Title: A Phase 1 Study of TAK-925 to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of a single dose of TAK-925 in Healthy Adult and Elderly Volunteers and Patients with Narcolepsy

NCT Number: NCT03332784

Protocol Approve Date: 06-Mar-2018

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1 Study of TAK-925 to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of a single dose of TAK-925 in Healthy Adult and Elderly Volunteers and Patients with Narcolepsy

Phase 1 Study of TAK-925 in Healthy Adult and Elderly Volunteers and Patients with Narcolepsy

Study Identifier: TAK-925-1001

Compound: TAK-925 (Research Name: TAK-925 iv)

Date: 06 March 2018

Version/Amendment Number: Amendment 2

Amendment History

Date	Amendment Number	Region
11 September 2017	First Edition	all sites
22 January 2018	Amendment 1	all sites
06 March 2018	Amendment 2	all sites

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-925
Study Identifier: TAK-925-1001	**Phase:** 1
Protocol Title: A Phase 1 Study of TAK-925 to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of a single dose of TAK-925 in Healthy Adult and Elderly Volunteers and Patients with Narcolepsy	

Trial Design:

This study consists of two parts: Part 1 and Part 2.

Part 1 is an alternating panel, randomized, double-blind, placebo-controlled, crossover study to assess the single rising dose safety, tolerability and pharmacokinetics (PK) of a single rising dose of TAK-925 in healthy adult and elderly volunteers. In Part 1, the safety, tolerability and the PK including the concentration in the cerebrospinal fluid (CSF) at a single dose of TAK-925 in healthy adult volunteers will be also evaluated in an open cohort.

Part 2 is a sequential panel, randomized, double-blind (unblended for the sponsor), placebo-controlled, 2-period crossover study to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of one or more dose levels of TAK-925 vs. placebo in patients with type 1 narcolepsy.

(1) Part 1

Part 1 of the study will enroll 16 healthy adults into two separate cohorts of 8 subjects each, Cohort 1 and Cohort 2. In Cohort 3, 8 healthy elderly will be enrolled. In Cohorts 1 and 2 consisting of 8 subjects each, 6 subjects will receive TAK-925 and 2 subjects will receive placebo, assigned randomly in each dosing period (each period is composed of a single dose level), and 2 subjects each in Cohorts 1 and 2 will be randomly assigned to Groups A to H. To assess the safety, tolerability, and PK of TAK-925 including concentration of TAK-925 in CSF, 4 healthy adults will be enrolled as Cohort 4.

Administration of the study drug in Cohorts 1 and 2 will be performed alternately, with at least a 3-day interval between the cohorts and with a 7-day interval as well as more than 5 times the terminal half-life ($t_{1/2}$) of TAK-925 within the same cohort. Each subject will be given the study drug a maximum of three times.

The summary of the study design including the starting dose and the target plasma concentrations of TAK-925 for each panel are shown in Figure 2.a.

Once the safety and tolerability in healthy adults has been confirmed, a dose level that is not higher than that investigated in healthy adults will be evaluated in the healthy elderly in Cohort 3.

Additionally, the concentration of TAK-925 in the CSF will be evaluated in healthy adults in Cohort 4.

TAK-925 will be administered as an intravenous (IV) infusion over a 9 hour period.

The first dose level cohort (Cohort 1, Dose Level 1) is designed to obtain the safety and tolerability information when a single dose of TAK-925 is administered as well as to obtain the information on the pharmacokinetic parameters that will determine the dosing regimen (infusion rate) and doses in the subsequent periods in Part 1. For example, if the time to achieve a steady state at a constant intravenous infusion rate is too long, and if the initial dose is safe and well tolerated, the infusion rate for the first 2 hours may be accelerated to achieve a steady state earlier in the subsequent periods. In Cohort 1 Dose Level 1, a small number of subjects will be given the study drug first as a sentinel group. One subject each in the sentinel group (two subjects) will receive either TAK-925 or placebo first prior to the remaining six subjects and those remaining 6 subjects will be dosed at least two hours after the sentinel group was dosed. In Cohort 3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort (in the event that a cohort is added) following Cohort 2 Dose Level 2, all subjects should not receive TAK-925 simultaneously. (such that 4 subjects will be dosed at first time, and if there are no safety issues, then the remaining 4 subjects will be dosed about 1 hour later.)

Doses following Cohort 1 Dose Level 1 will be determined depending on the safety, tolerability and available PK data

obtained from the previous doses. After evaluating the safety, tolerability and PK in Cohort 1 Dose Level 1, dosing in Cohort 2 Dose Level 2 will be commenced. After evaluating the safety, tolerability and PK in Cohort 2 Dose Level 2, dosing in Cohort 1 Dose Level 3 will be commenced. After evaluating the safety, tolerability and available PK data in Cohort 1 Dose Level 3, Cohort 2 Dose Level 4 will be commenced. In a similar fashion, Cohort 1 Dose Level 5 and Cohort 2 Dose Level 6 will be commenced. Not all the Cohorts should be run, and the dose may be higher or lower than or the same to that of prior cohort dose levels, or an intermediate dose between two prior doses.

In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 2 Dose Level 6, Healthy Adult Supplement Cohorts that will include 8 healthy adults per cohort (up to maximum of 4 additional cohorts that include 32 healthy adults) may be commenced without amendment of the protocol. The cohort names of S1 to S4 will be assigned for the Healthy Adult Supplement Cohorts. Six subjects will be randomly assigned to the TAK-925 group and 2 subjects to the placebo group, to evaluate the safety, tolerability and PK. In the Healthy Adult Supplement Cohort, the dose may be higher or lower than or the same to that of the prior cohort dose levels, or an intermediate dose between two prior doses.

In Cohort 3, 8 healthy elderly will be enrolled. Of these 8 subjects, six will be randomly assigned to the TAK-925 group and 2 to the placebo group. This cohort will be initiated after started with the dose of which the safety and tolerability has been established in healthy adults. In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 3, a maximum of 1 additional cohort for Healthy Elderly Supplement Cohort that enrolls 8 healthy elderly per cohort will be commenced without amendment of the protocol. The cohort name of R1 will be assigned for the Healthy Elderly Supplement Cohort. Six subjects will be randomly assigned to the TAK-925 group and 2 subjects to the placebo group, to evaluate the safety, tolerability and PK. InHealthy Elderly Supplement Cohort, the dose may be higher or lower than or the same to that of prior cohort dose levels, or an intermediate dose between two prior doses.

In Cohort 4, 4 healthy adults will be enrolled to evaluate the safety, tolerability and the CSF concentration of TAK-925 measured at one time point and the plasma concentration of TAK-925. In Cohort 4, subjects, study sites and the sponsor will not be blinded. This cohort will be initiated after the safety and tolerability of the dose to be evaluated in Cohort 4 has been established in healthy adults.

Cohort 3, Healthy Elderly Supplement Cohort and Cohort 4 may be started at the discretion of the sponsor, considering the status of Cohorts 1, 2 and Healthy Adult Supplement Cohort.

(2) Part 2

In Part 2, patients with type 1 narcolepsy will be enrolled in three cohorts: Cohorts 5 to 7. Part 2 is a 2-period crossover study to assess the safety, tolerability, PK and PD effects of a single dose of TAK-925. Part 2 may begin prior to the completion of Part 1. However, the dose to be used in Cohort 5 should be lower thanthe dose used in Part 1 as well as be lower than 1/3 of the maximum dose of TAK-925 of which the safety and tolerability has been already confirmed. If Cohort 3 is not completed prior to starting Part 2, subjects aged 56 years or older should not be enrolled in Cohorts 5, 6 and 7 until Cohort 3 is completed. The outline of the study design is shown in Figure 2.a.

In Cohorts 5 and 6, 4 subjects each will be enrolled, and TAK-925 or placebo will be intravenously infused for 9 hours on Day 1 and Day 3. Of 4 subjects in each cohort, 2 subjects each will be randomly assigned to one of the defined sequences (Groups I to L, TAK-925 may be given at one dose level in each cohort). In Cohort 7, a maximum of 12 patients with type 1 narcolepsy will be enrolled. Of a maximum of 12 patients, 6 each will be randomly assigned to Group M or Group N. The dose level to be used in Cohort 5 will be determined based on the safety, tolerability and PK data obtained from Part 1. After the safety, tolerability, PD effects (Maintenance Wakefulness Test : MWT) in Cohort 5 and available PK data have been investigated, dosing in Cohort 6 will be started using another 4 new subjects. The same trial design as Cohort 5 will be used in Cohort 6. The dose to be used in Cohort 6 will be discussed by the sponsor's unblinded team. The sponsor's unblinded team must not directly be involved in the execution of the study at a study site or directly contact the site. This team will review unblinded data on the safety, tolerability and PD effects (MWT) and available PK of TAK-925, and recommend a dose based on those data. The dose level to be used in Cohort 6 may be higher or lower than the one used in Cohort 5. Cohort 7 will be composed of up to 12 subjects. The dose and the number of subjects to be used in Cohort 7 will be recommended by the sponsor’s unblinded team on the basis of safety, tolerability, PD effects (MWT) obtained from Cohorts 5 and 6 and available PK data of TAK-925. The

dose may be higher or lower than the doses used in Cohorts 5 and 6, or intermediate dose between these cohorts.

Primary Objectives:

- To evaluate the safety and tolerability of TAK-925 when a single dose of TAK-925 is administered to healthy adult and elderly volunteers and patients with type 1 narcolepsy.
- To evaluate the PK of TAK-925 when a single dose of TAK-925 is administered to healthy adult and elderly volunteers and patients with type 1 narcolepsy.

Secondary Objectives:

- To evaluate PD effects (mainly, sleep latency in the MWT) of TAK-925 when a single dose of TAK-925 is administered to patients with type 1 narcolepsy.

