Title: A Randomized, Double-blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Ascending Dose and Multiple Doses with Titration of TAK-935 in Healthy Japanese Subjects

NCT Number: NCT04461483

Protocol Approve Date: 02-JUL-2020

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

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Ascending Dose and Multiple Doses with Titration of TAK-935 in Healthy Japanese Subjects

Study Identifier:	TAK-935-1004
Compound:	TAK-935
Date:	02 July 2020
Version/Amendment Number:	Amendment 2

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-935
Study Identifier: TAK-935-1004	**Phase: 1**
Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Ascending Dose and Multiple Doses with Titration of TAK-935 in Healthy Japanese Subjects.	
Trial Design: This study consists of 2 parts. Part 1 is a randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics (PK) and [CCI] single ascending doses (SAD) of TAK-935 in healthy Japanese subjects. Part 2 is a randomized, double-blind, placebo-controlled study to assess the safety, tolerability, PK and PD of multiple doses (MD) with titration of TAK-935 in healthy Japanese subjects when administered daily for 21 days. The subjects enrolled in Part 2 will initially receive TAK-935 or placebo at 100 mg twice daily (BID) followed by escalation to 200 mg BID, and then followed by 300 mg BID, with 7 days for each titration period.	
Trial Primary Objective: To evaluate the safety and tolerability of TAK-935 in healthy Japanese subjects when administered as single oral dose or multiple oral doses with titration. **Secondary Objectives:** To evaluate the pharmacokinetics of TAK-935 in healthy Japanese subjects when administered as single oral dose or multiple oral doses with titration.	
Trial Subject Population: Healthy Japanese subjects	
Planned Number of Subjects: Part 1 (SAD): 24 subjects; 8 subjects per cohort Part 2 (MD): 9 subjects	**Planned Number of Sites:** 1
Dose Levels: <Part 1> Cohort 1: Single dose at 200 mg(fasted) Cohort 2: Single dose at 600 mg (fasted) Cohort 3: Single dose at 1200 mg (fasted) <Part 2> Cohort 4: Multiple doses with titration at 100 mg BID from Day 1 to Day 7, 200 mg BID from Day 8 to Day 14 and 300 mg BID from Day 15 to Day 21 (fasted)	**Route of Administration:** Oral
Duration of Treatment: Part 1: 1 day per each cohort Part 2: 7 days per each dose level and 21 days for complete treatment	**Planned Trial Duration:** <Part 1> Screening period: Days -28 to -3 Check-in: Day -2 Treatment period: Days 1 to 3 Follow-up period: Day 8 <Part 2> Screening period: Days -28 to -3

	Check-in: Day -2 Treatment period: Days 1 to 24 Follow-up period: Day 35

Main Criteria for Inclusion:

In order to be eligible for study participation,

1. The subject must understand the study procedures and agree to participate by providing written informed consent.
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be a Japanese healthy adult male or female, aged 20 to 55 years, inclusive, at the time of informed consent.
4. The subject must have a body mass index ≥18.5 and ≤25.0 kg/m^2 at the Screening Visit.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months prior to the first dose of study drug or first invasive procedure.
6. The subject must be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, CCI [redacted] performed at the Screening Visit and prior to the first dose of study drug.
7. The subject must meet the following birth control requirements:

- Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 90 days after the last dose of study drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1-year postbilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
- Is a male subject who agrees to not donate sperm from the first dose of study drug until 90 days after the last dose of study drug.
- Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
  a. Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or ≥6 months of spontaneous amenorrhea in females aged >45 years with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels should be required.
  b. Hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
  c. Had a tubal ligation with appropriate documentation of surgical procedure.
  d. Congenital conditions such as uterine aplasia etc.

Main Criteria for Exclusion:

The subject must be excluded from participating in the study if the subject:

1. Has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular (including arrhythmia), hematological, hepatic, immunological, renal, respiratory, genitourinary, major neurological (including stroke and epileptic seizure), or degenerative ophthalmological abnormalities or diseases.
2. Has participated in another investigational trial within 4 weeks or 5 half-lives (whichever is longer) before the pretrial visit (Screening). The 4-week or 5 half-lives window will be derived from the date of the last trial procedure and/or adverse event (AE) related to the trial procedure in the previous trial to the pretrial/Screening Visit of the current trial.
3. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of the sponsor.
4. Has a history of cancer (malignancy).
5. Has any lifetime history of a suicide attempt, or have suicidal ideation or, any suicidal behavior within 12 months, or who are at significant risk to commit suicide, as judged by the investigator using the Columbia Suicide Severity

Rating Scale (C-SSRS) or are clinically judged by the investigator to be at risk for suicide.

6. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
7. Has a positive alcohol or drug screen.
8. Had major surgery, donated or lost whole blood prior to the start of study drug administration as any of below:

   For both male and female subjects,

   ≥200 mL within 4 weeks (28 days)

   For male subjects,

   ≥400 mL within 12 weeks (84 days)

   ≥800 mL in total within 52 weeks (364 days)

   For female subjects,

   ≥400 mL within 16 weeks (112 days)

   ≥400 mL in total within 52 weeks (364 days)
9. Had gastrointestinal surgery that could impact the absorption of study drug.
10. Has a history of a major psychiatric disorder as diagnosed utilizing Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria.
11. Has a known hypersensitivity to any component of the formulation of TAK-935 or related compounds.
12. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of study drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
13. Has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
14. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
15. Has a substance abuse disorder.
16. Has a QT interval with Fridericia's correction method (QTcF) >450 msec confirmed with one repeat testing, at the Screening Visit.
17. Had abnormal Screening or Day -1 laboratory values that suggested a clinically significant underlying disease or subject with the following laboratory abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5 times the upper limit of normal (ULN).
18. Has tested positive for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody, HIV antibody/antigen, or serologic reactions for syphilis at Screening.
19. In the opinion of the investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

Safety:

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).

The secondary endpoints will be assessed through evaluation of the following parameters:

PK parameters of TAK-935:

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}) (Part 1 only).
- AUC from time 0 to time of infinity (AUC_{∞}) (Part 1 only).
- AUC from time 0 to 24 hours (AUC_{24}) (Part 1 only).

- AUC during a dosing interval (AUC_τ) at steady state (Part 2 only).

Statistical Considerations:

Safety analysis:

Analyses will be conducted using the safety analysis set.

A TEAE is defined as an AE that occurs on or after the start of study drug administration. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and tabulated by the system organ class (SOC) and the preferred term (PT). Percentage of subjects who experience at least 1 TEAE (the primary endpoint of the study) will be calculated within the following analyses.

- The frequency of all TEAEs
- The frequency of drug-related TEAEs
- The frequency of TEAEs by intensity
- The frequency of drug-related TEAEs by intensity
- The frequency of TEAEs leading to study drug discontinuation
- The frequency of serious TEAEs

CCI [redacted]

PK Measures:

Concentrations of TAK-935 and its metabolite M-I in plasma will be summarized in each of Part 1 and Part 2 by cohort over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. Plasma PK parameters will be calculated using noncompartmental modeling and summarized by cohort and day using descriptive statistics. Dose proportionality in plasma PK parameters (C_{max} and AUCs) will be assessed graphically for those parameters in Part 1. Additional analyses will be included if appropriate.

Sample Size Justification:

The sample sizes of 8 subjects for each of the cohorts in Part 1 and 9 subjects for Part 2 (Part 1: 6 active 2 placebo in each cohort, Part 2: 6 active 3 placebo as total) are considered to be sufficient for the evaluation of safety, tolerability, and PK of each cohort. Sample sizes were not based on statistical power considerations.

2.0 STUDY SCHEMATIC

Table 2.a Outline of the Study Parts and Planned Dosing Cohorts

Part	Cohort	Daily dose level (mg)	Dosing regimen	Randomization
Part 1	1	200	Single oral dose under fasted condition	Subjects will be randomized to TAK-935 or placebo at a ratio of 6:2 in each cohort, double-blind. No stratification variables will be used for randomization.
	2	600		
	3	1200		
Part 2	4	Day 1-7: 200 (100 mg BID) Day 8-14: 400 (200 mg BID) Day 15-21: 600 (300 mg BID)	Multiple oral doses up/titration with TAK-935 for 7 days per each dose level within the same subjects under fasted condition	Subjects will be randomized to TAK-935 or placebo at a ratio of 6:3, double-blind. No stratification variables will be used for randomization.

BID: twice daily

3.0 SCHEDULE OF STUDY PROCEDURES

Part 1

	Screening	Check-in	Baseline	Treatment		Study Exit	Follow-up	Early Termination
	Days -28 to -3	Day -2	Day -1	Day 1	Day 2	Day 3	Day 8	
Informed consent	x							
Inclusion/exclusion criteria	x	x	x	x (predose)				
Demographics and medical history	x							
Medication history	x							
Physical exam	x		x	x (predose)		x	x	x
Eye exam [a]			x				x	x
Neuropsychiatric assessment (MMSE and pre-determined questions)			x			x	x	x
CCI								
Weight, height, and BMI [c]	x	x				x		x
Concomitant medications [d]	x	x	x	x	x	x	x	x
Concurrent medical conditions	x	x						
CCI								
Hormone laboratory tests [f]			x			x		x
Hepatitis panel	x							
HIV, Syphilis	x							
Serum FSH (if applicable)	x							
Urine drug and alcohol screen	x		x					
CCI								
CCI								
Confinement [i]		x	x	x	x	x		
PK blood collection [j]				x	x	x		x
CCI								
PGx DNA collection [l]				x				
Study drug dosing				x				
C-SSRS assessment	x	x				x		x
AE assessment [m]	x	x	x	x	x	x	x	x

AE: adverse event; BMI: body mass index; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; FSH: follicle-stimulating hormone; MMSE: mini mental state examination; PGx: pharmacogenomic(s); PK: pharmacokinetic(s); TSH: thyroid stimulating hormone; CCI

[a] Eye exam includes visual field evaluation, best corrected visual acuity, fundoscopy without pupillary dilation, and a slit lamp microscopy.

CCI

[c] Height and BMI will only be collected at Screening.

[d] Record all ongoing medications from Screening and throughout the study.

CCI [redacted]

Hormone laboratory tests (prolactin, growth hormone, cortisol, and TSH) will be collected on Day-1 (upon rising), and Discharge (upon rising) or Early Termination under fasted conditions.

CCI [redacted]

[i] Subjects will be discharged on Day3.

