
 HCV RNA detection by qPCR (e)
 hCG (for pregnancy) (f)

Urine (a)

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.

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. The results of clinical laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

If subjects experience ALT or AST $>3\times$ ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed preferably within 48 to 72 hours and no later than 5 days after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria and Section 10.2.3 for reporting requirements related to ALT or AST $>3\times$ ULN in conjunction with total bilirubin $>2\times$ ULN.)

If the ALT or AST remains elevated $>3\times$ ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 for reporting requirements).

If urine cannot be collected due to the subject's cooperation or because the subject is wearing a diaper, the reason should be documented in the source document and, for female subjects, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the investigator prior to randomization.

9.1.12 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for up to 30 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list of adequate contraception below.

From signing of informed consent, throughout the duration of the study, and for 30 days after the last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as ≥ 1 year since last regular menses with an FSH >40 IU/L or ≥ 5 years since last regular menses, confirmed before any study drug is administered).

**Sterilized males should be ≥ 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate per year when used consistently and correctly. In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are as follows:

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Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices:

- Copper T PLUS condom or spermicide.

Sterilization:

- Bilateral tubal occlusion.
- Vasectomized partner (provided that the partner is the sole sexual partner of the study participant and the absence of sperm in the ejaculate has been confirmed).

Abstinence:

- Sexual abstinence, if it is the preferred and usual lifestyle of the subject, will be considered an acceptable method of contraception on a case-by-case basis upon prior approval by the Medical Monitor. Subjects practicing abstinence as a method of contraception must refrain from heterosexual intercourse throughout the duration of the study and for 30 days after last dose of study drug.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study and for 30 days after the last dose of study drug. This may be signed by the legal representative of the subject.

All female subjects of childbearing potential must have a negative serum hCG pregnancy test at Screening (Visit 1) and a negative urine hCG pregnancy test on Day 1 (Visit 2), before receiving any dose of study drug. During the course of the study, subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. An additional serum hCG pregnancy test will be performed at the Final Visit.

9.1.13 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 days after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, for example, after Visit 2 or within 30 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded study drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies, including those in female partners of male subjects, will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.14 ECG Procedure

A 12-lead ECG will be recorded. If the subject cannot tolerate being supine, a sitting ECG may be obtained. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The interpretation of the ECG will be recorded in the source documents and in the eCRF. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval with QTcF, and corrected QT interval. ECG traces recorded on thermal paper will be photocopied to avoid degradation of trace over time.

9.1.15 Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed using the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) [8].

Two versions of the C-SSRS will be used in this study: The Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS.

If the subject is unable to comply with the C-SSRS due to developmental status, a parent proxy may be used for the completion of the C-SSRS. The investigator may also use clinical judgment to assess for suicidal ideation and behavior.

9.1.16 Aberrant Behavior Checklist

Behavior will be assessed by the use of the Community (ABC-C) questionnaire, which is a rating scale that measures the severity of a range of problem behaviors commonly observed in individuals with intellectual and developmental disabilities [9]. It is completed by the caregiver. It is an empirically developed scale designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals across 5 domains with 58 items: irritability, agitation, and

crying (15 items); lethargy, social withdrawal (16 items); stereotypy (7 items); hyperactivity/noncompliance (16 items); and inappropriate speech (4 items).

9.1.17 Collection of Blood Samples for PGx Evaluation

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters, or drug targets, and may be evaluated for the genetic contribution to how the drug is broken down, or how the drug affects the body. This is called a “PGx research study.” Specific purposes of this study include the following:

- Identifying genetic reasons why certain people respond differently to TAK-935.
- Finding out more information about how TAK-935 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to TAK-935.
- Identifying variations in genes related to the biological target of TAK-935.

This information may be used, for example, to develop a better understanding of the safety and efficacy of TAK-935 and other study drugs, to increase understanding of the disease/condition being studied, and to improve the efficiency, design, and methods of future research studies.

In the current study, collection of PGx blood samples is optional for each subject. A separate informed consent form pertaining to collection, storage, and analysis of the samples must be signed before the PGx blood samples can be collected. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study.

One 6-mL whole blood sample for DNA isolation is to be collected before the morning dose of study drug on Day 1 from each subject in the study, into a plastic K₂EDTA spray-coated tube. If necessary and feasible, a second aliquot of blood may be collected if isolation of DNA from the first sample was not successful or possible.

Two 2.5-mL whole blood samples for RNA isolation are to be collected before the morning dose of study drug on Days 1 and 31 from each subject in the study, into a PaxGene tube.