Trial Subject Population:

Healthy adult and elderly volunteers and patients with type 1 narcolepsy

Planned Numberof Subjects:	**Planned Number of Study Sites:**
(1) Part 1 • Cohort 1: 8 subjects (cumulative total of 24 subjects) • Cohort 2: 8 subjects (cumulative total of 24 subjects) • Cohort 3: 8 subjects • Cohort 4: 4 subjects In the event that a cohort is added, a maximum of 5 cohorts (40 additional subjects) can be enrolled. (2) Part 2 • Cohort 5: 4 patients (cumulative total of 8 subjects) • Cohort 6: 4 patients (cumulative total of 8 subjects) • Cohort 7: A maximum of 12 patients (up to a cumulative total of 24 subjects)	(1) Part 1 1 study site (2) Part 2 2 study sites Total: 3 study sites
Dose Levels: • Dosage (1) Part 1 A single dose of TAK-925 will be administered intravenously for 9 hours on Day 1. (2) Part 2 A single dose of TAK-925 or placebo will be administered intravenously for 9 hours on Day 1 or Day 3 alternately. If placebo is given on Day 1, TAK-925 is to be given on Day 3. If TAK-925 is given on Day 1, placebo is to be given on Day 3. • Administration In Part 1, the starting dose (Cohort 1 Dose Level 1) of TAK-925 will be 7 mg. From Cohort 2 Dose Level 2 through Cohort 5 in Part 2, the dose will be determined based on the safety, tolerability and pharmacokinetic data obtained from the prior cohorts. In Cohorts 6 and 7 in Part 2, the dose will be determined based on the safety, tolerability, PD effects (MWT) obtained in Part 1 and the previous cohort and available pharmacokinetic data so far.	**Route of Administration:** IV

Duration of Treatment:	**Planned Trial Duration:**
(1) Part 1 A single administration on Day 1 for each cohort (2) Part 2 A single administration on Day 1 and Day 3 for each cohort (TAK-925 will be given only once)	(1) Part 1 Screening period (Cohort 1 Dose Level 1, Cohort 2 Dose Level 2, Cohorts 3 and 4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort) Days -28 to -2 Hospital admission day: Day -1 Treatment period: Day 1 and 2 Follow-up period: Day 7 (2) Part 2 Screening period: Days -42 to -2 Hospital admission day: Day -1 Crossover period: Day 1 to 4 Follow-up Period: Day 7

Main Criteria for Inclusion:

All Subjects

- Sex: Male and/or female
- A male subject who is nonsterilized and sexually active and has a female partner of childbearing potential agrees to use adequate contraception from the signing of informed consent to 12 weeks (84 days) after the last dose of study drug. The female partner of a male subject should also be advised to use adequate contraception (See Appendix B).

Healthy Adults (Cohort 1, 2, 4 and Healthy Adult Supplement Cohort)

- A subject who is a healthy adult, aged between 20 and 55 years, at the time of signing the informed consent form.
- A subject weighing at least 50 kg and has a body mass index (BMI) of 18.5 to 30 kg/m^2 at Screening.

The Healthy Elderly (Cohort 3 and Healthy Elderly Supplement Cohort)

- A subject who is a healthy elderly aged between 65 and 80 years at the time of signing the consent form.
- A subject weighing at least 40 kg and has a BMI of 18.5 to 30 kg/m^2 at Screening.

Patients with type 1 narcolepsy (Cohorts 5-7)

- A patient aged between18 and 80 years at the time of signing the consent form.
- A patient weighing at least 40 kg at Screening.
- Patients with type 1 narcolepsy: Those diagnosed with type 1 narcolepsy, as defined by the International Classification of Sleep Disorders, Third Edition (ICSD-3)
- A patient who is positive for HLA-DQB1*06:02
- Epworth Sleepiness Scale (ESS) score on Day -1 is ≥10
- A female patient of childbearing potential who is sexually active and has a nonsterilized male partner agrees to routinely use an adequate contraception from the time of signing the consent form throughout the study.

Main Criteria for Exclusion:

All Subjects

- Creatinine clearance (Ccr) of ≤50 mL/min at Screening or on hospital admission (Day -1)
- Blood pressure (BP) of ≥140 mmHg(systolic) or ≥ 90 mmHg(diastolic) at Screening, Day -1 or before study drug administration on Day 1, confirmed by repeated measurements of BP after resting in a supine position for approximately 10 or 30 minutes.
- A subject who has a risk of suicide according to the investigator's judgment based on the assessment of the Columbia Suicide Severity Rating Scale (C-SSRS) or has made a suicide attempt within 6 months before the start of study drug administration.
- A subject who has a current or past history of epilepsy, convulsion, tremor or related symptoms.
- A subject who has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, arteriovenous malformation.
- A subject who has known coronary artery disease, and a history of myocardial infarction (MI), angina, cardiac rhythm abnormality or heart failure.

Healthy Adult and The Healthy Elderly (Cohorts 1-4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort)

- A subject unwilling to stop smoking during the study period.
- A female subjects of childbearing potential who is sexually active (premenopausal and nonsterilized).
- A subject who has clinically significant sleep disorders (including sleep apnea syndrome and insomnia).

Healthy Adults (Cohort 4 only)

- A subject whose CSF was collected within 14 days prior to hospitalization (Day -1).
- A subject who has known hypersensitivity to anesthetics or medications used for CSF collection or lumbar puncture.
- A subject who has clinically significant vertebral deformities (scoliosis or kyphosis), which, in the opinion of the investigator, may interfere with lumbar puncture.
- A subject who has a clinically significant back pain and/or back injury.
- A subject who has a local infection at the puncture site.
- A subject who has thrombocytopenia or bleeding tendencies noted before the beginning of study procedures.
- A subject who has signs and symptoms of radiculopathy including in leg pain and paresthesia.
- A subject who has focal neurological deficit that might suggest an increase in intracranial pressure.
- A subject who has abnormal findings on ophthalmological examination/fundoscopy suggestive of raised intracranial pressure (eg, optic disc swelling/papilledema, uncontrolled hypertensive retinopathy).
- A subject who suffers from moderate to severe headaches requiring analgesics.

Patients with type 1 narcolepsy (Cohorts 5-7)

- A patient unwilling to quit smoking 40 minutes before the scheduled MWT and one hour before sleeping.
- A patient who has sleep disorder(s) associated with excessive sleepiness (including sleep apnea syndrome) other than narcolepsy.
- Excessive caffeine consumption (>400 mg/day) within seven days before hospital admission (Day -1).
- Use of drugs with stimulating or sedating properties, anti-parkinson drugs or anti-convulsant drugs within 7 days before the start of study drug administration or 5 times the half life of each drug. For selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, there should be a washout period (at least 5 times the elimination half-life of each drug or for 7 days, whichever is longer) prior to the start of study drug administration, and the administration should be discontinued with gradual dose reductions.

Main Criteria for Evaluation and Analyses:

The primary endpoints

- Safety and tolerability: adverse events, vital signs, body weight, 12-lead electrocardiogram (ECG) and clinical laboratory tests (hematology, serum chemistry and urinalysis)
- Pharmacokinetics: Plasma concentrations and pharmacokinetic parameters, urine pharmacokinetic parameters of TAK-925, and CSF concentrations and pharmacokinetic parameters of TAK-925 and its metabolites (CCI [redacted]).

The secondary endpoint

- The average sleep latency in the Maintenance Wakefulness Test (MWT)

Statistical Considerations:

Safety:

For Cohorts 1-2 and Healthy Adult Supplement Cohort, Cohort 3 and Healthy Elderly Supplement Cohort, Cohort 4, Part 2, the following analyses will be performed for each dose level using the safety analysis set.

A treatment emergent adverse event (TEAE) is defined as an AE that occurs on or after the start of study drug. TEAEs are tabulated by the number of all TEAEs, the drug-related TEAEs, the intensity of all TEAEs, the intensity of drug-related TEAEs, the TEAEs leading to study drug discontinuation, and the number of serious TEAEs. TEAEs will be coded into the System Organ Class (SOC) and the Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

For continuous variables, the observed values and the changes from baseline will be summarized for each scheduled sampling time using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post- baseline scheduled sampling time will be provided.

PK:

For Cohorts 1-2 and Healthy Adult Supplement Cohort, Cohort 3 and Healthy Elderly Supplement Cohort, Cohort 4, Part 2, the following analyses will be performed for each dose level using the PK analysis set.

Plasma and CSF concentrations of TAK-925 and its metabolites (CCI [redacted]) will be summarized for each scheduled sampling time using descriptive statistics.

Plasma, urine and CSF pharmacokinetic parameters of TAK-925 and its metabolites (CCI [redacted]) will be summarized using descriptive statistics.

PD:

The following analysis will be conducted using the PD analysis set.

For the average sleep latency in MWT in Part 2, descriptive statistics for the observed values will be provided by dose level. An analysis of variance (ANOVA) for crossover design with the observed value as a response, the dose level, the group and the period as factors will be conducted. The differences in the least square means between each dose level of TAK-925 and the placebo (each dose level of TAK-925 – the placebo) and the two-sided confidence intervals will be provided. Bayesian posterior probabilities that the mean differences are greater than the value (specified in the SAP) will be provided based on the Bayesian posterior distributions for the mean differences between each dose level of TAK-925 and the placebo (each dose level of TAK-925 – the placebo).

Sample Size Justification:

For Cohorts 1 to 3 in Part 1, 8 subjects (6 in TAK-925 group, 2 in placebo group) will be enrolled in each Cohort to evaluate the safety, tolerability and PK of TAK-925 when a single dose of TAK-925 is administered to healthy adults and the healthy elderly. If further investigation on the safety, tolerability and PK in healthy adults is needed after completion of Cohorts 1-2, a maximum of 4 additional cohorts (a total of 32 healthy adult subjects; 8 subjects [6 in TAK-925 group, 2 in placebo group] per cohort) may be enrolled. If further investigation on the safety, tolerability and PK in healthy elderly is needed after completion of Cohort 3, a maximum of 1 additional cohort (a total of 8 healthy elderly subjects [6 in TAK-925 group, 2 in placebo group] per cohort) may be enrolled.

For Cohort 4 in Part 1, 4 subjects will be enrolled to evaluate the safety, tolerability, PK of TAK-925 including the concentration of TAK-925 in the CSF when a single dose of TAK-925 is administered intravenously to healthy adults.

For Part 2, 4 patients each in Cohorts 5 and 6 and a maximum of 12 patients in Cohort 7 will be enrolled to evaluate the safety, tolerability, PK and PD effects of TAK-925 when a single dose of TAK-925 is administered intravenously to patients with type 1 narcolepsy. These sample sizes are not based on any effect size or obtained by the MWT statistical evidence.