[j] Blood samples for pharmacokinetic analyses will be collected at predose and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 10, 12, 16, 24 and 48 hours postdose or Early Termination.

CCI [redacted]

One blood sample will be collected for PGx DNA analysis on Day 1.

[m] Any event from signing of informed consent will be captured as an AE.

Part 2

	Screening	Check-in	Baseline	Dose Level 1			Dose Level 2			Dose Level 3				Study Exit	Follow-up	
	Days -28 to -3	Day -2	Day -1	Day 1	Day 2-6	Day 7	Day 8	Day 9-13	Day 14	Day 15	Day 16-20	Day 21	Day 22-23	Day 24	Day 35	Early Termination
Informed consent	x															
Inclusion/exclusion criteria	x	x	x	x (predose)												
Demographics and medical history	x															
Medication history	x															
Physical exam	x		x				x (predose)			x (predose)				x	x	x
Eye exam [a]			x												x	x
Neuropsychiatric assessment (MMSE and pre-determined questions)			x			x			x			x		x	x	x
CCI																
Weight, height, and BMI [c]	x	x												x		x
Concomitant medications [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent medical conditions	x	x														
CCI																
Hormone laboratory tests [f]			x				x			x			x			x
Hepatitis panel	x															
HIV, Syphilis	x															
Serum FSH (if applicable)	x															
Urine drug and alcohol screen	x		x													
CCI																
CCI																
Confinement [i]		x	x	x	x	x	x	x	x	x	x	x	x	x		
PK blood collection [j]				x		x			x			x				x
CCI																
PGx DNA collection [l]				x												
Study drug dosing				x	x	x	x	x	x	x	x	x				
C-SSRS assessment	x	x												x		x
AE assessment [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

AE: adverse event; BMI: body mass index; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; FSH: follicle-stimulating hormone; MMSE: mini mental state examination; PGx: pharmacogenomic(s); PK: pharmacokinetic(s); TSH: thyroid stimulating hormone; CCI

[a] Eye exam includes visual field evaluation, best corrected visual acuity, fundoscopy without pupillary dilation, and a slit lamp microscopy.

CCI

[c] Height and BMI will only be collected at Screening.

[d] Record all ongoing medications from Screening and throughout the study.

CCI

[f] Hormone laboratory tests (prolactin, growth hormone, cortisol, and TSH) will be collected on Day-1 (upon rising), Day 8 (upon rising), Day 15 (upon rising), and Day 22 (upon rising) or Early Termination under fasted conditions.

CCI

[i] Subjects will be discharged on Day 24

[j] Blood samples for pharmacokinetic analyses will be collected at pre-morning dose and at 0.25, 0.5, 1, 2, 4, 8, 10 and 12 hours after morning dose on Day 1, Day 7, Day 14 and Day 21, or Early Termination.

CCI

One blood sample will be collected for PGx DNA analysis on Day 1.

[m] Any event from signing of informed consent will be captured as an AE.

4.0 INTRODUCTION

4.1 Background

Around 50 million people worldwide suffer from epilepsy, and nearly 80% of these are in developing countries [1]. Annual new cases run between 40 and 70 per 100,000 in the general population in developed nations, and in undeveloped nations, the figure is often close to twice that due to the higher risk of experiencing conditions that lead to permanent brain damage [1]. Epilepsy is a prevalent disease (0.4% to 0.8%) with the highest incidence rates in early childhood and in the elderly [2]. With nearly one-third of patients having symptoms refractory to available medications [2], the National Institute of Neurological Diseases and Stroke has identified "an urgent need for novel chemical entities… that will provide a greater likelihood of complete control of seizures in patients who are currently treatment-resistant [3]".

All currently available medications for epilepsy are anticonvulsant rather than antiepileptogenic or disease-modifying [4]. Their mechanism of action involves the modulation of ion channels, receptors, or neurotransmitter metabolism, with none primarily targeting astrocyte function. There is a significant need and opportunity to develop drugs that not only influence the seizure threshold but also mitigate the neurobiological changes that occur in epileptogenesis.

TAK-935 is the first potent, selective, and central nervous system (CNS)-penetrant inhibitor of the cholesterol 24-hydroxylase (CH24H) to have entered clinical development. CH24H converts brain cholesterol 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. CH24H, which is expressed by the *CYP46A1* gene, is a brain-specific enzyme responsible for cholesterol catabolism [5-7]. Deletion of the CH24H gene in knock out mice is compatible with normal life and does not significantly decrease or increase the total brain cholesterol, as catabolism appears tightly linked with synthesis. Therefore, when CH24H is deleted, an adaptation occurs reducing ~40% of *de novo* cholesterol synthesis [6]. While the enzyme is predominantly expressed in neurons in a normal state, nonclinical and human postmortem studies have shown that neurodegeneration and brain insults lead to induction of CH24H expression in astrocytes and microglia [8,9].

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 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 receptor channel or as a positive allosteric modulator of the receptor. The processes may be equally important in contributing to the enhanced glutamatergic activity observed in epilepsy disorders. TAK-935 target engagement has been confirmed in the human brain with a proprietary positron emission tomography ligand.

There have been reports that some eye diseases (such as glaucoma and cataract) may be associated with cholesterol metabolism. Subjects in the study will have ophthalmological evaluations.

To date, TAK-935 has been studied in 4 phase 1 studies in healthy adult subjects and in a phase 2a study in adult subjects with developmental and epileptic encephalopathies (DEEs) in the United States. Overall, 108 healthy subjects have been enrolled in phase 1 studies, of which 86 subjects have received active treatment with TAK-935. Safety results from these studies showed that TAK-935 up to a single dose of 1350 mg (Study TAK-935-101) and multiple doses up to 400 mg once daily (QD) for 14 days (Study TAK-935-1002) is generally safe and well tolerated. However, multiple doses of 300 mg twice daily (BID) and 600 mg QD for 10 days, both without up-titration, did not appear to be well tolerated due to the emergence of neurologic and psychiatric adverse events (AEs) in healthy subjects in the Study TAK-935-1002. Two subjects discontinued study drug due to a treatment-emergent adverse event (TEAE) of acute psychosis (Cohort 4: TAK-935 600 mg QD) and a TEAE of confusional state (Cohort 3: TAK-935 300 mg BID). The former acute psychosis event was reported on Study Day 10, for a CC[redacted]-year-old male, and was considered of severe intensity, lasting through Day 14; the investigator considered the TEAE to be related to study treatment. The latter, a confusional state TEAE, was reported for a CC[redacted]-year-old subject on Study Day 9, lasting through Day 11; the event was of mild intensity and also considered related to study drug. As a result of these events, dosing for all subjects in Cohorts 3 and 4 was stopped after Day 10. For the subsequent Cohort 5, the dose of TAK-935 was reduced to 400 mg QD, and additional safety monitoring measures as well as stopping rules were implemented. All subjects in the 400 mg QD Cohort 5 completed the 14-day dosing as planned.

Subsequently in 18 subjects with DEEs (Study TAK-935-2001), TAK-935 was titrated to the target dose of 300 mg BID over 30 days followed by maintenance period up for a total duration of 85-91 days and was generally well tolerated, although fully reversible psychiatric AEs were observed; consisting of insomnia, agitation, communication disorder, irritability, and listlessness.

After single-dose oral administration of TAK-935 from 15 to 1350 mg as solution under fasted conditions in healthy Western subjects, TAK-935 C_{max} was reached rapidly at 0.25 to 0.52 hours postdose (median t_{max}). Mean TAK-935 $t_{1/2z}$ ranged from 0.82 to 7.16 hours. Exposure to TAK-935 increased in a greater than dose-proportional manner over the 15 to 1350 mg dose range. Over the 90-fold dose range of 15 to 1350 mg, mean TAK-935 C_{max} and AUC_{∞} increased by 183- and 581-fold, respectively. CCI [redacted] CCI [redacted]

Following multiple doses (10 to 14 days) of TAK-935 100 mg QD, 300 mg QD, 300 mg BID, 400 mg QD, and 600 mg QD (without up-titration) as solution under fasted conditions, TAK-935 C_{max} was reached rapidly at 0.33 to 0.5 hours across the dose range studied. Mean TAK-935 $t_{1/2z}$ was similar between Days 1 and 14, ranging from 3.49 to 4.83 hours across the 100 to 600 mg dose range. Over the 4-fold dose range of 100 to 400 mg QD after multiple-dose administration, mean TAK-935 C_{max} and AUC_{τ} on Day 14 increased 6.08- and 6.12-fold, respectively. Doses of 100 or 400 mg QD for 14 days did not show apparent exposure accumulation on Day 14 when compared with Day 1, while 300 mg QD for 14 days showed about 1.74- and 1.42-fold increase of C_{max} and AUC_{τ} on Day 14, respectively. CCI [redacted]

CCI [redacted]

Target occupancy in humans correlates with plasma 24HC levels, validating the use of 24HC as a soluble biomarker to monitor TAK-935 activity in the brain (Study TAK-935-1003). After multiple-dose administration of 100 mg QD, 300 mg QD, 400 mg QD, 300 mg BID, and 600 mg QD of TAK-935, a generally dose-dependent decrease in plasma 24HC concentrations was observed, with more profound decreases at higher doses. Plasma 24HC level appeared to approach steady state on Day 7 after multiple-dose treatment. Time-matched percent change in 24HC $AUEC_{24}$ showed a decreasing trend on Day 14, ranging from 46.82% to 62.66% across the doses of 100 to 400 mg QD (Study TAK-935-1002).

4.2 Rationale for the Proposed Study

The objective of the current study is to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending dose (SAD) and multiple doses (MD) with titration of TAK-935 in healthy Japanese subjects to support further development of TAK-935 as a potential treatment for epilepsy. The available nonclinical pharmacology, PK, and toxicology data and the data from the precedent 4 phase 1 studies in healthy subjects and a phase 2a study in adult subjects with DEEs in overseas support the current trial design. The safety, tolerability, PK and PD data obtained from the proposed SAD and MD studies will inform the design of and dosing regimen selection for subsequent studies with TAK-935 in Japanese subjects. Several key aspects of interests were considered to formulate the study design. First, it is essential to evaluate the safety of TAK-935 in healthy Japanese subjects. This will be evaluated in healthy subjects by AE assessment. Second, the PK profile of TAK-935 will also be evaluated in healthy Japanese subjects. CCI [redacted]

4.3 Benefit/Risk Profile

TAK-935 is the first potent, selective, and CNS-penetrant inhibitor of the CH24H to have entered clinical development.