Each PGx sample should be identifiable on the requisition form with an 8-digit subject ID number (the 5-digit site number plus the 3-digit subject number). Detailed instructions for the handling and shipping of samples are provided in the laboratory manual.

A portion of the DNA sample will be analyzed for the presence of allelic variants in drug metabolizing enzymes, drug transporters, or putative drug targets of relevance to epileptic disorders. Additional PGx analyses may be performed.

The samples will be stored for no longer than 15 years after completion of the TAK-935 study and/or until the drug development of TAK-935 is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. “Stored samples” are defined as samples that are coded (the samples are stripped of all personal identifying information but a key links the

samples to the clinical data collected from the sample donor) and are used in the analysis of study drug or related drugs. Subjects can request that their stored samples be destroyed at any time.

9.1.18 PK Sample Collection and Analysis

9.1.18.1 Collection of Plasma Samples for TAK-935 and M-I PK Evaluation

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 into chilled vacutainers containing the K₂EDTA according to the sparse sampling schedule shown in [Table 9.c](#).

Table 9.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	Day 31, 41, and 85	Before morning dose

Subjects and/or subjects' caregivers will be instructed to not administer the morning dose of study drug on Days 11, 21, 31, 41, and 85. On these days, the predose (ie, within 30 minutes prior to dosing) blood sample will be collected at the same time point as the blood samples for clinical laboratory tests. The morning dose of study drug will be administered immediately after the predose PK blood samples have been collected. The exact date and time of last morning and evening study drug doses before each scheduled visit, the exact time of study drug dose taken in the clinic, the exact time of the last meal relative to dosing, and exact time of the PK blood draws will be recorded on the source document and eCRF.

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 and the exact time of the last meal relative to dosing must be recorded in the eCRF upon collection of the PK sample(s).

Instructions for the collection, handling, and shipping of plasma PK samples are provided in the Laboratory Manual.

9.1.18.2 Bioanalytical Methods for TAK-935 and M-I

Plasma concentrations of TAK-935 and M-I will be measured by high-performance liquid chromatography with tandem mass spectrometry.