2.0 STUDY SCHEMATIC

Figure 2.a Summary of the Study Design

<Part 1>

1. Cohorts 1 and 2 (Healthy Adults) and Cohorts S1-S4 (Healthy Adult Supplement Cohorts)

	Dose Level						
Cohort	1	2	3	4	5	6	7-10
1	7 mg		28 mg		112 mg		
2		14 mg		56 mg		134.4 mg	
S1-4							TBD

TBD=To be determined

1) Cohorts 1 and 2 will be implemented as alternating panel design during a maximum of 3 dosing periods.
2) The doses of Dose Levels 7-10 are planned as follows. However based on the available the safety, tolerability and PK data, there is a possibility that the dose may be appropriately increased or decreased within the range not exceeding 420 mg. Dose Level 7: 180 mg, Dose Level 8: 240 mg, Dose Level 9: 320 mg, Dose Level 10: 420 mg.
3) See Figure 9.a for randomization scheme for Dose Levels 1-6.
4) In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohorts 1 and 2, a maximum of 4 additional cohorts that include 32 healthy adults can be implemented without amendment of the protocol.
5) Double-blind. Each Cohort consists of 8 subjects. Of 8 subjects, 6 will receive TAK-925 and 2 will receive placebo.

2. Cohort 3 (The healthy elderly) and Cohort R1 (The Healthy Elderly Supplement Cohort)

Cohort 3/Cohort R1
112 mg/TAK-925 TBD
Placebo

1) Double-blind. Each Cohort consists of 8 subjects. Of 8 subjects, 6 will receive TAK-925 and 2 will receive placebo.

3. Cohort 4 (Healthy adults)

Cohort 4
112 mg

1) Unblinded. Cohort 4 consists of 4 subjects.

<Part 2>

4. Cohorts 5-7 (Patients with narcolepsy)

Cohort 5	
Period 1	Period 2
TAK-925 TBD	Placebo
Placebo	TAK-925 TBD

cohort transition →

Cohort 6	
Period 1	Period 2
TAK-925 TBD	Placebo
Placebo	TAK-925 TBD

cohort transition →

Cohort 7	
Period 1	Period 2
TAK-925 TBD	Placebo
Placebo	TAK-925 TBD

1) Double-blind (the sponsor is unblinded), 2x2 crossover study.
2) See Figure 9.d for randomization scheme.
3) Cohorts 5 and 6 consist of 4 subjects each. 2 subjects each in a group will be randomized to each sequence. On Days 1 and 3, TAK-925 or placebo will be administered intravenously to these subjects for 9 hours.
   Cohort 7 consists of a maximum of 12 subjects, and 6 subjects each at maximum in a group will receive TAK-925 or placebo intravenously for 9 hours on Days 1 and 3, TAK-925 or placebo will be administered intravenously to these subjects for 9 hours.
4) Each Cohort will be investigated in different patients.

3.0 SCHEDULE OF STUDY PROCEDURES

Part1(Cohorts 1-4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort)

	Screening Day -28 to Day-2 (a)	Day -1	Predose Day 1	Day1	Day 2/Early Termination	Follow-Up Visit (b)
Administrative Procedures						
Informed Consent	X					
Inclusion/Exclusion Criteria	X		X (a)			
Medical History/Demographics	X	X				
Prior and Concomitant Medication	---------- Continuous Monitoring ----------					
Clinical Procedures/Assessments						
Physical Examination	X		X		X	X
Height	X					
Weight	X	X			X	X
BMI	X					
Vital Signs (pulse rate, SBP and DBP) (c)	X	X	X	X	X	X
Vital Signs (respiratory rate, body temperature) (d)	X		X	X	X	
12-Lead Electrocardiogram (e)	X	X		X	X	
C-SSRS	X				X	
TAK-925/Placebo Administration				X		
Adverse Events	---------- Continuous Monitoring ----------					
Laboratory test/Assessments						
Hematology	X	X			X	X
Urinalysis	X	X			X	X
Serum Chemistry	X	X			X	X
Urine Drug Screen, Cotinine Testing, Alcohol Testing	X					
Hepatitis Screen, HIV Antigen-Antibody Detection Assay, Syphilis Serum Reaction Test	X					

	Screening Day -28 to Day-2 (a)	Day -1	Predose Day 1	Day1	Day 2/Early Termination	Follow-Up Visit (b)
Blood Collection for Retained Samples and Pharmacogenomic Research				X (a)		
Pharmacokinetic Evaluations						
Blood Sample Collection for Pharmacokinetic Evaluations of TAK-925 and its Metabolites (CCI [redacted]) (f)			X	X	X	
Urine Sample Collection for Pharmacokinetic Evaluations of TAK-925 and its Metabolites (CCI [redacted]) (g)			X	X	X	
CSF Sample Collection for Pharmacokinetic Evaluations of TAK-925 and its Metabolites (CCI [redacted]) (h)				X		
Other						
Hospitalization		X (i)	X	X	X	

Abbreviations: BMI=body mass index, C-SSRS=The Columbia Suicide Severity Rating Scale, HIV=human immunodeficiency virus, CSF= cerebrospinal fluid

(a) This will be performed once only in each subject during the study period. Blood samples for pharmacogenomic research will be collected after the start of study drug administration.

(b) Follow-up visit will occur on Day 7 (±2).

(c) Vital signs (pulse rate, SBP and DBP) will be measured:
Screening period
Day -1: Measurements will be performed at 15:00 and 19:00, totally 2 times. (No Measurement in Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort)
Day1: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours after the start of infusion
On Day -1 and Day 1 in Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort, measurement will be performed at following the same time point.
Day -1: -24, -23.75, -23.5, -23.25, -23, -22.5, -22, -21.5, -21, -20.5, -20, -19, -18, -17, -16, -15, -14, -13 and -12 hours after the start of infusion.
Day 1: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after the start of infusion.
On Day 1, Measurement ats 24 hours after the start of infusion will also be performed.
Follow-Up visit.
Orthostatic BP (1 and 5 minutes after standing up) will also be measured after the above vital signs were measured 1, 2 and 4 hours after the start of infusion (only on Day 1). Each BP will be measured after lying on a bed with the head of the bed up to 30 degrees and taking a rest for 5 minutes, using the same arm. BP will be measured predose, at every 15 minutes for the first one hour, then at every 30 minutes for 1 to 4 hours and then at every 1 hour for 4 to 12 hours after the start of infusion, and at 24 hours thereafter. In Cohort 4, BP will be basically measured after lying on a bed with the head of the bed up to 30 degrees, however BP can be measured with the bed flat except for the case of lumbar puncture for CSF sampling. In the event that blood sampling for PK are scheduled

at the same time as BP measurement, the blood sampling for PK should be performed first.

(d) Vital signs (respiratory rate, body temperature) will be measured during the screening period, 1 hour predose on Day 1, and 5 hours after the start of infusion on Day 1 and on Day 2.

(e) 12-Lead ECG will be measured during the screening period, on Day -1 and between 2 and 9 hours after the start of infusion on Day 1 and on Day 2.

(f) Blood samples for TAK-925 PK analysis will be collected: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 9 hours after the start of infusion, and 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 10 and 15 hours after the end of infusion. However, Dose Levels 1 and 2 of Cohorts 1 and 2 will be excluded at 10 hours after the end of infusion.

(g) Urine samples for TAK-925 PK analysis will be collected: Predose (spot urine), 0-9 hours after the start of infusion, and 0-3, 3-6, 6-15 hours after the end of infusion.

(h) In Cohort 4 only, CSF samples for PK analysis of TAK-925 and its metabolites will be collected: 6 hours after the start of infusion

(i) Hospitalization from Day -2 may be allowed for Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort as needed.

Part 2

	Screening Day -42 to Day-2	Day -1	Predose Day 1	Day 1	Day 2	Predose Day 3	Day 3	Day 4/ Early Termination	Follow-Up Visit (a)
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria (b)	X	X	X(c)						
Medical History/Demographics	X	X							
HLA DQB1 *06:02 Typing (d)	X								
Washout of Prior Medications (e)	X								
Prior and Concomitant Medication	---------- Continuous Monitoring ----------								
Clinical Procedures/Assessments									
Physical Examination	X	X	X		X	X		X	X
Height	X								
Weight	X	X			X			X	X
BMI	X								
Vital Signs (pulse rate, SBP and DBP) (f)	X	X	X	X	X	X	X	X	X
Vital Signs (respiratory rate, body temperature) (g)	X		X	X	X	X	X	X	
12-Lead Electrocardiogram (h)	X	X		X	X		X	X	
C-SSRS	X							X	
TAK-925/Placebo Administration				X			X		
CCI [redacted]									
MWT (Maintenance of Wakefulness Test) (i)		X		X			X		
CCI [redacted]									
CCI [redacted]									
CCI [redacted]									
Adverse Events	---------- Continuous Monitoring ----------								

	Screening Day -42 to Day-2	Day -1	Predose Day 1	Day 1	Day 2	Predose Day 3	Day 3	Day 4/ Early Termination	Follow-Up Visit (a)
Laboratory test/Assessments									
Hematology	X	X			X (m)	X		X (m)	X
Urinalysis	X	X			X (m)	X		X (m)	X
Serum Chemistry	X	X			X (m)	X		X (m)	X
Urine Drug Screen	X								
Hepatitis Screen, HIV Antigen-Antibody Detection Assay, Syphilis Serum Reaction Test	X								
Blood Collection for Retained Samples and Pharmacogenomic Research							X (n)		
Pregnancy Test (o)	X								
Pharmacokinetic Evaluations									
Blood Sample Collection for Pharmacokinetic Evaluations of TAK-925 and its Metabolites (CCI) (p)			X	X	X	X	X	X	
Other									
Hospitalization		X	X	X	X	X	X	X	

Abbreviations: CCI , CCI , C-SSRS=The Columbia Suicide Severity Rating Scale; HIV=Human immunodeficiency virus, CSF= Cerebrospinal fluid

(a) Follow-up visit will occur on Day 7 (±2).

(b) To confirm thatthe subject meets the inclusion criteria or does not meet the exclusion criteria, the CCI or the multiple sleep latency test (MSLT) (including the number of sleep-onset REM periods [SOREMPs]) can be performed as a study procedure (s) at the screening visit, if necessary.

(c) Day 1 only

(d) This genotyping will be performed only for subjects of whom the presence or absence of HLA-DQB1*06:02 cannot be identified by his/her medical records.

(e) Washout of prior medications may require for about 7 days of hospital stay. The need for hospital stay and its duration can be determined by the investigators.

(f) Vital signs (pulse rate, systolic and diastolic BP) will be measured:
Screening period
Day -1: Measurements will be performed at 15:00 and 19:00, totally 2 times.
Day 1 and Day 3: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after the start of the infusion.