Based on the mechanism of action of TAK-935, the risk profiles of compounds that affect glutamate excitotoxicity, known class effect of antiepileptic drugs, nonclinical data of TAK-935, and the literature information on the association between CH24H inhibition and visual disturbances, potential risks for this investigational product are as follows:

- Neurologic and psychiatric effects (clinical data).
- Cognitive effects (clinical data).
- Suicidal ideation or behaviors (observed in antiepileptic drugs [AEDs]).

- Convulsions (nonclinical data).
- Cataracts (nonclinical data).
- QTc prolongation (nonclinical data).

The exclusion criteria No.10 (Section 7.2) is applicable for the mitigation of neurologic and psychiatric effects, and cognitive effects in the potential subjects enrolled in this study.

Suicidal ideation or behaviors, generally observed in the use of AEDs, will be assessed in the examination using Columbia Suicide Severity Rating Scale (C-SSRS). Any suicidal ideation or suicidal behavior during the trial periods detected by C-SSRS will be recorded as AEs in this study.

A single escalating-dose oral toxicity study was performed in dogs at doses of 10, 30, and 100 mg/kg. At 100 mg/kg, clonic and tonic convulsions, resting tremors of the head, hole-body twitches, clonic convulsion, and tachypnea were observed, all of which resolved within 8 hours postdose.

Incipient posterior cortical/subcapsular cataracts, which were not dose related, were observed at ≥100 mg/kg/day in the 26-week rat toxicological study. Diffuse feathery opacity around the posterior suture lines in the lenses also observed was very slight to slight except for 1 male at 300 mg/kg/day and 1 female at 100 mg/kg/day, which were moderate. The male at 300 mg/kg/day had a microscopic correlate of focal mild lens fiber degeneration. Partial recovery from the very slight to slight opacities was present after a 4-week recovery period. In this study, eye examination will be conducted accompanied with physical examination. Considering that this incident was reversible, if this AE was observed in this study, the study should continue.

CCI [redacted] No cardiovascular alterations were observed at a 20 mg/kg dose at ≥10 times the exposure modeled for a 300-mg BID human dose. CCI [redacted]

Clinical data from the ongoing clinical studies demonstrate TAK-935 is safe and well tolerated at dose levels up to a single dose of 1350 mg and multiple doses up to 400 mg QD for 14 days and titration from 100 mg BID to 300 mg BID is generally safe and well tolerated (Study TAK-935-101, TAK-935-1002, and TAK-935-2001). Review of available nonclinical and clinical drug safety data, when viewed in context of the potential benefit for patients with epilepsy supports a favorable benefit/risk ratio for TAK-935. To date, the observed safety data for TAK-935, including mild or reversible AEs, are acceptable considering the potential clinical benefit of TAK-935, and clinical study of TAK-935 should continue.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed on the basis of the following hypotheses.

- Safety results from overseas phase 1 studies showed that TAK-935 up to a single dose of 1350 mg (Study TAK-935-101) and multiple doses up to 400 mg QD for 14 days (Study TAK-935-1002) is generally safe and well tolerated.
- In 18 subjects with DEEs, TAK-935 was titrated to the target dose of 300 mg BID over 30 days followed by maintenance period up for a total duration of 85-91 days and was generally well tolerated, although fully reversible psychiatric AEs were observed (Study TAK-935-2001).
- CCI [redacted]

5.2 Trial Objectives

5.2.1 Trial Primary Objective

- The primary objective of the study is to evaluate the safety and tolerability of TAK-935 in healthy Japanese subjects when administered as single oral dose or multiple oral doses with titration.

5.2.2 Trial Secondary Objective

- The secondary objective of the study is to evaluate the PK of TAK-935 in healthy Japanese subjects when administered as single oral dose or multiple oral doses with titration.

CCI [redacted]

CCI [redacted]

5.3 Endpoints

5.3.1 Primary Endpoint

The primary endpoint of the study includes:

Safety endpoint:

- Percentage of subjects who experience at least 1 TEAE

5.3.2 Secondary Endpoints

Secondary endpoints include:

Pharmacokinetic endpoints:

- Maximum observed plasma concentration (C_{max}).
- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}) (Part 1 only).
- AUC from time 0 to time of infinity (AUC_{∞}) (Part 1 only).
- AUC from time 0 to 24 hours (AUC_{24}) (Part 1 only).
- AUC during a dosing interval (AUC_{τ}) at steady state (Part 2 only).

CCI

CCI

[redacted]

CCI

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This study consists of 2 parts, which is a randomized, double-blind, placebo-controlled study to assess safety, tolerability, and PK [CCI] of TAK-935 when administered via oral administration in healthy Japanese subjects.

Part 1 is a SAD study, consisting of 3 cohorts containing 8 subjects each. On Day 1 of each dose level, a single dose of TAK-935 or placebo will be administered, and safety, PK [CCI] will be evaluated.

Part 2 is a MD with titration study within the same subjects. TAK-935 or placebo will be administered to the 9 subjects at the dose of 100 mg BID from Day 1 to Day 7, then 200 mg BID from Day 8 to Day 14, and finally 300 mg BID from Day 15 to Day 21, and safety, PK [CCI] will be confirmed. The planned dose levels of TAK-935 to be evaluated are outlined in Table 6.a.

Table 6.a Outline of the Study Parts and Planned Dosing Cohorts

Part	Cohort	Daily dose level (mg)	Dosing regimen	Randomization
Part 1	1	200	Single oral dose under fasted condition	Subjects will be randomized to TAK-935 or placebo at a ratio of 6:2 in each cohort, double-blind. No stratification variables will be used for randomization.
	2	600		
	3	1200		
Part 2	4	Day 1-7: 200 (100 mg BID) Day 8-14: 400 (200 mg BID) Day 15-21: 600 (300 mg BID)	Multiple oral doses up/titration with TAK-935 for 7 days per each dose level within the same subjects under fasted condition	Subjects will be randomized to TAK-935 or placebo at a ratio of 6:3, double-blind. No stratification variables will be used for randomization.

BID: twice daily

Study Population

Study Population: Healthy Japanese subjects.

Planned Number of Subjects

Part 1 (SAD): Total of 24 subjects

- Cohort 1: 8 subjects

- Cohort 2: 8 subjects
- Cohort 3: 8 subjects

Part 2 (MD): Total of 9 subjects

- Cohort 4: 9 subjects (dose up/titration within the same subjects)

Key Study Procedure Overview

<Part 1>

After the screening visit, eligible participants will check-in on Day-2. On Day 1, eligible participants will be randomized 6:2 to TAK-935 or placebo in each dose group in double-blinded fashion. No stratification variables will be used for randomization. On the same day, study drug will be administered by oral administration of single dosing of TAK-935 to each cohort at each dose level. The subjects will be discharged on Day 3. Intensive PK sampling will be performed from Day 1 to Day 3. A schedule of the events in this part is shown in Section 3.0.

<Part 2>

After the screening visit, eligible participants will check-in on Day-2. On Day 1, eligible participants will be randomized 6:3 to TAK-935 or placebo in double-blinded fashion. No stratification variables will be used for randomization. Study drug will be administered every day by oral administration of multiple dosing with up-titration of TAK-935 to 9 subjects firstly at 100 mg BID from Day 1 to Day 7, then at 200 mg BID from Day 8 to Day 14, and finally at 300 mg BID from Day 15 to Day 21, successively. The subjects will be discharged on Day 24. Intensive PK sampling will be performed on Day 1, Day 7, Day 14 and Day 21. A schedule of the events in this part is shown in Section 3.0.

6.2 Dose Escalation

<Part 1>

Blinded safety and PK will be evaluated at the end of treatment for each cohort and prior to dose escalation.

For each dose level administered/completed cohort, the principal investigator and the sponsor will carefully review the available safety, tolerability, and blinded PK data and determine whether dosing should stop or continue in this study.

If the C_{max} and/or the AUC is expected to be much greater than the maximum exposure at maximum dose evaluated in precedent clinical studies, the dose level in the subsequent cohort may be lower than the planned dose.

All AEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge on Day 3, will be evaluated to assess the need for subject and/or study termination in accordance with the pre-specified criteria for discontinuation/termination (Section 6.5.4.1).

Following assessment of the AE data and pre-defined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis.

If agreement regarding a dose escalation decision cannot be reached between the principal investigator and the sponsor, the study will be stopped.

<Part 2>

Part 2 (Cohort 4) will be initiated after the evaluation of blinded safety and PK at 600 mg single dose in Part 1 (Cohort 2).

All AEs reported during the Treatment Period up to the time of discharge on Day 24 will be evaluated to assess the need for subject and/or study termination in accordance with the pre-specified criteria for discontinuation/termination (Section 6.5.4.1).

Figure 6.a shows the dose escalation scheme.

Figure 6.a Dose Escalation

Part 1 (Single dose)			Part 2 (Multiple dose)
Cohort 1 [a] ⟶	Cohort 2 [a] ⟶	Cohort 3 [a]	Cohort 4 [b]
TAK-935 200 mg or placebo	TAK-935 600 mg or placebo	TAK-935 1200 mg or placebo	TAK-935 100 mg BID or placebo, then TAK-935 200 mg BID or placebo, and finally TAK-935 300 mg BID or placebo with up-titration within the same subjects

[a] The subsequent cohort should be run after the evaluation of blinded safety and PK in the prior cohort and confirmed that the prior cohort is well tolerated.
[b] Cohort 4 will be initiated after the evaluation of blinded safety and PK in Cohort 2.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

The subjects of this study will be healthy Japanese adult subjects who do not have any significant diseases including cardiovascular or cerebrovascular diseases. This population will allow evaluation of the safety, tolerability, PK, [redacted] profile of TAK-935 in healthy subjects after single and repeated daily oral administration. Results of this study of Japanese healthy subjects will support further development of TAK-935 for the treatment of DEEs.

This study consists of 2 parts, which is a randomized, double-blind, placebo-controlled study to assess safety, tolerability, and PK [redacted] of TAK-935 when administered via oral administration in healthy Japanese subjects. Part 1 is a SAD study, consisting of 3 cohorts containing 8 subjects each, with each cohort randomized 6:2 (active vs. placebo). Part 2 is a MD with titration study containing 9 subjects randomized 6:3 (active vs. placebo). These parts are intended to support the design of and dosing regimen selection for subsequent studies with TAK-935 in patients with DEEs.