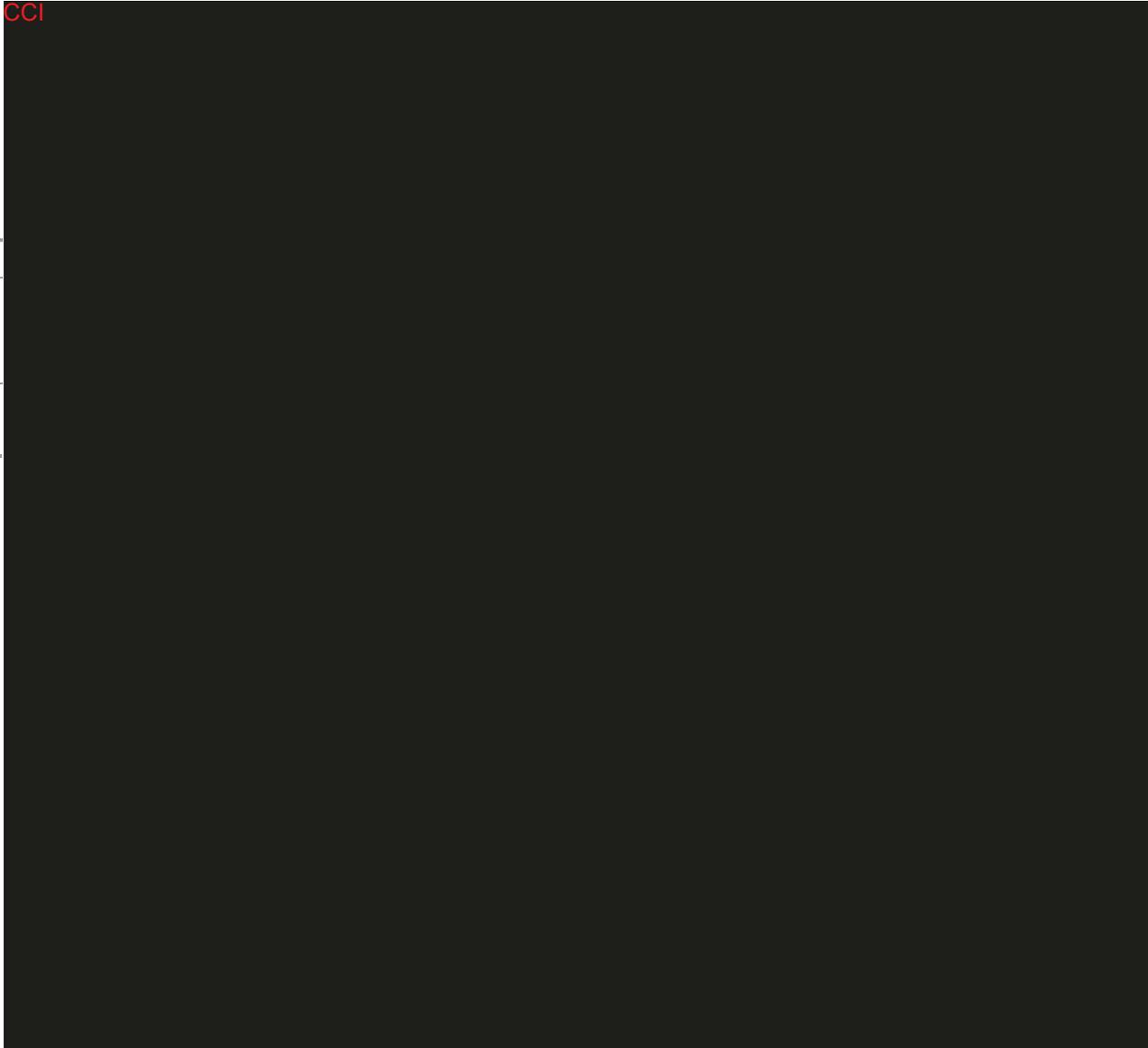
9.1.18.3 PK Parameters

The PK parameters of TAK-935 will be determined from the concentration-time profiles for all evaluable subjects using a population PK approach. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times.

The population PK/PD/EO model developed for TAK-935 based on the data from single- and multiple-dose phase 1 studies in healthy subjects will be updated using data from this study. The detailed population analysis approach will be described in a separate Data Analysis Plan before database lock. The results will be described in more detail in a Population PK Analysis Report.

9.1.19 PD Sample Collection and Analysis

CCI



CCI

9.1.20 Concomitant AEDs Sample Collection and Analysis

CCI

9.1.21 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be ineligible for the study at this visit, the investigator should complete the eCRF screen failure form. The IVRS/IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is to be recorded in the eCRF using the following categories:

- AE.
- Did not meet entrance criteria (specify reason).

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- Significant protocol deviation.
- Lost to follow-up.
- Withdrawal by subject.
- Study terminated by sponsor.
- Other (specify reason).

Subjects may be re-screened after consultation with the Medical Monitor.

Subject ID numbers assigned to subjects who fail screening should not be reused. If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject ID number and treated as a stand-alone subject.

9.1.22 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the Part 1 Double-Blind Treatment Period.

If the subject is found to be not eligible, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

On in-clinic dosing days, after administration of study drug orally, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. For those subjects receiving study drug via G-tube/PEG-tube, the site monitor, the caregiver's preparation as provided in the instruction document and monitor that the caregiver has given the dose. If a site visit is not possible during the morning hours, the subject should take their morning dose prior to attending the visit during the afternoon hours. The date and time of each dose will be recorded in the source documents and on the eCRFs.

Subjects and/or subjects' caregivers will be required to bring study drug containers/unused study drug and the daily recording in the dosing card to each dispensing site visit. All subjects and/or subjects' caregivers should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures is shown in [Appendix A](#). Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening/Baseline Period

Eligibility of subjects will be assessed in accordance with predefined inclusion and exclusion criteria as described in Section 7.0 at the Screening Visit (Visit 1). See Section 9.1.21 for procedures for documenting screening failures. At the Screening Visit, subjects will be given a seizure diary. Subjects and/or subjects' caregivers will be instructed to record seizure activity on a daily basis during the Screening/Baseline Period and throughout the study after the consent has been signed. Diary data can begin at the Screening Visit and record 4 weeks of Baseline Period.

Eligible subjects will be notified by phone of their study entry, after completing the Baseline Period, including the Baseline seizure diary.

9.3.2 Randomization

Randomization for eligible subjects will take place on Day 1 in Part 1 (Visit 2).

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS, as described in Section 8.2.

9.3.3 Part 1

In Part 1, subjects will receive the first dose of double-blind IP (double-blind TAK-935 or placebo) on the morning of Day 1 (Visit 2) in the clinic after randomization and after collection of predose PK, PD, AED and optional PGx blood samples. Subjects will remain in the clinic until completion of all study procedures on Day 1, including collection of the PK and PD blood samples at 1, 3, and 5 hours after the morning dose. Subjects will return to the clinic on Day 11 (Visit 3) and Day 21 (Visit 4) for the collection of blood samples for PK (before and approximately 1 hour after the morning dose), PD (before and approximately 1 hour after the morning dose), and AED (before the morning dose); study drug dosing; and collection of the seizure diary data. 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).