Day 2 and Day 4: 24 hours after the start of infusion
Follow-up visit.
At 1 hour after the start of infusion, orthostatic BP (at 1 and 5 minutes after standing up) will also be measured after the above vital signs were measured. Each BP will be measured after lying on a bed with the head of the bed up to 30 degrees and taking a rest for 5 minutes, using the same arm. BP will be measured predose and at every 15 minutes for the first 1 hour, then at every 30 minutes for 1 to 2 hours, then at every 1 hour for 2 to 12 hours after the start of infusion, and at 24 hours thereafter. In the event that blood sampling for PK are scheduled at the same time as BP measurement, the blood sampling for PK should be performed first. In the event that BP is scheduled at the same time as the MWT procedures, BP measurement should be performed both before and after the MWT procedures. During the MWT procedures, BP may be measured in a sitting position, if necessary.

(g) Vital signs (respiratory rate, body temperature) will be measured during the screening period, within 1 hour predose on Day 1 and Day 3, at 5 hours after the start of infusion on Day 1 and Day 3, and at the same time period on Day 2 and Day 4.
(h) 12-Lead ECG will be measured during the screening period, on Day -1, between 2 and 9 hours after the start of infusion on Day 1 and Day 3, and at the same time period on Day 2 and Day 4.
(i) MWT procedures will be conducted:
Day -1: MWT procedures will be completed by 17:00.
Day 1 and 3: MWT procedures will be conducted at 10:00, 12:00, 14:00 and 16:00 following the start of infusion dosing at 7:45.
(j) CCI
ESS will be conducted on Day -1 only.
CCI
(k) CCI
(l) CCI
(m) These tests will be conducted using the blood samples collected at the same time point on Day 2 and Day 4.
(n) Blood sampling will be performed only once for each subject after the start of infusion on Day 3.
(o) Only for female subjects of childbearing potential
(p) Blood samples for the PK evaluations of TAK-925 (and its metabolites) will be collected on Day 1, Day 2, Day 3 and Day 4: Predose, 1, 2, 4, 6 and 9 hours after the start of infusion, and 0.17 0.5, 1, 2 and 15 hours after end of infusion, just before sleep and right after wake-up.

4.0 INTRODUCTION

4.1 Background

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness and cataplexy. Narcolepsy is a relatively rare disease beginning in prior to, during and after puberty, with a prevalence rate of 0.16-0.18% (1 in 600 people) in Japan [1] . Narcolepsy is reported to be caused by a decrease in the level of orexin (OX) peptides with dropouts of orexin-producing neurons [2][3]. OX has been shown to significantly affect individual's ability to maintain an appropriate balance between sleep and wakefulness [4].

Patients with narcolepsy suffer from disadvantages in various aspects of daily life, especially because of excessive daytime sleepiness. This reduces the patient's ability to work and learn effectively and results in a severely impaired quality of life (QOL). Moreover, patients with narcolepsy have a high risk of mistakes during working, loss of employment, traffic accidents and occupational injuries, and may suffer serious disadvantages in their social lives as well as in their QOLs [5].

The treatment for narcolepsy is intended "to minimize any disadvantages due to excessive daytime sleepiness with minimum medication quantities and to inhibit undesirable side effects and the development of drug dependence" in accordance with the Guidelines on the Diagnosis and Management of Narcolepsy [5]. Therapeutic drugs for narcolepsy currently approved in Japan are modafinil, methylphenidate, pemoline, methamphetamine and clomipramine. Among these drugs, methamphetamine is designated as a stimulant and has a risk of drug addiction. Therefore, it is not recommended as a treatment option in the Guidelines on the Diagnosis and Management of Narcolepsy. For excessive daytime sleepiness, modafinil is the first-line drug, however, as the effect is moderate, there exist a certain number of patients with unsatisfactory response [6][7]. Methylphenidate and pemoline also inhibit excessive daytime sleepiness, but the development of drug addiction has become a problem. Consequently, methylphenidate and pemoline can only be used when modafinil is not effective [5]. Although clomipramine is the only drug approved for the treatment of cataplexy, continuous use leading to reduced therapeutic effects has been concerned [5]. These drugs are symptomatic treatment that do not directly have effects on the pathophysiology of narcolepsy and therefore, the effects themselves may be limited and, conventional therapies are almost impossible to improve the level of sleepiness to the normal range, especially for excessive daytime sleepiness. In addition, current treatments only exert an effect on either excessive daytime sleepiness or cataplexy. This results in the need for combination therapies in patients with both symptoms [8]. Thus, a novel drug that directly tackles the pathological mechanism of narcolepsy to meet this high medical need and is effective in treating both excessive daytime sleepiness and cataplexy with high efficacy.

TAK-925 is an orexin 2 receptor (OX2R)-selective agonist produced by Takeda Pharmaceutical Company Limited (TPC). Orexin is a neuropeptide which exerts its action via two different types of orexin receptors (OX1R and OX2R). The role of orexin in humans has not been fully identified, but animal studies conducted so far indicated that it influenced a variety of behaviors, such as feeding, sleep/wakefulness, reward/dependence, and emotion/stress[4]. The physiological action

of each receptor has also been identified, which demonstrated that stabilization of sleep and wakefulness was mainly involved in OX2R [9], while the development of drug addiction is involved in OX1R [10].

In non-clinical studies in mice and monkeys, TAK-925 demonstrated high specificity for OX2R, and activated OX2R, penetrated the blood-brain barriers of these animals to reach theie brains and increased the duration of wakefulness, and when TAK-925 was given to mouse models of narcolepsy-like symptoms[11], it mitigated the fragmentation of waking/sleep and cataplexy-like symptoms.

Consequently, TAK-925 may reduce the risk of addiction induced by activation of OX1R and improve both symptoms of excessive daytime sleepiness and cataplexy through its selective effects on OX2R. Currently, no drug with similar mechanism has been tested in humans, and therefore, TAK-925 would be the first drug to be developed in this class in the world, potentially providing an innovative treatment option to patients with narcolepsy, which had been impossible with preexisting drugs.

4.2 Rationale for the Proposed Study

In non-clinical studies using mice and monkeys, TAK-925 demonstrated a high specificity for OX2R and activates OX2R, penetrated the blood-brain barriers of these animals to reach the brains and increased the duration of wakefulness, and when TAK-925 was administered to mouse models of narcolepsy-like symptoms (orexin/ataxin-3 transgenic mice), it improved narcolepsy-like symptoms such as fragmentation of sleep and wakefulness, and cataplexy-like symptoms. The results of non-clinical studies of TAK-925 revealed no significant toxicity findings to be concerned about when TAK-925 is assumed to be administered to humans. Results of the preclinical toxicology and safety studies also support the administration of TAK-925 in humans.

This phase 1 single dose study was designed to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) effects of TAK-925 when it is administered as a single dose to healthy adults, the healthy elderly and patients with narcolepsy.

4.3 Benefit/Risk Profile

There are no benefits for the subjects of the present study other than receiving medical examinations to obtain information about their overall health conditions, but it is possible that the information obtained from the present study will become beneficial to the patients with narcolepsy in the future.

With respect to the risks of subjects, safety information is limited to the data obtained from non-clinical studies.

CCI

[redacted]

CCI

CCI The details of the management of BP increase are provided in Section 7.6. As TAK-925 is expected to have a short half-life, discontinuation of TAK-925 will lead to a rapid decline in BP if a tolerance does not develop with continued study drug infusion.

Please refer to the investigator's brochure for detailed information of TAK-925.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed based on the following hypotheses:

- One or more safe and well-tolerated IV infusion TAK-925 dosage levels will achieve a Ceoi (plasma concentration at the end of infusion) greater than or equal to the threshold estimated to be required for efficacy (expected to be 20-30 ng/ml).
- At least 1 dose of TAK-925 shows a more significant wake-promoting effect when measured by the mean sleep latency using the Maintenance Wakefulness Test (MWT) and is safer and better tolerated than placebo.

5.2 Trial Objectives

5.2.1 Trial Primary Objectives

- To evaluate the safety and tolerability of TAK-925 when a single dose of TAK-925 is administered to healthy adults, the healthy elderly and patients with type 1 narcolepsy.
- To evaluate the PK of TAK-925 when a single dose of TAK-925 is administered to healthy adults, the healthy elderly and patients with type 1 narcolepsy.

5.2.2 Trial Secondary Objective

- To evaluate the PD effects of TAK-925 (mainly, sleep latency in the MWT) when a single dose of TAK-925 is administered to patients with type 1 narcolepsy.

5.2.3 Trial Exploratory Objectives

CCI

5.3 Endpoints

5.3.1 Primary Endpoints

- Safety and tolerability: adverse events, vital signs, body weight, 12-lead electrocardiogram (ECG) and clinical laboratory tests (hematology, serum chemistry and urinalysis)
- Pharmacokinetics (PK): plasma concentrations and pharmacokinetic parameters, urine pharmacokinetic parameters and cerebrospinal fluid (CSF) concentrations and pharmacokinetic parameters of TAK-925 and its metabolites ([redacted]).

5.3.2 Secondary Endpoint

- The average sleep latency in the MWT

5.3.3 Exploratory Endpoints

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This study consists of two parts.

Part 1 is an alternating panel, randomized, double-blind, placebo-controlled, crossover study to assess the safety, tolerability and pharmacokinetics (PK) of a single rising dose of TAK-925 in healthy adult and elderly volunteers. In Part 1, the safety and tolerability, and the PK including the concentration in the cerebrospinal fluid (CSF) at a single dose of TAK-925 in healthy adult volunteers will be also evaluated in an open cohort.

Part 2 is a sequential panel, randomized, double-blind (unblinded for the sponsor), placebo-controlled, 2-period crossover study to assess the safety, tolerability, PK and PD of one or more dose levels of TAK-925 vs. placebo in patients with type 1 narcolepsy.

(1) Part 1

Part 1 of the study will enroll 16 healthy adults into two separate cohorts of 8 subjects each, Cohort 1 and Cohort 2. In Cohort 3, 8 healthy elderly will be enrolled. In Cohorts 1 and 2 consisting of 8 subjects each, 6 subjects will receive TAK-925 and 2 subjects will receive placebo, assigned randomly in each dosing period (each period is composed of a single dose level),and 2 subjects each in Cohorts 1 and 2 will be randomly assigned to Groups A to H. To assess the safety, tolerability, and PK of TAK-925 including CSF-PK of TAK-925, 4 healthy adults will be enrolled as Cohort 4.