Study safety assessments are selected based on data from nonclinical and clinical studies with TAK-935. In nonclinical studies in rats, cataracts were observed after TAK-935 administration. Therefore, eye examination will be conducted accompanied with physical examination in this

study. Based on the potential risk of TAK-935 on neurologic and psychiatric effects which were observed in clinical studies, neuropsychiatric assessment will be conducted during the study.

6.3.2 Rationale for Dose

To date, 86 subjects have received active treatment with TAK-935 and safety results from Phase 1 studies conducted previously showed that TAK-935 up to a single dose of 1350 mg (Study TAK-935-101) and multiple doses up to 400 mg QD for 14 days (Study TAK-935-1002) is generally safe and well tolerated. However, multiple initial doses of 300 mg BID and 600 mg QD, without up-titration, did not appear to be well tolerated due to the emergence of neurologic AEs in healthy subjects. Subsequently in 18 subjects with DEEs (Study TAK-935-2001), TAK-935 was titrated to the target dose of 300 mg BID over 30 days followed by maintenance period up for a total duration of 85-91 days and was generally well tolerated, although fully reversible psychiatric AEs were observed. In the current on-going Phase 2a study in adult subjects with complex regional pain syndrome, the up-titration scheme from TAK-935 100 to 300 mg BID over 21 days (7 days per each dose level) was selected based on population PK/PD simulations showing that the target dose of 600 mg/day is associated with a greater probability of demonstrating effectiveness in the majority of subjects, while maintaining an acceptable tolerability profile in this target patient population. The same dosing regimen, based on subject's body weight is also used in the ongoing Phase 2 studies with pediatric epileptic syndromes such as Dravet Syndrome, Lennox-Gastaut syndrome, Duplication 15q syndrome, and Cyclin-dependent kinase-like 5 deficiency syndrome. Consequently, 200 mg is selected as starting dose and 1200 mg as highest dose for Part 1 and similar titration regimen, ie, TAK-935 100 to 300 mg BID was selected for Part 2. The highest dose level in Part 1 (ie, 1200 mg) allows the evaluation of QT intervals at supratherapeutic exposure and may be adjusted on the basis of review of the emerging safety and PK data available at that point. Only doses lower than or equal to 1200 mg will be assessed.

The relative bioavailability BA of TAK-935 tablets vs solution was evaluated in Study TAK-935-1005. Following administration TAK-935 300 mg (as three 100 mg tablets) vs TAK-935 300 mg solution in the fasted state, median TAK-935 t_{max} was 0.53 and 0.35 hours, respectively. The geometric mean C_{max}, AUC_{last}, and AUC_{∞} was 995 ng/mL, 1260 h*ng/mL, and 1294 h*ng/mL, respectively, following administration of the tablet, and 1577 ng/mL, 1481 h*ng/mL, and 1440 h*ng/mL, respectively, following administration of the solution. The ratio (tablet vs solution) TAK-935 C_{max} was 0.63 (90% CI, 0.41-0.97), AUC_{last} was 0.85 (90% CI, 0.71-1.02), and AUC_{∞} was 0.84 (90% CI, 0.68-1.05).

Under the fasting conditions, oral administration of the TAK-935 tablet formulation had a C_{max} 37% lower than that observed with the solution, but only a minor decrease (15%-16%) in total exposure when TAK-935 was administered as a tablet relative to the solution.

Food decreased TAK-935 C_{max} by 60% but had little impact on the total TAK-935 exposure of the tablet formulation, as AUC_{last} and AUC_{∞} decreased by only 11%. Therefore, fasted condition is selected for both single and multiple dose part.

This study is also intended to support inclusion of Japanese subjects in future late phase clinical studies.

6.3.3 Rationale for Endpoints

6.3.3.1 Safety Endpoints

Since this is the first study in Japanese subjects, the standard safety endpoints for early clinical will be included.

There have been reports that some eye diseases (such as glaucoma and cataract) may be associated with cholesterol metabolism. Subjects in the study will have ophthalmological evaluations.

CCI [redacted]

6.3.3.2 Pharmacokinetic Endpoints

To characterize the PK of TAK-935 and its metabolites M-I in Japanese subjects, the pharmacokinetic parameters will be estimated as data permit. See Section 9.3.1 for more details.

6.3.3.3 CCI [redacted]

CCI [redacted]

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, the blood samplings for PK and PD evaluation are the critical procedures.

- At any postdose time point, the blood sampling for PK evaluation need to be performed as close to the exact nominal time point/scheduled time as possible.
- All other procedures should be performed as close as possible either before or after the scheduled times.
- CCI [redacted]
- The order of priority of which procedure can be changed during the study with joint agreement of the investigator and the sponsor.
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.
- Safety evaluation will be performed within the specified time frame as close as possible.
- Blood sampling for PK evaluation should occur before the nominal time of standard meal, if scheduled together.

- If the times for meals and the study procedures are conflicted, meals should be taken basically after all of the study procedures are completed.

6.4 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The maximum daily dose may not exceed that currently outlined in Section 6.3.2. In other words, the highest dose level in Cohort 3 of Part 1 (ie, 1200 mg) may be adjusted on the basis of review of the emerging safety and PK data available at that point. Only doses lower than or equal to 1200 mg will be assessed. No modification will be made except for the dose level of Cohort 3.

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at the discretion of the investigator. Above alterations will also be reflected in future protocol amendment as needed to avoid possible confusion at the site.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

The overall study begins when the first subject signs the study informed consent form.

6.5.2 Definition of End of the Trial

The overall study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit, discontinues from the study, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.5.3 Definition of Trial Discontinuation

Study discontinuation because of nonsafety reasons, such as the following:

- A finding (eg, PK, PD, efficacy, biologic targets) from another nonclinical or clinical study using the study treatment(s) results in the study being stopped for a nonsafety-related reason.
- Data from drug(s) of the same class, or methodology(ies) used in this study become available and results in the study being stopped for a nonsafety-related reason.
- The study is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.

Study discontinuation because of safety reasons:

- Early study termination because of unanticipated concerns of safety to the study subjects arising from clinical or nonclinical studies with the study treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

6.5.4 Criteria for Premature Termination or Suspension of the Trial

6.5.4.1 Criteria for Premature Termination or Suspension of the Trial

The study will be completed as planned unless one 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 medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit 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.
- Study-specific criteria for terminating the study (eg, study meets predefined rule for futility or benefit, study meets predefined stopping rules within or between cohorts per Section 6.2).
- One or more subjects in any single cohort develop acute psychosis.
- Two or more subjects in any single cohort or across more than one cohort experience any of the Takeda Medically Significant AE List (as outlined in Table 10.a).*
- Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5×upper limit of normal (ULN) in the absence of a concomitant bilirubin increase (see below).*
- One or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3×ULN in the presence of a total bilirubin increase >2×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (ie, “Hy’s Law cases”).
- Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).*

* Please note that the study may be terminated early prior to full attainment of these criteria (eg, if just 1 subject experiences 1 of these events) if warranted by safety data from the other subjects dosed in the study to date.

6.5.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the sponsor, an IRB/IEC, or regulatory authority elects to terminate or suspend the study, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by the study site during the course of termination or study suspension.

6.5.5 Definition of Trial Completion

The overall study is to be considered as completed as per the same definition as in Section 6.5.2.

6.5.6 Criteria for Premature Termination or Suspension of a Site

6.5.6.1 Criteria for Premature Termination or Suspension of a Site

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, or is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.5.6.2 Procedures for Premature Termination or Suspension of a Site

In the event that the sponsor, an IRB/IEC, or regulatory authority elects to terminate or suspend 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 the study site during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

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

1. The subject must understand the study procedures and agree to participate by providing written informed consent.
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be a Japanese healthy adult male or female, aged 20 to 55 years, inclusive, at the time of informed consent.
4. The subject must have a body mass index (BMI) ≥18.5 and ≤25.0 kg/m^2 at the Screening Visit.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months prior to the first dose of study drug or first invasive procedure.
6. The subject must be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical [CCI redacted] performed at the Screening Visit and prior to the first dose of study drug.
7. The subject must meet the following birth control requirements:
   - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 90 days after the last dose of study drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1-year postbilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
   - Is a male subject who agrees to not donate sperm from the first dose of study drug until 90 days after the last dose of study drug.
   - Is a female subject of nonchildbearing potential, defined by at least 1 of the following criteria:
     a. Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or ≥6 months of spontaneous amenorrhea in females aged >45 years with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels should be required.
     b. Hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
     c. Had a tubal ligation with appropriate documentation of surgical procedure.

d. Congenital conditions such as uterine aplasia etc.

7.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has a history of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular (including arrhythmia), hematological, hepatic, immunological, renal, respiratory, genitourinary, major neurological (including stroke, epileptic seizure), or degenerative ophthalmological abnormalities or diseases
2. Has participated in another investigational trial within 4 weeks or 5 half-lives (whichever is longer) before the pretrial visit (Screening). The 4-week or 5 half-lives window will be derived from the date of the last trial procedure and/or AE related to the trial procedure in the previous trial to the pretrial/Screening Visit of the current trial.
3. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of the sponsor.
4. Has a history of cancer (malignancy).
5. Has any lifetime history of a suicide attempt, or have suicidal ideation or, any suicidal behavior within 12 months, or who are at significant risk to commit suicide, as judged by the investigator using the C-SSRS or is clinically judged by the investigator to be at risk for suicide.
6. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
7. Has a positive alcohol or drug screen.
8. Had major surgery, donated or lost whole blood prior to the start of study drug administration as any of below:

   For both male and female subjects,

   ≥200 mL within 4 weeks (28 days)

   For male subjects,

   ≥400 mL within 12 weeks (84 days)

   ≥800 mL in total within 52 weeks (364 days)

   For female subjects,

   ≥400 mL within 16 weeks (112 days)

   ≥400 mL in total within 52 weeks (364 days)
9. Had gastrointestinal surgery that could impact the absorption of study drug.
10. Has a history of a major psychiatric disorder as diagnosed utilizing Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria.