Subjects and/or subjects' caregivers will administer the evening dose of IP to the subjects on study visit days and BID on all other days during the 30-day 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. Seizure data will be recorded by diary throughout Part 1 and collected and reviewed by the investigator with the subject and/or subject's caregiver at each clinic visit.

9.3.4 Part 2

In Part 2, subjects will receive the first dose of study drug (open-label TAK-935) on the morning of Day 31 (Visit 5) in the clinic. Subjects will remain in the clinic until completion of all study

procedures during this Visit 5, including the collection of PK, PD, AED, and PGx blood samples. Subjects will return to the clinic on Day 41 (Visit 6) for the collection of PK, PD, and AED blood samples (all before the morning dose), study drug dosing, and collection of the seizure diary data. 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).

Subjects and/or subjects' caregivers will administer the evening dose of study drug to the subjects on study visit days and BID on all other days during the approximately 60-day Open-Label 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. Seizure diary data will be collected and reviewed by the investigator with the subject and/or subject's caregiver at each clinic visit.

9.3.5 Final Visit

The Final Visit (Visit 7) is on Day 85, at which time, the appropriate dose de-escalation schedule begins (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). PK, PD, and AED blood samples (all before the morning dose) will be collected at this visit. 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).

Subjects who do not enter Part 2 or withdraw early from the study should complete all procedures scheduled for the Final Visit (Visit 7) at time of withdrawal, including dose de-escalation as appropriate, followed by the Follow-up Period (Visits 8 and 9).

For all subjects receiving study drug, the investigator must complete the End-of-Study eCRF page.

Subjects who are withdrawn early from the study should undergo all procedures scheduled for the Final Visit at the time of withdrawal.

9.3.6 Follow-up Phone Call

A Follow-up Phone Call will be conducted on Day 91 (Visit 8). All subjects, including those who withdraw early from the study, must complete this Follow-up Phone Call.

9.3.7 Follow-up Visit

At the end of the 30-day Follow-up Period, subjects will return to the clinic for a Follow-up Visit on Day 121 (Visit 9). PD and AED blood samples will be collected at this visit. All subjects, including those who withdraw early from the study, must complete this Follow-up Visit.

9.3.8 Poststudy Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required. Subjects may be eligible to enroll in an open-label extension study expected to be initiated in 2018.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.17. The genetic material will be preserved and retained at Covance for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The samples will be initially stored at PPD Central Laboratory. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

Subjects who consented and provided PGx samples for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. Notify sponsor of consent withdrawal.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in the study; it does not necessarily have to have a causal relationship with study participation or treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with study participation or use of a drug whether or not it is considered related to study participation or the drug.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding is not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of...”).
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious, or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg “worsening of...”).
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).
- For the purpose of this study, seizures will not be considered (S)AEs unless: 1) there is a clear increase in frequency of seizures compared to the subject’s baseline, 2) there is an emergence of a new seizure type, or 3) the subject experiences status epilepticus, and any other time the investigator feels the seizure should be captured as an (S)AE in which case the investigator should document her/his reasoning.

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented in the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List ([Table 10.a](#)).

Table 10.a Takeda Medically Significant AE List

	Term
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product Neuroleptic malignant syndrome/malignant hyperthermia Spontaneous abortion/stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as “Important Medical Events” satisfying SAE reporting requirements.

10.1.4 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

- Mild: The event is transient and easily tolerated by the subject.
Moderate: The event causes the subject discomfort and interrupts the subject’s usual activities.
Severe: The event causes considerable interference with the subject’s usual activities.

10.1.5 Causality of AEs

The relationship of each AE to study drug will be assessed using the following categories:

- Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications, and concurrent treatments, may also be responsible.
Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.6 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.7 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.8 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

10.1.9 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events either occur once or are continuous.

10.1.10 Action Concerning Study Drug

- Drug Withdrawn – a study drug is stopped due to the particular AE.
- Dose Not Changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE, eg, the study has been terminated, the subject died, or dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.

10.1.11 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving”.
- Not Recovered/Not Resolved – there is no change in the diagnosis or signs/symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining “not recovered/not resolved”.

- Resolved with Sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time informed consent is provided at Screening (Visit 1) and continue until screen failure or until the Follow-up Visit (Visit 9). For subjects who discontinue prior to study drug administration, AEs are collected until the subject discontinues study participation.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator’s opinion of the causal relationship between the event and administration of study drug (related or not related).
6. Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.