Administration of the study drug in Cohorts 1 and 2 will be performed alternately, with at least a 3-day interval between the cohorts and with a 7-day interval as well as more than 5 times the terminal half-life ($t_{1/2}$) of TAK-925 within the same cohort. Each subject will be given the study drug a maximum of three times.

The first dose level cohort (Cohort 1, Dose Level 1) is designed to obtain the safety and tolerability information when a single dose of TAK-925 is administered as well as to obtain the information on pharmacokinetic parameters that will determine the dosing regimen (infusion rate) and doses in the subsequent periods in Part 1. For example, if the time required to achieve a steady state at a constant intravenous infusion rate is too long, if and the initial dose is safe and well tolerated, the infusion rate for the first 2 hours may be accelerated to achieve a steady state earlier in the subsequent periods. In Cohort 1 Dose Level 1, a small number of subjects will be given the study drug first as a sentinel group. One subject each in the sentinel group (two subjects) will receive either TAK-925 or placebo first prior to the remaining six subjects and those remaining 6 subjects will be dosed at least two hours after the sentinel group was dosed. In Cohort 2 Dose Level 2 and subsequent dose levels in Cohorts 1 and 2, Cohort 3, Healthy Adult Supplemental Cohort and Healthy Elderly Supplement Cohort (in the event that the cohort is actually added) receive TAK-925 or placebo simultaneously. (such that 4 subjects will be dosed at first, and if there are no safety issues, the remaining 4 subjects may be dosed about 1 hour later.)

Doses following Cohort 1 Dose Level 1 will be determined depending on the safety, tolerability and available PK of previous doses. After evaluating the safety, tolerability and PK in Cohort 1

Dose Level 1, dosing in Cohort 2 Dose Level 2 will be commenced. After evaluating the safety, tolerability and PK in Cohort 2 Dose Level 2, dosing in Cohort 1 Dose Level 3 will be commenced. After evaluation the safety, tolerability and available PK in Cohort 1 Dose Level 3, dosing in Cohort 2 Dose Level 4 will be commenced. In a similar fashion, dosing in Cohort 1 Dose Level 5 and Cohort 2 Dose Level 6 in a similar fashion. Not all the Cohorts should be run necessarily, and the dose may be higher or lower than or the same to that of prior cohort dose levels, or intermediate dose between two prior doses.

In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 2 Dose Level 6, Healthy Adult Supplement Cohorts that will include 8 healthy adults per cohort (up to 4 additional cohorts that include 32 healthy adults) may be commenced without amendment of the protocol. The cohort names of S1 to S4 will be assigned for Healthy Adult Supplement Cohort. Six subjects will be randomly assigned to the TAK-925 group and 2 subjects to the placebo group in a cohort, to evaluate the safety, tolerability and PK. In Healthy Adult Supplement Cohort, the dose may be higher or lower than or the same to that of prior cohort dose levels, or an intermediate between two prior doses.

In Cohort 3, 8 healthy elderly subjects will be enrolled. Of these 8 subjects, six will be randomly assigned to the TAK-925 group and 2 to the placebo group. This cohort will be initiated after started with the dose of which the safety and tolerability has been established in healthy adults. In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 3, a maximum of 1 additional cohort for Healthy Elderly Supplement Cohort that enrolls 8 healthy elderly per cohort will be commenced without amendment of the protocol. The cohort name of R1 will be assigned for the Healthy Elderly Supplement Cohort. Six subjects will be randomly assigned to the TAK-925 group and 2 subjects to the placebo group, to evaluate the safety, tolerability and PK. In Healthy Elderly Supplement Cohort, the dose may be higher or lower than or the same to that of prior cohort dose levels, or an intermediate dose between two prior doses.

In Cohort 4, 4 healthy adults will be enrolled to evaluate the safety, tolerability and the CSF concentration of TAK-925 measured at one time point and the plasma concentration of TAK-925. In Cohort 4, subjects, study sites and the sponsor will not be blinded. This cohort will be initiated after the safety and tolerability of the dose to be evaluated in Cohort 4 has been established in healthy adults.

Cohort 3, Healthy Elderly Supplement Cohort and Cohort 4 may be started at the discretion of the sponsor, considering the status of Cohorts 1, 2 and Healthy Adult Supplement Cohort. (Cohorts 3 and 4 may be implemented in parallel with Cohorts 1 and 2. The doses to be used in Cohorts 3 and 4 will be determined based on the available safety, tolerability and PK data, and nonclinical study results.)

(2) Part 2

In Part 2, patients with type 1 narcolepsy will be enrolled in three cohorts: Cohorts 5 to 7. Part 2 is a 2-period crossover study to assess the safety, tolerability, PK and PD effects of a single dose of TAK-925. Part 2 may begin prior to the completion of Part 1. However, the dose to be used in

Cohort 5 should be lower than the one used in Part 1 as well as be lower than 1/3 of the maximum dose of TAK-925 of which the safety and tolerability has been already confirmed. If Cohort 3 is not completed prior to starting Part 2, subjects aged 56 years or older should not be enrolled in Cohorts 5, 6 and 7 until Cohort 3 is completed.

In Cohorts 5 and 6, 4 subjects each will be enrolled, and TAK-925 or placebo will be intravenously infused for 9 hours on Day 1 and Day 3. Of 4 subjects in each cohort, 2 subjects each will be randomly assigned to one of the defined sequences (Groups I to L, TAK-925 may be given at one dose level in each cohort). A maximum of 12 patients with type 1 narcolepsy will be enrolled in Cohort 7. Of a maximum of 12 patients, 6 each will be randomly assigned to Group M or Group N. The dose level to be used in Cohort 5 will be determined based on the safety, tolerability and PK data obtained from Part 1. After the safety, tolerability, PD effects (MWT) in Cohort 5 and available PK have been investigated, dosing in Cohort 6 will be started using another 4 new subjects. The same trial design as Cohort 5 will be used in Cohort 6. The dose level to be used in Cohort 6 will be discussed by the sponsor's unblinded team. The sponsor's unblinded team must not directly be involved in the execution of the study at a study site or directly contact the site. This team will review unblinded data on the safety, tolerability, PD effects (MWT) and available PK of TAK-925, and recommend a dose based on those data. The dose level to be used in Cohort 6 may be higher or lower than the one used in Cohort 5. Cohort 7 will be composed of up to 12 subjects. The dose and the number of subjects to be used in Cohort 7 will be recommended by the sponsor’s unblinded team on the basis of safety, tolerability, PD effects (MWT) obtained from Cohorts 5 and 6 and available PK data of TAK-925. The dose may be higher or lower than the doses used in Cohorts 5 and 6, or intermediate dose between these cohorts.

See section 3.0 for the schedule of tests/observations /evaluations. Summary of Cohorts is shown in Table 6.a.

Table 6.a Summary of Cohorts

Part	Cohort	Subjects Sample Size	Study Design	Dosage	Randomization
1[1)]	1[2)]	Healthy adults n=8	Double-blind, Cross-over	TAK-925 7 mg (Dose Level 1) or placebo	Each Cohort TAK-925: 6 subjects, Placebo: 2 subjects
	2			TAK-925 14 mg (Dose Level 2) or placebo	
	1			TAK-925 28 mg (Dose Level 3) or placebo	
	2			TAK-925 56 mg (Dose Level 4) or placebo	
	1			TAK-925 112 mg (Dose Level 5) or placebo	
	2			TAK-925 134.4 mg (Dose Level 6) or placebo	
	S1 – S4[3)]	Healthy adults n=8	Double-blind, parallel group	TAK-925 TBD mg (Dose Level 7-10)[3)] or placebo	
	3	Healthy elderly n=8	Double-blind, parallel group	TAK-925 112 mg or placebo	
	4	Healthy adults n=4	Unblinded	TAK-925 112 mg	TAK-925: 4 subjects
	R1[4)]	Healthy elderly n=8	Double-blind, parallel group	TAK-925 TBD mg or placebo	TAK-925: 6 subjects, Placebo: 2 subjects
2[1)]	5	Patients with type 1 narcolepsy n=4	Double-blind (unblinded for the sponsor) 2 x 2 Cross-over	TAK-925 TBD[5)] mg or placebo	Each period TAK-925: 2 subjects, Placebo: 2 subjects
	6	Patients with type 1 narcolepsy n=4	Double-blind (unblinded for the sponsor) 2 x 2 Cross-over	TAK-925 TBD mg or placebo	
	7	Patients with type 1 narcolepsy n=12	Double-blind (unblinded for the sponsor) 2 x 2 Cross-over	TAK-925 TBD mg or placebo	Each period TAK-925: max. 6 subjects, Placebo: max. 6 subjects

1) In Part 1, Dose Levels 1, 3 and 5 will be tested in the same set of subjects, and similarly, Dose Levels 2, 4 and 6 will be evaluated in the different set of the same subjects. In Part 2, different subjects will be used in each Cohort.
2) In Cohort 1 Dose Level 1, 2 subjects will be enrolled and one subject each will be assigned randomly to either the TAK-925 or placebo group to evaluate the safety and tolerability of TAK-925. Once the safety and tolerability of these two subjects is evaluated, additional 6 subjects will be enrolled and 5 subjects and 1 subject of the 6 subjects will be assigned randomly to the TAK-925 and placebo groups, respectively, to evaluate the safety and tolerability of TAK-925.
3) In the event that further investigation on the safety, tolerability and PK of TAK-925 is needed after completion of Cohorts 1 and 2, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol. The Dose Levels 7-10 are planned as follows. However based on the available safety, tolerability and PK data, there is a possibility that the dose may be appropriately increased or decreased within the range not exceeding 420 mg. Dose Level 7: 180 mg, Dose Level 8: 240 mg, Dose Level 9: 320 mg, Dose Level 10: 420 mg.
4) In the event that further investigation on the safety, tolerability and PK of TAK-925 is needed after completion of Cohort 3, up to 1 additional cohort that include 8 healthy elderly can be commenced without amendment of the protocol.
5) In Part 2, the dose level to be used in Cohort 5 should be equal or lower than one-third of the maximum dose of TAK-925 of which the safety and tolerability has been already confirmed in Part 1.