11. Has a known hypersensitivity to any component of the formulation of TAK-935 or related compounds.
12. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 7 days before administration of the initial dose of study drug, throughout the trial (including washout intervals between trial periods), until the Follow-up Visit.
13. Has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
14. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
15. Has a substance abuse disorder.
16. Has a QTcF >450 msec confirmed with one repeat testing, at the Screening Visit.
17. Had abnormal Screening or Day -1 laboratory values that suggested a clinically significant underlying disease or subject with the following laboratory abnormalities: ALT and/or AST >1.5 time ULN.
18. Has tested positive for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody, HIV antibody/antigen, or serologic reactions for syphilis at Screening.
19. In the opinion of the investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

7.3 Excluded Medications, Supplements, Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until subject is discharged from the unit.

Subjects must be instructed not to take any medications including over-the-counter (OTC) products, until the study is completed, without first consulting with the investigator.

Table 7.a Prohibited Medications

28 days prior to Check-in (Day -2)	7 days prior to Check-in (Day -2)	72 hours prior to Check-in (Day -2)
Prescription medications (including perampanel and oral contraceptives)	OTC medications [a]	Products containing caffeine or xanthine
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	Poppy seeds
Immunization/Vaccines [b]	Foods or beverages containing grapefruit or grapefruit juice, star fruit or star fruit juice, Seville-type (sour) oranges and marmalade, apple juice, orange juice, pineapple juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	Green tea
Nicotine-containing products	Alcohol containing products	
Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 [c]		

CYP: cytochrome P-450; OTC: over-the-counter.

[a] Occasional use of acetaminophen (≤1 g/day) or other medication as approved by the sponsor on a case-by-case basis is allowed except on Day 1 for Part 1 and Days 1, 7, 14 and 21 for Part 2.

[b] Inclusive of but not limited to flu vaccinations.

[c] Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

During the confinement period, subjects will be given a menu for the dosing period that includes 3 meals, however the breakfast will not be provided on Day 1 in Part 1. The meals served on the days of dosing should be identical for each cohort in the study. In addition, meals served on PK assessment days (Day 1 for Part 1and Day 1, 7, 14 and 21 for Part 2) should be identical. Subjects should remain fasted until 4 hours (Part 1) or 2 hours (Part 2) after dosing after which point breakfast will be served except on Day 1 in Part 1. Evening meals will be provided after dosing. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

On the dosing days, TAK-935 or placebo will be administered with 150 mL of water. The morning dose should occur after a fast of at least 10 hour (Part 1) or 8 hours (Part 2). In Part 1 Cohort 3, in which 1200 mg of study drug will be administered, subjects can ingest up to 150 mL of water as

needed (ie, subjects in this cohort are not required to ingest the full 150 mL of water). Subjects will continue to fast for an additional 4 hours (Part 1) or 2 hours (Part 2) after dosing. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration.

7.4.2 Activity

Subjects will remain upright (seated, standing, or ambulatory) for 4 hours following the dose administration, except as necessitated by the occurrence of an AE or study procedures. Subjects will refrain from strenuous and/or unaccustomed exercise throughout the entire course of the study, from 72 hours prior to check-in through Study Exit/Early Termination.

Blood donation within at least 12 weeks (84 days) for male subjects and 16 weeks (112 days) for female subjects after the last laboratory test is prohibited.

7.5 Documentation of Subject Failure

The investigator must account for all subjects who sign informed consent. If a subject discontinues the study before the first study drug administration, the investigator should complete the electronic case report form (eCRF).

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

- Death
- AE
- Screening failure (failed inclusion criteria or did meet exclusion criteria) <specify the reasons>
- Protocol deviation
- Lost to follow up
- Withdrawal by subject <specify the reasons>
- Study terminated by the Sponsor
- Sample size sufficient
- Other <specify the reasons>

Any subject identification number, once assigned to a subject, should not be reused if the assigned subject discontinues the study prior to the first study drug administration.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The study drug will be immediately discontinued if a condition meets any following criteria during the treatment. The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories:

1. Death
   The subject died on study.

   Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). Refer to Section 10.2.9.3 for reporting procedures.

2. 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.

   The study drug will be immediately discontinued if a condition meets any following criteria during the treatment, and appropriate follow-up will be performed (clinical laboratory tests will be repeatedly performed until the clinical laboratory test profiles have normalized or returned to baseline, refer to Section 9.2.11):

   - Liver Function Test (LFT) Abnormalities
     - ALT or AST >8×ULN, or
     - ALT or AST >5×ULN and persists for more than 2 weeks, or
     - ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or INR >1.5, or
     - ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
   - Prolonged QT/QTcF intervals

     If at least one remarkable prolonged QT interval was observed on 12-lead ECG (eg, absolute value of QTcF intervals >500 msec or an increase >60 msec from baseline), and the investigator considered inappropriate to continue the study.

3. Protocol deviation.
   The discovery after the start of the first study drug administration 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.

4. 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 documentation.

5. Withdrawal by subject.
   The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

6. Study terminated by the Sponsor
   The Sponsor terminates the study.
7. Other.

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

7.7 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 7.6. 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 Early Termination Visit.

7.8 Subject Replacement

If a subject has not received the study drug owing to any reason occurring before the study drug administration, a reserve subject will be allowed to participate in the study.

For Part 2, if a subject discontinues or withdraws from the study after initiation of the study drug, the subject may be replaced at the discretion of the investigator and sponsor.

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 clinical trial material.

8.1 Clinical Study Drug

Study drug refers to TAK-935 100 mg tablet and matching placebo.

[Compound]

Code name: TAK-935

Dosage forms:

TAK-935 100 mg tablets and matching placebo tablets are used in this study. The TAK-935 tablets and placebo tablets are yellow-red film-coated tablets for oral administration. A film coating is applied to protect against the photosensitivity exhibited by the uncoated tablets.

Manufacturing:

TAK-935 100 mg tablets and matching placebo tablets are manufactured by SPERA Pharma Inc. Osaka, Japan.

8.1.1 Clinical Study Drug Labeling

Study drug will be delivered to the study site in an unblinded manner. A clinical label is affixed to study drug containers in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

TAK-935 100 mg tablets and matching placebo tablets must be stored per the label at 1°C to 30°C.

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

8.1.3 Clinical Study Drug Blinding

This is a double-blind study; the investigator and subjects are blinded to treatment assignment. The study drug will be provided as TAK-935 100 mg tablets and matching placebo tablets to the study site and unblinded randomization personnel designated by the study site will retain the blind according to the randomization schedule and procedure, by affixing a label with a medication identification number on each dispensing container containing TAK-935 100 mg tablet(s) or matching placebo tablet(s); this should be done in the room where the other site personnel or the sponsor employees are kept out. The randomization personnel at the study site will manage and prepare blinded doses throughout the study.

8.1.4 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.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

The study drug blindness will be maintained through a randomization schedule and randomization procedure held by the randomization personnel at the study site and by the sponsor or designee. Randomization code/disclosure envelopes or lists (emergency key code) will be provided to the study site. The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. The sponsor or designee must be notified as soon as possible if the blind is broken.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The head of the site or its delegate(s), such as the investigator or pharmacist, is responsible for keeping accurate records of the study drug received from the sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the end of the study. For all study sites, the sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction.

9.0 STUDY PROCEDURES

The following sections describe the study procedures to be performed and data to be collected as indicated in the schedule of study procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters into the study and before any protocol-directed procedures are performed. The requirements of informed consent are described in Section 13.2.

9.1.1.1 Assignment of Subject Identification Number

A unique 7-digit subject identification number will be assigned to each subject at the time that informed consent is explained; this subject identification number will be used throughout the study.

9.1.1.2 Study Drug Assignment

Each subject will be assigned a medication identification number to receive treatment in accordance with the randomization schedule. The medication identification number will be a 4-digit number, starting with the following numbers:

Cohort 1: 1101, Cohort 2: 1201, Cohort 3: 1301, Cohort 4: 2001

The assigned medication identification number will be used to identify the samples for PK/PD by the study site and the only number to identity a subject during blood sampling for PK/PD. The number will always be shown on the sample vials, which are sent to the laboratory to evaluate PK/PD. The laboratory will report the results using this number. The number will only be used for the purpose described in this section and cannot be replaced with the 7-digit subject identification number, which is assigned at the time of informed consent procedure and used in all other procedures during the clinical study period to identify a subject. In case of subject replacement before the study drug administration, the medication identification number for the withdrawn subject will be re-used by the replacing subject. For Part 2, if a subject is replaced after initiation of the study drug administration, an unused medication identification number will be used by the replacing subject.

9.1.2 Inclusion and Exclusion

Each subject will be assessed before randomization, according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Demographic information to be obtained will include date of birth, sex, height, weight, caffeine use, alcohol use, and smoking status of the subject.

Medical history to be obtained will include determining whether the subject has any clinically significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions. Medication history information to be obtained will include any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Qualified site personnel will review subject prior and concomitant medication use. Medications are defined as prescription and OTC drugs, vaccines, supplements, nutraceuticals, and oral herbal preparations. Subjects will be asked whether they have taken any medications other than the study drug (during a period from the signing of informed consent through the end of the study), and all medications including vitamins, OTC drugs and Chinese herbal medicines used by a subject must be recorded in each subject's eCRF. The nonproprietary name, route of administration, dates of initial and final administrations and reasons for use must also be recorded in the eCRF.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam and Eye Exam

Qualified site personnel will conduct full physical examinations. And qualified site personnel will conduct an eye exam including visual field evaluation, best corrected visual acuity,fundoscopy without pupillary dilation, and a slit lamp microscopy.

9.2.2 Height and Weight

Body weight and height will be obtained with the subject's shoes off, and jacket or coat removed. Height will be measured in centimeters (cm) and the measured value will be rounded off to the nearest whole number. Weight will be measured in kilograms (kg) and the measured value will be rounded off to 1 decimal place.

9.2.3 BMI

BMI equals a subject's weight in kilograms divided by height in meters squared (BMI=kg/m^2). The measured value should be rounded off to 1 decimal place. The inclusion criteria for BMI will be defined based on the values after rounding.