9. Seriousness.

The seizure diary will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information recorded in the diary, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up, if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied (see Section 10.1.2).

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be completed in EDC with all mandatory information. If EDC is not available, a Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject ID number.
- Investigator's name.
- Name of the study drug.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated $>3 \times \text{ULN}$ on 2 consecutive occasions, as specified in Section 9.1.11, the abnormality should be recorded as an AE.

If a subject is noted to have ALT or AST $>3 \times \text{ULN}$ and total bilirubin $>2 \times \text{ULN}$ for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.11 must also be performed. In addition, relevant eCRFs must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete the follow-up information with additions or changes to the SAE in EDC. A paper SAE form should only be used if EDC is not available. Paper SAE forms or other written documentation should be faxed immediately within 24 hours of receipt to the attention of the contact listed in Section 1.1. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or Independent Ethics Committee, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs or Independent Ethics Committees (IECs), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent form.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After submission of the eCRFs to the sponsor, any change of, modification of, or addition to the data on eCRFs should be made by the investigator with use of change and modification records of eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign and date the form.

After the lock of the study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with the approval from the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to

enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Council for Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as (1) or (2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The randomized set will include all subjects who were randomly assigned to 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 measurable TAK-935 or M-I plasma concentration.

CCI

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 postbaseline value for assessment of the efficacy endpoint(s). In FAS efficacy summaries, subjects will be analyzed according to the treatment to which they were randomized. To adjust for treatment noncompliance or insufficient treatment exposure, one or more modified FAS populations may be defined in the SAP.

The per-protocol set (PPS) for Parts 1 and 2 will include all subjects in the FAS who had no major protocol violations. Subjects to be excluded from the PPS, whether due to protocol violations or noncompliance to the dosing schedule, will be identified via a subject evaluability assessment performed before unblinding.

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 treatment they received.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed for enrolled subjects by treatment group and overall. Descriptive statistics will be used to summarize data for continuous variables such as age and weight (eg, number of subjects, mean, median, SD, and range) and for categorical variables such as sex, ethnicity, and race (number and percentage of subjects within each category). Medical history and medication history will be listed by subject.

13.1.3 Safety Analysis

13.1.3.1 AEs

AEs will be reported throughout the study. TEAEs will be a primary endpoint for each part of the study. TEAEs will be summarized using descriptive statistics (number and percentage of subjects) for the safety analysis set. No statistical testing will be performed or inferential statistics will be generated.

The definition of TEAEs will be provided in the SAP. AEs will be coded using MedDRA and will be summarized by system organ class and preferred term and by treatment group separately for each part of the study.

AEs that were reported more than once by a subject during a part of the study will be counted only once for that subject at the maximum severity.

13.1.3.2 Other Safety Endpoints

Absolute values and changes from Screening/Baseline for clinical laboratory tests, vital signs, and ECGs will be summarized by treatment group for each part of the study using descriptive statistics. Clinical laboratory test, vital sign, CCI [REDACTED] and ECG results that are outside the normal ranges and potentially clinically significant will be flagged and tabulated. The number and percentage of subjects with clinical laboratory test, vital sign, weight/BMI, and ECG parameter values that meet Takeda's predefined criteria for markedly abnormal values at least once postdose will be summarized by treatment and part of the study. Physical examination findings will be listed by subject and treatment group for each part of the study.

13.1.4 PK and PD Analysis

Plasma concentrations of TAK-935, its metabolite M-I, and CCI [REDACTED] will be listed for each subject and summarized by each time point for each dose and part of the study.

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

13.1.5 Secondary and Exploratory Analyses

Safety (clinical laboratory evaluations, vital signs, weight/BMI, and ECGs) and PK (TAK-935) endpoints will be analyzed as the secondary endpoints in the study. CCI [REDACTED]

CCI [REDACTED]

CCI



13.2 Interim Analysis and Criteria for Early Termination

After all subjects have completed the Double-Blind Treatment Period or have discontinued from the study (and prior to completion of the Open-Label Period), an unblinded safety summary may be generated. There will be no early stopping for efficacy or futility.

13.3 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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK and PD blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF.

Table 14.a defines the target windows for sample collections. Samples collected outside of these collection windows will not be considered a protocol deviation after Day 1 if the time and date of the sample collection is recorded in the eCRF AND the time and date of the dose prior to the sample collection is recorded in the eCRF. The only exception is the Day 1 predose sample, which must be collected prior to dosing on Day 1.