Figure 6.a Overview of the Trial Schedules

<Part 1>

Screening	Baseline	Treatment Period		Follow-up Period	Washout Period
		Study Drug Administration/Sampling	Sampling	Hospital Visit	
Day -28--2	Day -1	Day 1	Day 2	Day 7	*Till Day TBD
	← Hospitalization Period →				

*The washout period will be determined based on the pharmacokinetic data obtained from Cohort 1 Dose Level 1. Subjects will re-visit the hospital on Day 7 and the same schedule (after Day -1 and subsequent days) will be applied for the subsequent Dose Levels after washout period.

<Part 2>

Screening	Baseline	Crossover period				Follow-up Period
	MWT/CCI	Study Drug Administration /Sampling/MWT	Sampling/CCI	Study Drug Administration /Sampling/MWT/	Sampling	Hospital Visit
Day -42--2*	Day -1	Day 1	Day 2	Day 3	Day 4	Day 7
	← Hospitalization Period →					

*For the subjects receiving prohibited concomitant medications, a washout period will be added arranged during the screening period.

6.2 Cohort Transition/Dose Escalation

The starting dose in Cohort 1 Dose Level 1 will be TAK-925 7 mg to be given once a day as 9-hour continuous intravenous infusion (See Section 6.3.3(1) for further information on starting dose selection).

After investigating the safety, tolerability (adverse events, physical examination findings, vital signs, laboratory tests and 12-lead ECG findings) in Cohort 1 Dose Level 1 24 hours after the start of infusion and pharmacokinetics of TAK-925, the dose level be used in Cohort 2 Dose Level 2 will be selected.

After the investigating the safety, tolerability in Cohort 2 Dose Level 2 until 24 hours after the start of infusion and pharmacokinetics of TAK-925, and the dose level to be used in Cohort 1 Dose Level 3 will be selected. After investigating the safety and tolerability of TAK-925 in Cohort 1 Dose Level 3 until 24 hours after the start of infusion, the dose level to be used in Cohort 2 Dose Level 4 will be selected based on available PK data. After investigating the safety and tolerability of TAK-925 in Cohort 2 Dose Level 4 until 24 hours after the start of infusion, the dose level to be used in Cohort 1 Dose Level 5 will be selected based on available PK data. After investigating the safety and tolerability of TAK-925 in Cohort 1 Dose Level 5until 24 hours after the start of infusion, the dose level to be used in Cohort 2 Dose Level 6 will be selected based on available PK data. The investigator will comprehensively investigate in a blinded manner the safety and tolerability (adverse events, physical examination findings, vital signs, laboratory tests and 12-lead ECG findings) of each Dose Level in Part 1 obtained by 24 hours after the start of infusion (Day 2), or those of each Cohort in Part 2 obtaind by 24 hours after the start of final infusion (Day

4) as well as available PK data obtained so far, then determine whether to proceed to the next dose level or next cohort after discussion(s) with the sponsor (and the medical expert, if necessary).

In Part 1(Cohorts 1-3 and Healthy Adult Supplement Cohort), the AUC and C_{max} of the dose to be used in the next Dose Level or next Cohort will be estimated based on the available PK data. The dosage and infusion rate to be used in the next Dose Level or next Cohort will be determined so that the AUC, C_{max} and the infusion rate in the next Dose Level or the next Cohort will not be more than twice the AUC, C_{max} and the infusion rate in the previous Dose Level or the previous Cohort.

Dose escalation or cohort transition will not occur if any of the following is seen in any Dose Level or Cohort:

1. A serious adverse event of which causal relationship to the study drug cannot be ruled out occurred.
2. Severe adverse event(s) of which causal relationship to the study drug cannot be ruled out occurred in two or more subjects at one dose level during the treatment period (from the commencement of treatment to the washout period or at the end of follow-up period).
3. A significant increase in BP defined in Section 7.6, regardless of symptomatic or asymptomatic, occurred in three or more subjects at one dose level.

Dose selection for Cohort 5 in Part 2 will be made based on the blinded safety and tolerability data of the completed cohorts in Part 1 and the available PK results. The dose to be used in Cohort 5 should be equal to or less than one-third of the highest tolerated dose in Part 1. The inclusion criteria for patients with type 1 narcolepsy in Part 2 includes those aged 18-80, but subjects aged 56 years or older will be enrolled based on the assessments of the safety results and PK data of Cohort 3 (and the Healthy Elderly Supplement Cohort) in Part 1.

The maximum dose and the highest infusion rate in Part 2 shall not exceed the maximum dose and the highest infusion rate at which the safety and tolerability were confirmed in Part 1.

The sponsor will review the safety, tolerability in Part 1 and the available PK to determine the dose for Cohort 5. The investigator will decide whether to start Cohort 5 after discussion with the sponsor. The sponsor's unblinded team will review the safety, tolerability, PD effects (MWT results) and available PK to recommend the dose for Cohort 6 and the dose and the number of subjects for Cohort 7. Based on the recommendation by the sponsor's unblinded team, the investigator will decide whether to start Cohort 6 and Cohort 7 after discussion with the sponsor. The dose for Cohort 6, and the dose and the number of subjects for Cohort 7 will be determined before enrollment of subjects. The results of the sponsor's unblinded team's review and the information of the dose and the number of subjects determined will remain blinded to the on-site clinical study staff, except the administrator of study drug at the site and the sponsor's unblinded team.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Population

(1) Part 1

The subjects to be enrolled in Cohorts 1-2 and Healthy Adult Supplement Cohort will be healthy adults who do not have any significant diseases, including cardiovascular disease and cerebrovascular disease to appropriately evaluate the safety, tolerability and PK of TAK-925. The subjects to be enrolled in Cohort 3 will be the healthy elderly who do not have any significant diseases, including cardiovascular disease and cerebrovascular disease, to appropriately evaluate the safety, tolerability and PK of TAK-925 in the healthy elderly, prior to the commencement of Part 2. Evaluation of Cohort 3 is particularly important, since elderly patients with type 1 narcolepsy will be is enrolled in Part 2. Also, considering the possibility of performing Part 2 at high doses, the Healthy Elderly Supplement Cohort will be added. In Cohort 4, healthy adults will be enrolled in order to appropriately evaluate the safety and tolerability, and PK including the concentration of TAK-925 in the CSF six hours after the start of infusion of TAK-925.

(2) Part 2

The subjects to be enrolled in Part 2 will be patients with type 1 narcolepsy in order to apprpriately evaluate PD effects of TAK-925, in addition to evaluation of the safety, tolerability and pharmocokinetics of TAK-925.

6.3.2 Rationale for Trial Design

(1) Part 1

Cohorts 1-2 will be an alternating panel (consisting of eight subjects per Cohort), dose-escalation, double-blind study. In Cohorts 1 and 2, each 2 subjects will be randomly assigned to Groups A to H for each dosing period where TAK-925 may be given at one dose level to have 6 subjects dosed TAK-925 and 2 subjects dosed placebo. In Healthy Adult Supplement Cohort that consists of 8 subjects per cohort, 6 and 2 subjects will be randomly assigned to the TAK-925 group or the placebo group, respectively. In Cohorts 1 and 2 and Healthy Adult Supplement Cohort, setting the placebo group is essential in order to evaluate the safety and tolerability of TAK-925 in an unbiased manner. The nonclinical study results of TAK-925 revealed that there were no significant toxicological findings to be concerned about when the maximum dose of TAK-925 planned in this study is assumed to be administered to humans. However, CCI [redacted] criteria for discontinuation or withdrawal of a subject, and criteria for dose escalation will be established. Since this is a clinical study of a compound having a novel mechanism to be used in humans for the first time, the initial dose will be 7 mg, and the subsequent doses will be increased in a stepwise fashion according to the safety and tolerability of TAK-925. Subjects will be hospitalized throughout the trial. The recommended initial dose of 7 mg was calculated based on the nonclinical study results. This is a dose-escalation study, to increase the dose in a stepwise fashion after reviewing the safety data obtained until the time of discharge (Day 2) and available pharmacokinetic data. Since Cohort 1 Dose Level 1 is a first-in-human study for TAK-925, a sentinel dosing will be used. First, TAK-925 or placebo will

be administered to one subject each. Once 2 hours have passed since the infusion was started and it was judged to be safe to proceed (eg, in case the subject does not meet the criteria for discontinuation or withdrawal of a subject), then the drug will be administered to the remaining subjects (5 subjects in the TAK-925 group and 1 subject in the placebo group). After Cohort 2 Dose Level 2, dosing will not be started simultaneously in all subjects in Cohort 3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort (in the event that a cohort is added). (4 subjects will be dosed first, and if there are no safety issues, the remaining 4 subjects will be dosed approximately 1 hour later.)

Cohort 4 is an open-label study in order to appropriately evaluate the safety and tolerability, and PK of TAK-925 including the plasma and CSF concentrations of TAK-925.

(2) Part 2

In Cohorts 5-7, a double-blind crossover study design will be used. With this design, the results of MWT when TAK-925 was administered can be compared to the results of MWT when placebo was administered on an individual subject basis, minimizing variability between subjects. This will allow for early assessment of potential drug efficacy. It is important that the sponsor reviews the data in an unblinded fashion as the dose escalation study will be conducted based on the safety and tolerability as well as the mean sleep latency in the MWT. In order to maintain subjects and study sites blinded and reduce any sponsor bias, a sponsor's unblinded team will be organized. The sponsor's unblinded team must not directly be involved in the execution of the study at a study site or directly contact the site. This team will review the safety, tolerability, PD effects (MWT results) and available PK to determine the dose for Cohort 6 and the dose and the number of subjects for Cohort 7.

The results of nonclinical studies of TAK-925 revealed no significant toxicity findings to be concerned about when TAK-925 is assumed to be administered in humans at the maximum dose planned in this clinical study. [redacted] Therefore, in Part 2, the initial dose is to be equal to or less than one-third of the maximum dose of TAK-925 of which the safety and tolerability has been already confirmed in Part 1. In each Cohort, the washout period to be set after the 2nd or subsequent infusions will be set 5 times the $t_{1/2}$ of TAK-925 as a guide, which is considered not to affect the PD effect.

6.3.3 Rationale for Dose

(1) Starting Dose for This Trial

The starting dose of TAK-925 in this phase 1, first-in-human (FIH) trial will be 7 mg to be given as continuous intravenous infusion for 9 hours a day.