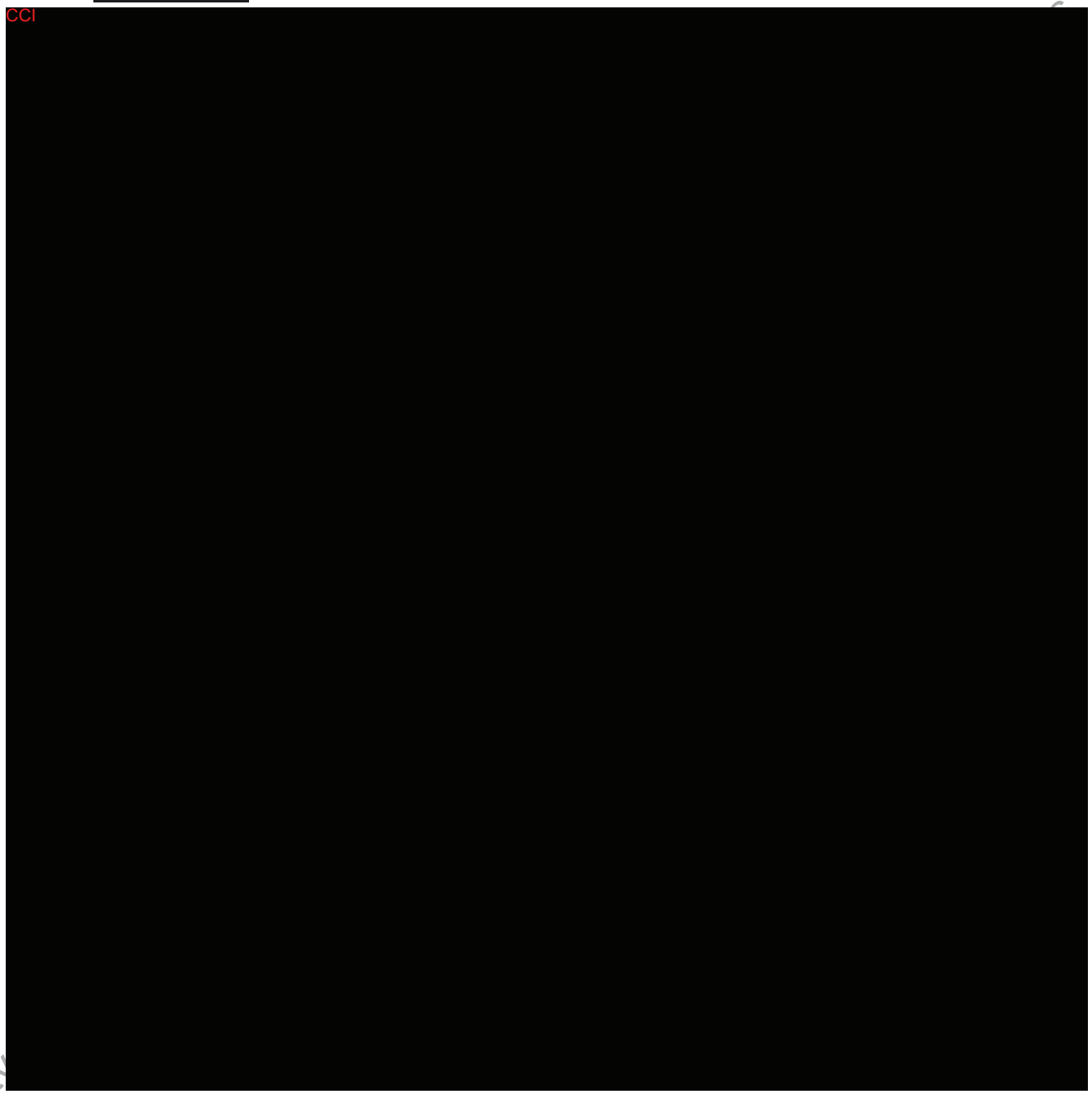
9.2.4 CCI

CCI

CCI

9.2.5 CCI

CCI



9.2.6 CCI

CCI

CCI

[redacted]

9.2.7 Study Drug Administration

<Part 1>

Subjects will receive a single dose of TAK-935 or placebo of 200 mg, 600 mg, or 1200 mg with 150 mL of water, after fasting for at least 10 hours and will remain fasted until 4 hours after dosing. In Cohort 3, in which 1200 mg of study drug will be administered, subjects can ingest up to 150 mL of water as needed (ie, subjects in this cohort are not required to ingest the full 150 mL of water).

<Part 2>

Subjects will receive multiple oral doses of TAK-935 or placebo escalating from 100 mg BID, 200 mg BID, and then to 300 mg BID with 150 mL of water for 7 days per each dose level. For the morning dose, subjects are kept fasted for at least 8 hours before administration and up to 2 hours after administration. The evening dose will be administered at any time between 8 hours and 12 hours after the morning dose, but prior to the evening meal except for Days 1, 7, 14, and 21. On Days 1, 7, 14, and 21, the evening dose will be administered 12 hours after the morning dose and prior to the evening meal.

9.2.8 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidal risk will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures (Screening, Day-2 and Day 3 [Part 1] or Screening, Day-2 and Day 24 [Part 2]). Two versions of the C-SSRS will be used in this trial: the screening/baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS. Any suicidal ideation or suicidal behavior during the trial periods detected by C-SSRS will be recorded as AEs by the investigator. The investigator will ensure that any suicidal ideation or behavior is medically addressed, including assessment and treatment by qualified medical personnel.

9.2.9 Neuropsychiatric assessment

Mini mental state examination (MMSE) and pre-determined questions are a set of cognitive function test for screening delirium and psychosis. The investigator, sub-investigator, or study coordinator will evaluate the cognitive functions of subjects using MMSE. The details of the

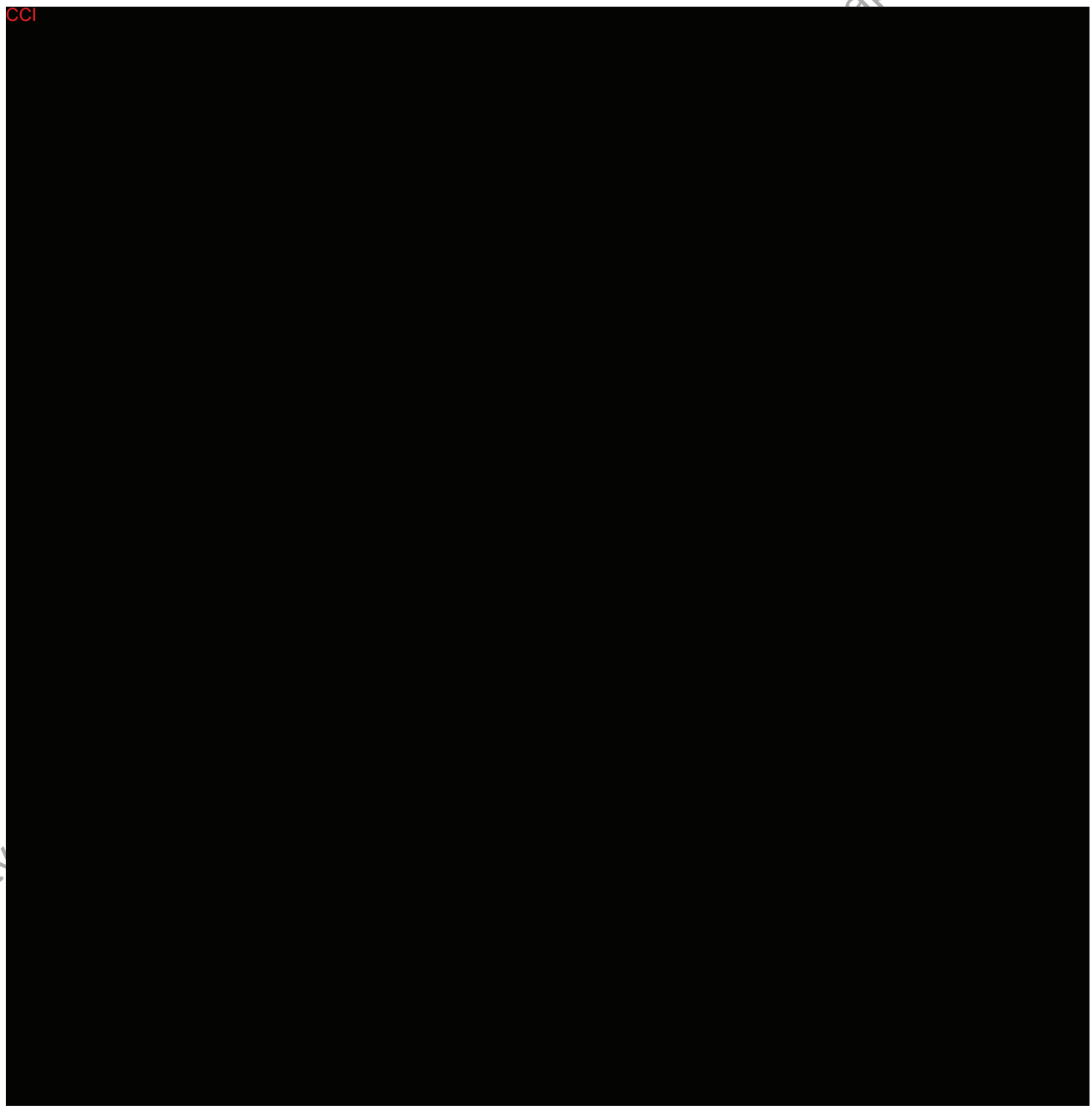
pre-determined questions are listed in Appendix D. These are recommended to screen and monitor for both delirium and psychosis.

9.2.10 AE Monitoring

AE monitoring begins after signing of the informed consent form. Changes in subject health status from the baseline assessment until study drug administration should be captured in the subject's medical history. A complete description of AE collections and procedures is provided in Section 10.0.

9.2.11 CCI

CCI



CCI

[redacted]

CCI

9.2.12 Follow-up Visit

The Follow-up Visit will occur by direct visit on Day 8 (Part 1) or Day 35 (Part 2) and will be for the purpose of assessing AE and inquiring about concomitant medications since completing the trial.

9.3 Biomarker, PK, and PGx, Samples

Samples for PK, biomarker, PD, and pharmacogenomic analysis will be collected at the time points stipulated in the schedule of procedures (Section 3.0). Please refer to the laboratory manual for information on the collection, processing, and shipment of samples to the central laboratory.

The decision as to which collected samples will be assayed for evaluation of PK and biomarkers will be determined by the sponsor. If indicated, these samples may also be assayed and/or pooled to measure metabolites and/or additional biomarkers in an exploratory manner.

Primary specimen collection parameters are provided in Table 9.b.