Table 14.a Windows for PK and PD Blood Sample Collection

Study Part and Day	Nominal/Target Sampling Time	Window
Part 1, Day 1	Predose (0 hour)	No more than 30 minutes predose
Part 1, Day 1	1, 3 and 5 hours postdose	±15 minutes of nominal time
Part 1, Days 11 and 21	Predose and 1 hour postdose	No more than 30 minutes predose, and ±15 minutes of nominal time, respectively
Part 2, Days 31, 41, and 85	Predose	No more than 30 minutes predose
Part 1, Day 1	Predose (0 hour)	No more than 30 minutes predose

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator’s final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a PGx sample for DNA (and RNA) analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with

this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

	Screening/ Baseline Period (a)	Part 1: Double-Blind Treatment Period (b)			Part 2: Open-Label Treatment Period (b)			Follow-up Period (c)	
Study Day	Days -41 to 0	Day 1	Day 11	Day 21	Day 31	Day 41	Day 85 (c,d)	Day 91	Day 121
Visit Window (days)			±2	±2	±2	±2	±2	±2	±2
Visit Number	1 Screening Visit	2	3	4	5	6	7 Final Visit	8 Follow-up Phone Call	9 Follow-up Visit
Informed consent and assent, if appropriate	X								
Optional PGx informed consent	X								
Inclusion/exclusion criteria	X	X							
Randomization		X							
Demographics, medical history, medication history	X								
Height, weight, BMI	X								
Concurrent medical conditions	X								
Concomitant medications, including AED	X	X	X	X	X	X	X	X	X
Urine drug and alcohol screen (e)	X								
HIV, HBsAg, HCV tests (f)	X								
C-SSRS, if appropriate (g)	X	X					X		
Aberrant behavior checklist	X		X	X	X	X	X		X
FSH and estradiol (h)	X						X		
Serum/urine pregnancy test (i)	X(serum)	X(urine)					X(serum)		
Pregnancy avoidance counseling	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X		X
Physical examination (j)	X			X			X		

(Footnotes follow table.)

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Appendix A Schedule of Study Procedures (continued)

Study Day	Screening/ Baseline Period (a)	Part 1: Double-Blind Treatment Period (b)			Part 2: Open-Label Treatment Period (b)			Follow-up Period (c)	
	Days -41 to 0	Day 1	Day 11	Day 21	Day 31	Day 41	Day 85 (c,d)	Day 91	Day 121
Visit Window (days)			±2	±2	±2	±2	±2	±2	±2
Visit Number	1 Screening Visit	2	3	4	5	6	7 Final Visit	8 Follow-up Phone Call	9 Follow-up Visit
Neurological exam, including fundoscopy and visual acuity (if possible) (k)	X			X			X		
12-lead ECG	X	X			X		X		
Clinical laboratory tests (l)	X	X			X		X		
CCI									
CCI									
Plasma sample for TAK-935 PK (m,n)		X	X	X	X	X	X		
Plasma sample for AED analysis (n,o)		X	X	X	X	X	X		X
Plasma sample for PD (n,p)	X	X	X	X	X	X	X		X
Blood sample for DNA PGx (q)		X							
Blood sample for RNA PGx (n,r)		X			X				
Access IVRS/IWRS for subject ID/medication ID/subject status (s)	X	X	X	X	X	X	X		
Assess benefit-risk analysis with subject and caregiver before increasing dose to 300 mg BID				X					
Dispense study drug with dosing card (t)		X	X	X	X	X	X		
In-clinic administration of morning dose of study drug (u)		X	X	X	X	X	X		

(Footnotes follow table.)

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Appendix A Schedule of Study Procedures (continued)

	Screening/ Baseline Period (a)	Part 1: Double-Blind Treatment Period (b)			Part 2: Open-Label Treatment Period (b)			Follow-up Period (c)	
Study Day	Days -41 to 0	Day 1	Day 11	Day 21	Day 31	Day 41	Day 85 (c,d)	Day 91	Day 121
Visit Window (days)			±2	±2	±2	±2	±2	±2	±2
Visit Number	1 Screening Visit	2	3	4	5	6	7 Final Visit	8 Follow-up Phone Call	9 Follow-up Visit
Study drug return/ accountability/compliance			X	X	X	X	X		X
Assess AEs (v)	X	X	X	X	X	X	X	X	X