The starting dose was calculated according to the procedures recommended by the FDA "Guideline for Industry for Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" [13] (hereinafter referred to as "FDA Guidance"). As a result of calculation of the human equivalent dose (HED) converted from the no-observed-adverse-effect level (NOAEL) based on the body surface area, rats were the animal

species with the highest sensitivity. The calculated HED in a human weighing 60 kg calculated using the conversion factor provided in the FDA Guideline was CCI mg/day (CCI x 0.16 [conversion factor] = CCI mg/day [HED in a human weighing 60 kg]). Moreover, when the safety factor was conservatively defined as 10, the maximum recommended starting dose (MRSD) of TAK-925 was calculated as CCI /day.

The FDA Guideline also recommends to consider using the pharmacologically active dose (PAD) in nonclinical studies when an initial dose is determined. In nonclinical pharmacology studies, the pharmacologically active concentration of TAK-925 in monkeys and common marmosets were CCI, respectively, which were CCI of the C_{max} at the NOAEL in rats, respectively.

Based on the results of CCI The C_{max} (C_{ss}) and the AUC when CCI TAK-925 is given as continuous intravenous infusion for 9 hours a day were calculated CCI, respectively. CCI

As mentioned above, the starting dose in this trial will be 7 mg to be given as continuous intravenous infusion for 9 hours a day.

(2) Maximum Dose/Exposure for This Trial

Based on the NOAEL in rats of which the sensitivity was the highest among animals used in the two-week, nonclinical, repeated-dose, toxicity studies, and the clinical dose of betadex sulfobutyl ether sodium (BSES), which is an excipient contained in the study drug, the acceptable upper limits of C_{max} and AUC and the maximum dose of TAK-925 in this study were set to be CCI. Meanwhile, in Cohort 2 Dose Level 6 CCI of Part 1 in this study, C_{max} and AUC of TAK-925 were CCI (preliminary result), respectively, and were safe and well-tolerated. These exposure levels of C_{max} and AUC are CCI lower than the acceptable C_{max} and AUC of TAK-925 in this study, respectively, CCI. Thus, it was judged possible to investigate at higher doses, and the maximum dose (the upper limit) was set to be CCI.

For example, "VFEND IV 200 MG" approved in Japan, contains BSES, an excipient contained in the study drug. Referring to the dosage of VFEND [14], the maximum amount of BSES per dose was set to be 3840 mg (when VFEND is administered to a human weighing 60 kg, as the maintenance dose on and after Day 2) in the protocol (first version and amendment 1). On the other hand, based on the result of Cohort 2 Dose Level 6 CCI of Part 1 of this study and with reference to the dosage of CARNEXIV [15] already approved in the United States, the maximum amount of BSES per dose was set to CCI in the study protocol (amendment 2), which is within the range of the dose of BSES, to be possibly administered within 9 hours as CARNNEXIV (CARNEXIV is infused every 6 hours, so this amount corresponds to 2 doses of CARNNEXIV).

Since TAK-925 used as a study drug contains [CCI] of BSES as an excipient [CCI] mg of TAK-925, [CCI] of TAK-925 contains [CCI] of BSES.

(3) Infusion Rate for This Trial

In the two-week, nonclinical, repeated-dose, toxicity study, the infusion rate at the NOAEL in rats was [CCI] When [CCI] is converted into the HED, the infusion rate will be [CCI] per adult weighing 60 kg. In the intravenous, single-dose, dose-escalation, toxicity study, convulsion was observed [CCI] at an infusion rate of [CCI]. When [CCI] is converted into the HED, the infusion rate will be [CCI] per adult weighing 60 kg.

The starting dose of TAK-925 in this trial will be 7 mg to be given as continuous intravenous infusion for 9 hours a day, and the infusion rate will be [CCI], which is slower than [CCI] of the infusin rate at the [CCI]

In order to accurately conduct the MWT procedures in patients with type 1 narcolepsy, the plasma concentration of TAK-925 is planned to reach the steady state in 2 hours. If additional PK data are newly obtained, the infusion rate may be adjusted accordingly. As the upper limit of C_{max} is set to be [CCI], based on the [CCI] in rats, it is estimated that the rate of increasing plasma drug concetration will be controlled to be [CCI] at fastest. [CCI]

6.3.4 Rationale for Endpoints

6.3.4.1 Safety Endpoints

Since this is a FIH study of TAK-925, adverse events, vital signs, body weight, 12-lead ECG and clinical laboratory tests will be included as safety endpoints. In the safety pharmacological study of TAK-925 in monkeys, transient mild to moderate BP increased was observed at all the dosages tested. In this study, therefore, BP will be measured frequently. See Section 7.6 for the details of the criteria for discontinuation or withdrawal of a subject.

6.3.4.2 PK Endpoints

In order to evaluate the PK of TAK-925 in healthy adults, the healthy elderly and patients with narcolepsy, the concentrations of TAK-925 and its metabolites ([CCI]) in the plasma, urine and CSF will be evaluated, and the following pharmacokinetic parameters will be calculated.

(1) Part 1

Pharmacokinetic parameters: C_{max}, C_{eoi}, AUC_{last}, AUC_{∞}, t_{max}, $t_{1/2z}$, [CCI] V_{ss} (TAK-925 only), V_z (TAK-925 only), Ae_{24}, fe_{24}, CL_R, CL (TAK-925 only), $R_{CSF/Plasma, SS}$ (=CSF concentration/C_{6h}) (Cohort 4 only)

(2) Part 2

Pharmacokinetic parameters: C_{max}, C_{eoi}, AUC_{last}, AUC_{∞}, t_{max}, $t_{1/2z}$, CCI, V_{ss} (TAK-925 only), V_z (TAK-925 only), CL (TAK-925 only)

In cases where it was considered necessary for interpretation of data, pharmacokinetic parameters other than the above may be calculated.

6.3.4.3 PD Endpoints

The PD endpoints will include MWT, CCI [redacted]. MWT is a test to measure the time of maintaining wakefulness using electroencephalogram, by which objective information about the patient's ability to sustain wakefulness can be obtained. CCI [redacted].

MWT is an indicator of evaluating objective sleepiness and used as a standardized and established method for evaluating the treatment of excessive sleepiness caused by narcolepsy, and this test has been widely used in clinical trials of a variety of investigational drugs including modafinil [16][17][18][19]. Therefore, the MWT will be used as the most important PD endpoint in this study. Parameters related to the mean sleep latency will be described in detail in the statistical analysis plan.

6.3.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

The purpose of including this section is to specify the order of procedures when two or more procedures are scheduled at the same time during the study.

- Safety evaluation will be performed within the specified time frame as close as possible.
- Blood samples for pharmacokinetic evaluation must be collected as close as the specified time. BP should be measured at the specified time. Frequent BP measurements should be performed, CCI [redacted]. In the event that BP measurement and blood sampling for PK are scheduled at the same time, the blood sampling for PK should be performed first then BP measurement should be performed within an acceptable time frame (Appendix C).
- Other procedures must be completed as close to the specified or scheduled time as possible, regardless of before or after the specified time.
- In the event that blood sampling and ECG or vital sign measurement are scheduled at the same time, blood sampling should be prioritized, then ECG or vital sign will be measured within an acceptable time frame (Appendix C).
- Priority ranking may be subject to change based on the agreement after discussion between the investigator and the sponsor.

- In the event an adverse event occurred, any tests or procedures required for urgently evaluating the event for safety purposes must be prioritized over any planned regular procedures, whatever it is.
- Since the secondary objective of this study is to evaluate the PD effects of TAK-925 in patients with narcolepsy, MWT to be performed in each Cohort of patients with narcolepsy is an important procedure. As BP measurement may interfere the MWT, BP should be measured before or after the test if these procedures are scheduled at the same time. If the BP measurement is performed during the MWT, it may be performed in a sitting position as needed.
- See the manuals for CCI and MWT for further details.

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

This is a FIH study of TAK-925, in which the PK, PD and safety profiles of the compound will be determined. This protocol is written with some flexibility to accommodate the unique nature of phase 1 clinical trial. The above-described dose, dosing regimen and/or clinical procedures and test procedures may be modified. Such modification is for scientific purposes of this trial and/or to ensure accurate safety monitoring of subjects.

The present dose and/or dosing regimen may be updated based on newly obtained data, but the maximum dose/exposure and the infusion rate detailed in Section 6.3.3 will remain unchanged.

The following modifications will be allowed:

- Addition of cohorts
- The dose of study drug previously administered may be adopted or may be decreased.
- Executions entire cohort or dose escalation may be omitted.
- Prolongation of a washout period based on the safety and pharmacokinetic data obtained. (In Part 2, infusion on Day 3 is changed to Day 4)
- Omission, extension or addition of the pharmacokinetic data review (if it is agreed by the sponsor and the investigator.)

The method for collecting PK/PD sampling data currently described in the protocol may be modified based on newly obtained PK or PD data during this trial (eg, to obtain data at the time closer to the peak plasma concentration achieved). Collected samples may be used in a study to explore metabolites and/or additional PD markers.

A maximum of 50 mL of blood samples may be additionally collected for PK and/or biomarker analyses during the study. This may occur because repeated sample collection may be needed to replace the current data by newly obtained data, or PK/biomarker sampling time points may be changed. The total blood volume to be collected from a single subject will not exceed the

maximum allowable volume (400 mL for subjects weighing 50 kg or more and 200 mL for a subject weighing less than 50 kg) during this trial.

The washout period between Period 1 and Period 2 in part 2 can be changed based on the newly obtained PK, safety and PD data. If this change occurs, the procedures and the schedule of study following CCI on the night on Day 2 will be shifted 1 day behind. (When the washout period is set to 2 days, refer to protocol Annex 3 in regard to the schedule, etc.)

The specified assessment time points of safety endpoints (eg, vital signs, ECG, laboratory tests) currently described in the protocol may be modified based on the newly obtained safety, tolerability, PK or PD/biomarker data (eg, to collect data at the time closer to the peak plasma concentrations achieved). These changes will not result in an increase the number of trial procedures for subjects participating in the trial.

Additional laboratory tests may be performed for additional safety evaluation using the blood samples previously collected (eg, to add a creatinine kinase tasting to the serum chemistry blood using the samples previously collected).

It is possible that some or none of the alterations described above may be employed in this study.

For any alterations made in this protocol to meet the trial objectives, the sponsor must issue a detailed letter and store it in the Trial Master File (TMF) and also ask the investigator to store it. This letter may be reviewed by the institutional review board (IRB)/independent ethics committee (IEC) at the discretion of the investigator.