Table 9.b Primary Specimen Collections

CCI [redacted]

9.3.1 PK Measurements

The PK parameters of TAK-935 CCI [redacted] will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following PK parameters will be calculated from plasma concentrations of TAK-935 CCI [redacted] unless otherwise specified:

Symbol/Term	Definition
Plasma	
C_{max}	Maximum observed plasma concentration
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (Part 1 only)
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity (Part 1 only)
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours (Part 1 only)
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval (Part 2 only)
t_{max}	Time of first occurrence of C_{max}
$t_{1/2z}$	Terminal disposition phase half-life
CL/F	Apparent clearance after extravascular administration (for TAK-935 only)
V_z/F	Apparent volume of distribution during the terminal phase (for TAK-935 only)
CCI [redacted]	CCI [redacted]
$R_{ac(AUC)}$	Accumulation ratio based on AUC (Part 2 only)
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max} (Part 2 only)

Additional PK parameters may be calculated as appropriate. A detailed PK analysis plan will be prepared before PK parameter computation.

9.3.1.1 Plasma for PK Measurements

Blood samples for PK analysis of TAK-935 CCI [redacted] will be collected into blood collection tubes (vacutainer) containing the anticoagulant K_2EDTA. The collected blood samples may be archived for additional analysis of potential metabolites.

The actual time of sample collection will be recorded on the source document and eCRF. Sampling time points may be adjusted based on the preliminary emerging concentration data collected from prior subject(s), but the total number of samples collected per subject should not exceed the planned number.

Table 9.c Sampling of Blood Samples for PK Analysis (Part 1)

Analyzed substances	Samples	Study date	Blood sampling time
TAK-935 CCI [redacted]	Plasma	Day 1-3	Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 10, 12, 16, 24 and 48 hours post dose or Early Termination

PK: pharmacokinetic(s).

Table 9.d Sampling of Blood Samples for PK Analysis (Part 2)

Analyzed substances	Samples	Study date	Blood sampling time
TAK-935 CCI [redacted]	Plasma	Day 1, 7, 14, 21	Pre-morning dose and at 0.25, 0.5, 1, 2, 4, 8, 10 and 12 hours after morning dose on Day 1, Day 7, Day 14 and Day 21, or Early Termination

PK: pharmacokinetic(s).

In the case when the subject prematurely discontinues the study between the first and the last scheduled PK sample blood draw, final blood samples to be used for PK analysis are sampled from subjects during hospitalization. The exact date and time of each sample should be recorded.

On the other hand, in the case of premature discontinuation during the period of follow-up after discharge, blood samples for PK analysis are not collected from the subjects who came to outpatient medical examination.

9.3.2 Biomarker Measurements

CCI [redacted]

9.3.2.1 CCI [redacted]

CCI [redacted]

CCI

9.3.3 PGx Measurements

9.3.3.1 Blood Sample for DNA PGx Measurements

Sampling of whole blood for pharmacogenomic analysis is optional in this study and will only be performed for subjects who provide consent to participate in this assessment.

Pharmacogenomics (PGx) is the study of variations of DNA characteristics as related to drug response. There is increasing evidence that an individual's genetic background may affect the PK (absorption, distribution, metabolism, and excretion), PD (pharmacologic effects), and/or clinical effects (efficacy and/or safety) of a drug.

Pharmacogenomic research in this study may be conducted to understand how individual genetic variation in subjects impacts their response to study drug treatment. This information may also 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 other related conditions, to gain a better understanding of the drug pharmacology, and to generate information needed for research, development, and regulatory approval of tests to predict response to TAK-935.

Whole blood samples for DNA isolation will be collected from each consented subject in the study.

Since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

9.3.3.2 Biological Sample Retention and Destruction

In this study, blood samples for pharmacogenomic analysis will be collected as described in Section 9.3.3.1. Genetic material will be initially stored at a vendor or comparable laboratory, under contract to the sponsor, with validated procedures in place, and then preserved and retained at a long-term storage vendor, or a comparable laboratory, with validated procedures in place, for up to but not longer than 15 years from the end of the study when the clinical study report is signed, or if less, the maximum period permitted under applicable law or until consent is withdrawn.

The sponsor and vendors 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.

The sample will be labeled with a unique sample identifier as in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The sample identifier will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA analysis can withdraw their consent at any time and request disposal of a stored sample. Any remaining sample that can be identified as coming from the subject will be destroyed. The investigator and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

9.4 Confinement

<Part 1>

Subjects will be admitted to a hospital during a period from Day -2 to Day 3 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 3, and confirmed by the investigator.

<Part 2>

Subjects will be admitted to a hospital during a period from Day -2 to Day 24 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 24, and confirmed by the investigator.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting 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 medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or CCI) 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).

CCI

CCI

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. The first evaluation (eg, laboratory test CCI X-ray, etc) after obtaining the consent should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or

complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). 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 condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or 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 severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- 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 captured appropriately 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.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0.

- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.9.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence on subjects who signed the informed consent forms as follows:

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
	Acute liver failure
Torsade de pointes / ventricular fibrillation/ ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures (including convulsion and epilepsy)	Pulmonary fibrosis (including interstitial pneumonia)
Agranulocytosis	Neuroleptic malignant syndrome/ malignant hyperthermia
Aplastic anemia	Spontaneous abortion/ stillbirth and fetal death
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxin shock

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the following manner (see Sections 10.2.9.3).

10.1.2 Adverse Events of Special Interest

An AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. The reporting of specific AEs of special interest is described in the following sections.

10.1.2.1 Psychiatric Effects: Psychosis

During the phase 1 multiple repetitive dose study, episodes of confusion, euphoria, and psychosis were seen at the highest dose of 600 mg/day. However, in that study subjects were not titrated. Psychiatric AEs will be monitored closely.

10.1.2.2 Convulsions

During nonclinical studies, convulsions were seen in the rat at extremely high doses. Convulsions will be considered an AE of special interest and subjects will be carefully monitored for any signs of convulsive activity.

10.1.2.3 Cataracts

During nonclinical studies, incipient posterior cortical, subcapsular lenticular cataracts of moderate grade were seen in 1 male rat at 300 mg/kg/day and 1 female rat at 100 mg/kg/day. Cataracts will be considered an AE of special interest and subjects will be carefully monitored for any signs of ocular abnormalities.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) 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 a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs 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.

10.2.3 Assigning Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

The causality 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 causality should be assessed as Not Related.

10.2.4 Start Date

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

10.2.5 End Date

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

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.

10.2.8 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; 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, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become 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."
- Recovered/ 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 – an AE that is 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.

10.2.9 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent and continue until the follow-up visit. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.9.2 Reporting AEs

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. Subjects experiencing an SAE prior to the first exposure to study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to study drug, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, after the first administration of the study medication, whether considered associated with the use of the study medication 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:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Investigators' opinion of the causal relationship between the event and administration of study drug.
- Investigators' opinion of the causal relationship between the event and the study procedure(s) (The details of study procedure(s) that may cause the event should also be provided).
- Action taken with trial drug.
- Outcome of event.
- Seriousness.
- Timing of occurrence (after administration of the study drug)

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator to the Sponsor (see Protocol Annex 1) within 1 business day of the first onset or notification of the SAE, along with any relevant information. The principal investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. 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 identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

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

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form copy or provide other written documentation and submit it to the Sponsor immediately. Copies of any relevant data from the hospital notes (eg,

CCI laboratory tests, discharge summary, postmortem results) should be sent to the Sponsor, 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.

10.2.9.4 Reporting AEs of Special Interest

If the subject experiences psychosis, convulsions, or cataracts during the treatment period or the safety follow-up period as described in Section 10.1.2, the event should be reported on a specific form within 1 business day of the investigator's awareness. Any relevant supporting documentation (ie, additional diagnostic testing, consultation reports) must be submitted to the sponsor.

If a convulsion occurs during the study, the investigator should document the following information:

- A complete description of the convulsion event. This description should include precise details of any eyewitness accounts that might be available. Particular attention should be paid to phenomena such as loss of consciousness (rapid or sudden), brief tonic posturing followed by more prolonged clonic contractions, loss of bowel/bladder control, tongue biting, or aura. Include the sequence of events and the time-course of notable signs and symptoms (eg, duration of the aura, if present, duration of the convulsion itself, and any postictal symptoms such as confusion or amnesia).
- The date and time of the last dose of the study medication.
- Full drug accountability information, including the number of study medication tablets that the subject took. Evaluate for the possibility that the subject took an incorrect dosage of medication within a few days of the convulsion.
- Was the tablet taken intact or was it crushed, chewed, etc.?
- The presence of any of the following at the time of the convulsion: eating disorders, changes in diet, and/or fever and dehydration.
- Any previous history of convulsions (including an early history of febrile seizures), accompanied by a description of the frequency and intensity. Evaluate for the possibility that partial convulsions may have occurred in the past but were not recognized as such.
- Any predisposing factors such as previous head trauma not recognized previously.
- Any family history of convulsions.
- Any alcohol consumption by the subject within the week preceding the event.
- The use of all concomitant medications, including sedatives/hypnotics (eg, benzodiazepines, barbiturates). Collect dosing information along with product names.
- Any concurrent use of illicit drugs.

- A urine sample for illicit drug use and a blood alcohol level should be obtained as soon as possible after the convulsion has occurred.
- Document any electrolyte abnormalities or other signs of systemic illness not otherwise evident. Other pertinent laboratory values that should be recorded include the subject's electrolyte panel results, blood urea nitrogen, creatinine, complete blood count with differential, and blood glucose level.

AEs of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.9.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE.

If a subject is noted to have ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator must contact the trial clinician or its delegates or designee (contact information may be found in Annex 1) for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.11 must also be performed.

10.2.10Safety Reporting to Investigators, IRBs or IECs, 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, investigators/head of the study site and IRBs or 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 report 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 study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definitions of analysis variables, and analysis methodologies 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.

11.1.1 Analysis Sets

11.1.1.1 Safety Analysis Set

The safety analysis set will be defined as all subjects who received at least 1 dose of study drug.

11.1.1.2 PK Analysis Set

The PK analysis set will be defined as all subjects who received at least 1 dose of study drug and had at least 1 estimable PK parameter.

11.1.1.3 CCI [redacted]

CCI [redacted]

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for each of Part 1 and Part 2 using the safety analysis set.

11.1.3 PK Analysis

The following analyses will be conducted using the PK analysis set.

Concentrations of TAK-935 and its metabolite M-I in plasma will be summarized in each of Part 1 and Part 2 by cohort over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing. Plasma PK parameters will be calculated using noncompartmental modeling and summarized by cohort and day using descriptive statistics. Dose proportionality in plasma PK parameters (C_{max} and AUCs) will be assessed graphically for those parameters in Part 1. Additional analyses will be included if appropriate.