Footnotes for Appendix A

- (a) The 4-week baseline seizure diary recording can begin as soon as the ICF has been signed. Randomization can occur once the 4-week baseline seizure count of ≥ 1 has been obtained and the subject meets all of the inclusion and none of the exclusion criteria.
- (b) 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.
- (c) Subjects who do not enter Part 2 or withdraw early from the study should complete all procedures scheduled for the Final Visit (Visit 7) at time of withdrawal, including dose de-escalation as appropriate, followed by the Follow-up Period (Visits 8 and 9). See Section 6.1 for details.
- (d) Dose de-escalation, as appropriate, begins at the Final Visit (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). See Section 6.1 for details.
- (e) If urine cannot be collected, the reason should be documented in the source document.
- (f) 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.
- (g) If the subject is unable to comply with the C-SSRS due to developmental status, a parent proxy may be used for the completion of the C-SSRS. The investigator may also use clinical judgment to assess for suicidal ideation and behavior.
- (h) For female subjects only at the Screening and Final Visits.
- (i) For female subjects of childbearing potential, a serum pregnancy (hCG) test will be performed at the Screening and Final Visits and a urine pregnancy test will be performed before the morning dose on Day 1 in Part 1 (Visit 2). If urine cannot be collected, the reason should be documented in the source document and the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the investigator prior to randomization. Additional pregnancy tests may be performed throughout the study at the investigator's discretion.
- (j) PE must be captured in the source document. Any clinically significant abnormalities noted prior to administration of study drug should be described and captured on the Medical History form. Any clinically significant changes in PE noted after administration of study drug should be captured on the AE page of the eCRF.
- (k) Any clinically significant abnormalities noted prior to administration of study drug should be described and recorded on the Medical History form. Any clinically significant changes in the neurological examination noted after administration of study drug should be captured on the AE page of the eCRF.
- (l) Hematology, serum chemistry, and urinalysis tests. If urine cannot be collected 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.
- (m) PK plasma samples for measurement of TAK-935 and M-I concentrations will be collected before and 1, 3, and 5 hours after the morning dose on Day 1; before and approximately 1 hour after the morning dose on Days 11 and 21; and before the morning dose on Days 31, 41, and 85.
- (n) On Days 11, 21, 31, 41, and 85, subjects should visit the clinic in the morning prior to taking their morning dose. For subjects who are not able to come for the visit during the

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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).

(o) Plasma samples for measurement of concomitant AED concentrations will be collected before the morning dose on Days 1, 11, 21, 31, 41, and 85; and at the Follow-up Visit (Day 121).

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(q) One PGx blood sample for DNA isolation will be collected before the morning dose on Day 1.

(r) Two PGx blood samples for RNA isolation will be collected before the morning dose on Days 1 and 31.

(s) The dose of IP will be increased on Days 11 and 21 in Part 1 and on Day 41 in Part 2, provided there are no safety or tolerability concerns. Subjects' dose may be increased or decreased before Day 41 (Visit 6) based on clinical condition (ie, increasing seizures) and investigator judgment. At the end of Part 2, the dose of TAK-935 will be de-escalated before dosing is discontinued. See Section 6.1 for details.

(t) A dosing card will be provided to record daily AM and PM study drug administration throughout the study, including changes in dosing regimen (de-escalation) that may occur between visits and during the de-escalation period of the study.

(u) On in-clinic dosing days, after administration of study drug, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. If a site visit is not possible during the morning hours, the subject should take their morning dose prior to attending the visit during the afternoon hours. The date and time of each dose will be recorded in the source documents and on the eCRFs.

(v) Collection of AEs will commence from the time informed consent is provided (Screening Visit) and continue until screen failure or the Follow-up Visit.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the “Statement of Investigator” (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject’s medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject’s personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject’s legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or

that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

- e) that the subject's identity will remain confidential in the event that study results are published.
25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 30 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
 26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 30 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
 27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarified that TAK-935 or placebo can be administered either orally or via stable G-tube/ PEG tube.

The primary change occurs in Section 6.1 Study Design

Added text: **or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube**

Rationale for Change: To allow administration of TAK-935 or placebo via G-tube/PEG tube after finalization of CMC in vitro studies demonstrating nearly 100% drug delivery through a G-tube when crushed and suspended in water.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
 - Section 4.1 Background
 - Section 6.1 Study Design
 - Section 6.2 Justification for Study Design, Dose, and Endpoints
 - Section 8.1.3 Dose and Regimen
 - Section 9.2 Monitoring Subject Treatment Compliance
-

Change 2: Clarified that a separate consent form will be obtained for subjects with G-tube/PEG tubes.