11.1.4 CCI [redacted]

CCI [redacted]

CCI [redacted]

11.1.5 Safety Analysis

A summary will be provided for Part 1 and Part 2 separately. In Part 1, subjects from different cohorts who received placebo will be pooled together to form one placebo group. Analyses will be conducted using the safety analysis set.

11.1.5.1 AEs

A TEAE is defined as an AE that occurs on or after the start of study drug administration. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and tabulated by the system organ class (SOC) and the preferred term (PT). Percentage of subjects who experience at least 1 TEAE (the primary endpoint of the study) will be calculated within the following analyses.

- The frequency of all TEAEs
- The frequency of drug-related TEAEs
- The frequency of TEAEs by intensity
- The frequency of drug-related TEAEs by intensity
- The frequency of TEAEs leading to study drug discontinuation
- The frequency of serious TEAEs

CCI [redacted]

CCI [redacted]

11.1.5.4 CCI [redacted]

CCI [redacted]

CCI

[redacted]

11.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned. Section 6.2 describes the blinded safety and PK reviews which will take place after completion of each cohort and prior to the next dose escalation stage in the study.

11.3 Determination of Sample Size

The sample sizes of 8 subjects for each of the cohorts in Part 1 and 9 subjects for Part 2 (Part 1: 6 active 2 placebo in each cohort, Part 2: 6 active 3 placebo as total) are considered to be sufficient for the evaluation of safety, tolerability, and PK of each cohort. Sample sizes were not based on statistical power considerations.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, trial drug, subject medical records, informed consent documentation, 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.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial 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 or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

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.

12.3 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, U.S. Food and Drug Administration [FDA], Medicines and Healthcare products Regulatory Agency [MHRA], Pharmaceuticals and Medical Devices Agency [PMDA]). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 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 International Conference on Harminsation (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 A. The principles of Helsinki are addressed through the protocol and through appendices containing investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local 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 or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC 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 or IEC for approval. The IRB's or IEC'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 or IEC 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 ship drug/notify 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 trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC 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 or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC 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 or IEC and Sponsor.

13.2 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 or IEC 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 or IEC 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 or IEC. 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 analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify Sponsor of consent withdrawal.

13.3 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 study database or documentation via a unique identification 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 identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs 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 13.2).

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).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 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 clinical 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 Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 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, the sponsor 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 facility names and city, country, and recruiting status will be registered and available for public viewing.

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.

13.4.3 Clinical Trial Results Disclosure

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

13.5 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.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

A contact information list (Protocol Annex 1) will be provided to each study site separately.

14.1.2 Investigator Agreement

An agreement will be provided to each study site separately.

14.1.3 Study-Related Responsibilities

A contact information list (Protocol Annex 1) will be provided to each study site separately.

14.1.4 List of Abbreviations

Term	Definition
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUEC	area under the effect-time curve
BID	twice daily
BMI	body mass index
BP	blood pressure
CH24H	cholesterol 24-hydroxylase
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
CNS	central nerve system
C-QTc	concentration-QTc
C-SSRS	Columbia Suicide Severity Rating Scale
DEE	developmental epileptic encephalopathies
CCI	CCI
eCRF	electronic case report form
E_{max}	maximum drug-induced effect
E_t	observed effect at time t
FDA	U.S. Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HR	heart rate

Term	Definition
ICH	International Conference on Harminsation of Technical Requirements for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
LFT	liver function test
MD	multiple doses
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMSE	mini mental state examination
MR	metabolic ratio
OTC	over the counter
PD	pharmacodynamics
PGx	pharmacogenomics
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred Term
QD	once daily
QTcF	QT interval with Frederica correction method
R_{ac}	accumulation ratio
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
24HC	24*S*-hydroxycholesterol

15.0 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 conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic)

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

The Sponsor or its designee will supply investigative 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.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

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.

The following data will not be recorded in the eCRF:

- PD results
- PGx results
- Laboratory results
- CCI [redacted]
- CCI [redacted]

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must e-sign.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. 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.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 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, 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 Clinical Study Site Agreement between the investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

1. World Health Organization. Epilepsy Fact Sheet N°999. Published October 2012. Accessed 13 December 2013. Available at: http://www.who.int/mediacentre/factsheets/fs999/en/.
2. Centers for Disease Control and Prevention. Targeting epilepsy: Improving the lives of people with one of the nation's most common neurological conditions at a glance 2011. Updated 06 June 2011. Accessed 16 January 2014. Available at: http://www.cdc.gov/chronicdisease/resources/publications/AAG/epilepsy.htm.
3. National Institute of Neurological Disorders and Stroke. Epilepsy research benchmarks progress report 2007 – 2012. National Institute of Neurological Disorders and Stroke. Updated 23 December 2013. Accessed 16 January 2014. Available at: http://www.ninds.nih.gov/research/epilepsyweb/benchmarks_2007-2012progress.pdf.
4. McNamara JO. Pharmacotherapy of the epilepsies. In: Brunton LL, editor. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York, NY: McGraw-Hill; 2006; Chapter 19, p. 501-26.
5. Xie C, Lund EG, Turley SD, Russell DW, Dietschy JM. Quantitation of two pathways for cholesterol excretion from the brain in normal mice and mice with neurodegeneration. J Lipid Res 2003;44(9):1780-9.
6. Lund EG, Xie C, Kotti T, Turley SD, Dietschy JM, Russell DW. Knockout of the cholesterol 24-hydroxylase gene in mice reveals a brain-specific mechanism of cholesterol turnover. J Biol Chem 2003;278(25):22980-8.
7. Russell DW, Halford RW, Ramirez DM, Shah R, Kotti T. Cholesterol 24-hydroxylase: an enzyme of cholesterol turnover in the brain. Annu Rev Biochem 2009;78:1017-40.
8. Cartagena CM, Ahmed F, Burns MP, Pajoohesh-Ganji A, Pak DT, Faden AI, et al. Cortical injury increases cholesterol 24S hydroxylase (Cyp46) levels in the rat brain. J Neurotrauma 2008;25(9):1087-98.
9. Bogdanovic N, Bretillon L, Lund EG, Diczfalusy U, Lannfelt L, Winblad B, et al. On the turnover of brain cholesterol in patients with Alzheimer's disease. Abnormal induction of the cholesterol-catabolic enzyme CYP46 in glial cells. Neurosci Lett 2001;314(1-2):45-8.

17.0 APPENDICES

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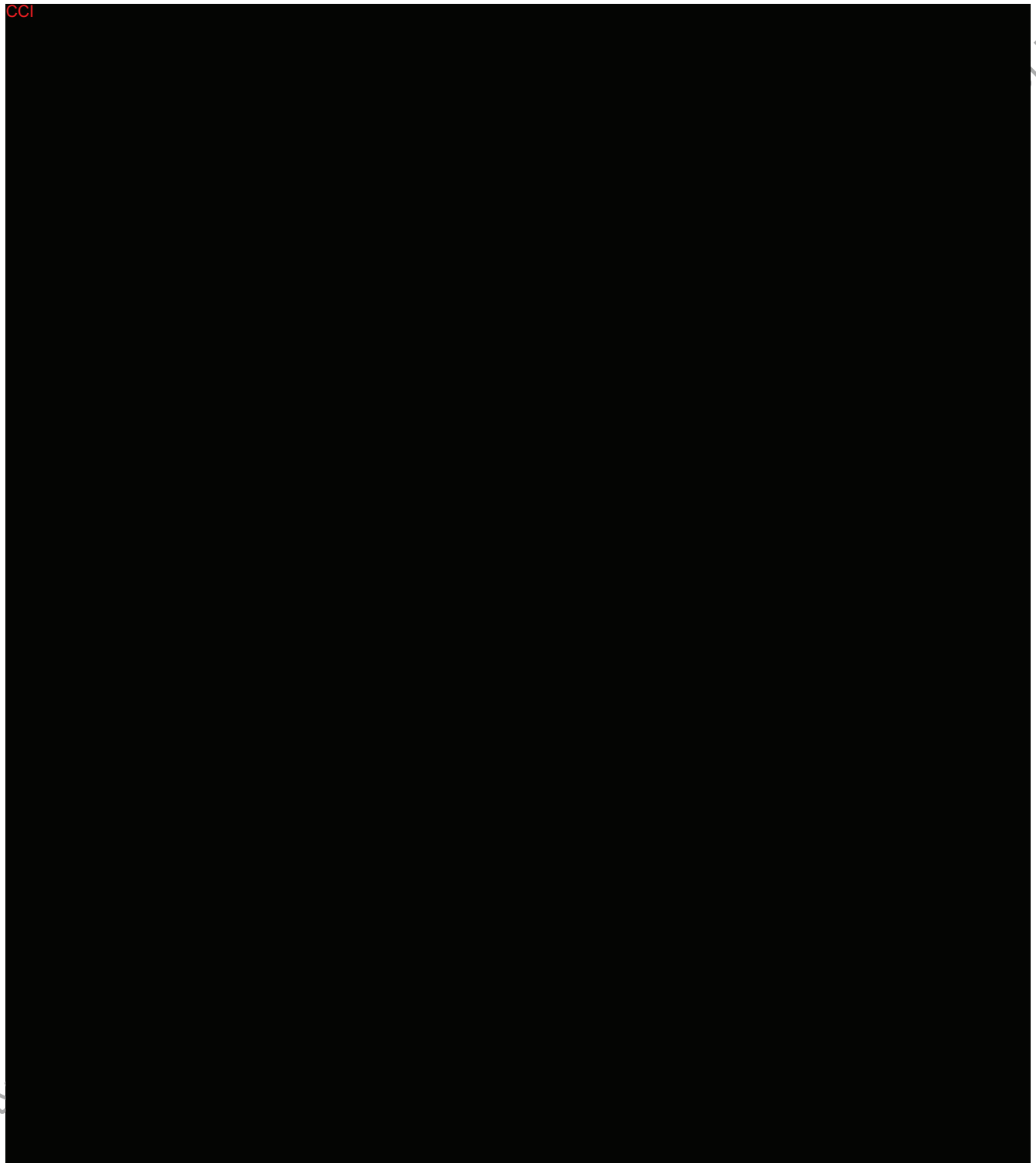

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A Randomized, Double-blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Ascending Dose and Multiple Doses with Titration of TAK-935 in Healthy Japanese Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date
PPD		