The primary change occurs in Section 9.1.1 Informed Consent Procedure

Added text: **In addition, a separate supplemental informed consent form (ICF) providing information on G-tube/PEG-tube administration of study drug will be signed.**

Rationale for Change: To provide detail on separate consent form for subjects with G-tube/PEG tubes.

The following sections also contain this change:

- Section 7.1 Inclusion Criteria

Change 3: Added inclusion criteria related to subjects with G-tube/PEG tubes.

The primary change occurs in Section 7.1 Inclusion Criteria

Added text: **For subjects with G-tube/PEG tube, G-tubes/PEG tubes should have been placed and been functioning for at least 3 months prior to screening. Naso-gastric tubes are not allowed.**

Rationale for Change: To clarify the subject population with G-tube/PEG tubes.

The following sections also contain this change:

- Section 7.4 Diet, Fluid, and Activity Control

Change 4: Modified exclusion criteria to allow the use of medical marijuana.

The primary change occurs in Section 7.2 Exclusion Criteria

Initial wording:	The subject has a history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, within the previous 2 years before Screening (Visit 1). Previous sporadic cannabis use is not exclusionary provided the subject is requested and agrees to not use cannabis during the study.
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Amended or new wording:	The subject has a history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, within the previous 2 years before Screening (Visit 1). Previous sporadic cannabis use is not exclusionary provided the subject is requested and agrees to not use cannabis during the study. Medical marijuana use is allowed.
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Rationale for Change: To allow enrollment of subjects in states where use of medical marijuana is legal.

The following sections also contain this change:

- Section 7.3 Excluded Medications, Procedures, and Treatments
-

Change 5: Modified secondary endpoints to remove estimation of additional parameters.

The primary change occurs in Section 5.2.2 Secondary Endpoints

Deleted text:

- 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-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. ~~Additional parameters may be estimated, if appropriate.~~

Rationale for Change: To keep endpoints specific and consistent guidelines for disclosure of study details.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
-

Change 6: Removed body weight/body mass index (BMI) from secondary and exploratory endpoints.

The primary change occurs in Section 5.2.2 Secondary Endpoints

Deleted text:

- Percentage of subjects with at least 1 markedly abnormal value for clinical laboratory evaluations, vital signs, ~~body weight/body mass index (BMI)~~, and electrocardiogram (ECG) parameters after TAK-935 treatment.

Rationale for Change: These parameters are only measured at screening and therefore change cannot be monitored.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
 - Section 5.2.3 Exploratory Endpoints
-

Change 7: Modified study drug dosing and regimen sections to clarify how study drug will be administered via G-tube/ PEG tube.

The primary change occurs in Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Added text: **For subjects receiving study drug via G-tube/PEG tube, tablets will be crushed, suspended in water, and the suspension will be administered via the G-tube/PEG tube using a syringe. Complete instructions will be provided to subjects/caregivers in a document provided outside of the protocol.**

Rationale for Change: To provide clarification on study dosing and regimen for subjects with G-tube/PEG tubes.

The following sections also contain this change:

- Section 8.1.3 Dose and Regimen
-

Change 8: Modified study drug dispensing procedures to clarify how the investigative product (IP) will be prepared for administration via G-tube/PEG tube.

The primary change occurs in

Added text: **In addition to the above, subjects/caregivers will be provided complete instructions on preparing the study drug for administration via G-tube/PEG-tube in a document provided outside of the protocol. They should follow these instructions carefully.**

Rationale for Change: To provide clarification on study dosing and regimen for subjects with G-tube/PEG tubes.

Change 9: Clarified when open-label extension study is expected to be initiated.

The primary change occurs in Section 9.3.8 Poststudy Care

Initial wording: Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required. Subjects may be eligible to enroll in an open-label extension study if and when available.

Amended or new wording: Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required. Subjects may be eligible to enroll in an open-label extension study ~~if and when available~~ **expected to be initiated in 2018.**

Rationale for Change: To provide information to sites/subjects as to when the open-label extension study will be initiated.

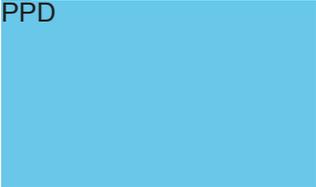
Change 10: Updated the medical monitor contact information.

The primary change occurs in Section 1.1 Contacts

Description of change: The contact information for the medical monitor was changed from **PPD** [redacted].

Rationale for Change: Due to a change in medical monitor at the Clinical Research Organization.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD 	Clinical Approval	21-Mar-2018 21:32 UTC
	Clinical Approval	21-Mar-2018 22:10 UTC
	Biostatistics Approval	22-Mar-2018 02:08 UTC