After Cohort 2 Dose Level 2, the further dose and the infusion rate will be determined based on the safety and pharmacokinetic data obtained from the previous cohorts in this study. In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 1 and Cohort 2 Dose Level 6, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol. In the event that further investigation on the safety, tolerability and PK of TAK-925 is needed after completion of Cohort 3, up to 1 additional cohort that includes 8 healthy elderly can be commenced without amendment of the protocol. In the event that a long-term washout period is needed on the basis of the pharmacokinetic or safety evaluation results in Part 1, the dosing order of TAK-925 and placebo and Part 2 may be changed to a single-blind (only subjects are blinded), fixed-sequence approach (TAK-925 will be given after a placebo is given to all subjects).

If the dose to be used in Cohort 7 is to be lower than the dose used in Cohort 5 or Cohort 6 based on the results of Cohort 5, Cohort 7 may be executed following Cohort 6.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

The overall trial begins when the first subject signed the trial's informed consent form.

6.5.2 Definition of End of the Trial

The overall trial ends when the last subject completed the last planned or follow-up visit (or the last communication related to the planned visit [this can be a phone contact]) was completed, or when the trial was discontinued, or the date of lost to follow-up (ie, the investigator is unable to contact the subject).

6.5.3 Definition of Trial Discontinuation

Trial discontinuation may occur because of non-safety reasons, such as:

- Findings from other nonclinical or clinical trials of the study drug (eg, PK, PD, efficacy, biologic targets) results in the discontinuation of the trial for non-safety reasons.
- Data on drug(s) of the same class as the study drug or methodology (ies) used in this trial become available, which results in the discontinuation of the trial for non-safety reasons.
- The trial is discontinued because of non-scientific and non-safety reasons, such as delayed enrollment.

Trial discontinuation due to safety reasons includes:

- Early trial termination because of unexpected safety concerns in subjects being identified in the clinical or preclinical trials of the study drug, reference drug(s), drug(s) of the same class as the study drug or methodology (ies) used in this trial.

6.5.4 Criteria for Premature Termination or Suspension of the Trial

6.5.4.1 Criteria for Premature Termination or Suspension of Trial

The study will be temporarily suspended or prematurely discontinued if it meets 1 or more of the following criteria:

1. Regarding the safety or efficacy of the study drug, new information or alternative evaluation that will change the known risk/benefit profile of TAK-925 was obtained, and such risk is no longer acceptable for subjects to participate in the study.
2. Significant Good Clinical Practice (GCP) violation that compromises the achievement of the primary study objectives or the subject safety.
3. Any events listed in the Takeda Medically Significant List (Table 10.a) occurred in two or more subjects at a single or multiple Dose Level(s) or in a single or multiple Cohort(s)
4. Liver function test abnormal:
    a. An elevation over 5 times the upper limit of normal (ULN) of ALT and/or AST occurred in two or more subjects at a single or multiple Dose Level(s) or in a single or multiple Cohort(s) in the absence of elevation of bilirubin.
    b. An elevation over 2 times the ULN of total bilirubin or an elevation over 1.5 times the ULN of prothrombin time (PT)-international normalized ratio (INR) with the elevation(s) over 3

times the ULN of ALT and/or AST were observed in one or more subjects at a single Dose Level or in a single Cohort, and such elevation cannot be explained by cholestasis or other factors (ie, Hy's Law case).

c. An elevation over 3 times the ULT of ALT and/or AST occurred in two or more subjects at a single or multiple Dose Level(s) or in a single or multiple Cohort(s) in the presence of fatigue, nausea, vomiting, right upper abdominal pain or tenderness, pyrexia, rash or eosinophilia (over 5%).

6.5.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the sponsor, IRB or regulatory authorities determines to terminate or suspend the entire study or the study at a site, study-specific procedures for suspension or early termination will be instructed by the sponsor. The procedures for suspension or premature termination of the study will be followed by the applicable study site.

6.5.5 Criteria for Premature Termination or Suspension of the Trial at a Site

6.5.5.1 Criteria for Premature Termination or Suspension of the Trial at a Site

The clinical study at study site may be terminated prematurely or suspended if a significant violation on GCP, protocol or study site agreement is found at the site (including the investigator), or the study at the site cannot be appropriately conducted, or as otherwise permitted by the agreement.

6.5.5.2 Procedures for Premature Termination or Suspension of the Trial at a Site

In the event that the sponsor, IRB or regulatory authorities determines to terminate or suspend the entire study or the study at a study site, a study-specific procedures for early termination or suspension will be instructed by the sponsor. The procedures for suspension or premature termination of the study will be followed by the applicable study site.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All inclusion/exclusion criteria, including laboratory test results, need to be confirmed prior to the randomization or the first dose of study drug.

7.1 Inclusion Criteria

Subject eligibility will be determined according to the following criteria:

All Subjects

1. In the opinion of the investigators, the subject is capable of understanding the clinical study and complying with the protocol requirements.
2. A subject (or subject's legally acceptable representative, if needed) is capable of signing and dating the informed consent form prior to the initiation of any study procedures.
3. A subject who is male or female.
4. In the opinion of the investigator, the subject is in good health condition to participate in the trial. The subject's health condition will be judged based on the clinical evaluations including laboratory test results, medical history, physical examination, 12-lead ECG and vital sign measurements performed at the screening and before the initial administration of the study drug or before an invasive procedure.
5. A male subject who is nonsterilized* and sexually active and has a female partner of childbearing potential agrees to use adequate contraception* from the time of signing the consent form to 12 weeks (84 days) after the last dose of study drug. A female partner of the male subject should also be advised to use adequate contraception* (See Appendix B).

Healthy Adults

6. A subject who is a healthy adult, aged between 20 and 55 years, at the time of signing the informed consent form.
7. A subject weighing at least 50 kg and has a BMI of 18.5 to 30 kg/m^2 at Screening.
8. A subject who has no history of hypertension or use of antihypertensive medication with normal BP. The normal BP is defined as below140 mmHg in systolic blood pressure (SBP) and below 90 mmHg in diastolic blood pressure (DBP).
9. A Female subjects who is not of child bearing potential (surgically sterile or postmenopausal).

Health Elderly

10. A subject who is the healthy elderly, aged between 65 and 80 years at the time of signing the consent form.
11. A subject weighing at least 40 kg and has a BMI of 18.5 to 30 kg/m^2 at Screening.
12. A subject who has no history of hypertension or use of antihypertensive medication with normal BP. The normal BP is defined as below 140 mmHg in SBP and below 90 mmHg in DBP.

Patients with type 1 narcolepsy

13. A patient aged between18 and 80 years at the time of signing the informed consent form.
14. A patient weighing at least 40 kg at Screening.
15. Patients with type 1 narcolepsy: Those diagnosed with type 1 narcolepsy, as defined by the International Classification of Sleep Disorders, Third Edition (ICSD-3)
16. A Patients who is positive for HLA-DQB1*06:02
17. Epworth Sleepiness Scale (ESS) score on Day -1 is ≥10
18. SBP and DBP at screening are <140 mmHg and <90 mmHg, respectively. If the BP measurements are within the above range, patients who have a history of hypertension and patients whose BP is well controlled by a specific dosage and administration of antihypertensive medication may be enrolled in this study.
19. A female subject of childbearing potential who is sexually active and has a nonsterilized* male partner agrees to use an adequate contraception* from signing the consent form throughout the study period (See Appendix B).

* Procedures for adequate contraception and pregnancy reporting are defined in Appendix B.

CCI

[redacted]

CCI

[redacted]

7.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be enrolled in the study:

All Subjects

1. A subject who has received another investigational compound within 30 days prior to the first dose of the study drug (including the case that the time longer than 5 times the $t_{1/2}$ of the another investigational compound has not passed yet).
2. A subject is a study site employee or his/her family member or has a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may give his/her consent under duress.
3. Hypersensitivity to any components of TAK-925 or related compounds
4. A male subject who intends to donate his sperm during the study period or within 12 weeks (84 days) after the last dose of the study drug.
5. A subject who has a history of drug abuse (defined as illicit drug use) or alcohol abuse within 2 years prior to the Screening.
6. Creatinine clearance (Ccr) ≤50 mL/min at the screening or on hospital admission (Day -1)
7. SBP of ≥140 mmHg or DBP of ≥90 mmHg at Screening, Day -1 or before study drug administration on Day 1, confirmed by repeated measurements of BP after resting in a supine position for approximately 10 or 30 minutes.
8. Excessive intake of caffeine, defined as consumption of over 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, coke, energy drinks, or other caffeinated beverages per day
9. A subject who needs to take excluded medications, vitamines, supplements or dietary products listed in a table in Section 7.3 during the study.
10. A subject who has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1.
11. A subject who has tested positive for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, or serologic reactions for syphilis at Screening.

12. A subject with poor peripheral venous access.
13. A subject who has undergone whole blood sampling of at least 200 mL within 4 weeks (28 days), or at least 400 mL within 12 weeks (84 days) in male subjects, within 16 weeks (112 days) in female subjects prior to the start of study drug administration.
14. A subject who has undergone whole blood sampling of at least 800 mL (male) and 400 mL (female) within 52 weeks (364 days) prior to the start of study drug administration.
15. A subject who has undergone blood component sampling within 2 weeks (14 days) prior to the start of study drug administration.
16. A subject who has a risk of suicide according to the investigator's judgment based on the assessment of the C-SSRS or has made a suicide attempt within 6 months before the start of study drug administration.
17. A subject who has a current or past history of epilepsy, convulsion, tremor or related symptoms.
18. A subject who has a history of major psychiatric disorder, including major depression, bipolar disorder or schizophrenia.
19. A subject who has a history of clinically significant head injury or trauma.
20. A subject who has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm or arteriovenous malformation.
21. A subject who has known coronary artery disease, and a history of myocardial infarction (MI), angina, cardiac rhythm abnormality or heart failure.
22. QT interval with Frederica correction method (QTcF) is >450 milliseconds (male) or >470 ms (Female) on a 12-lead ECG at Screening
23. A subject who has a resting heart rate (HR) outside the range of 45 to 100 beats per minute, confirmed by a repeated testing performed within a maximum of 30 minutes at Screening or on hospital admission (Day -1).
24. A subject who has a clinically significant and unstable cardiovascular, pulmonary, hepatic, renal or gastrointestinal disease or other abnormal conditions that may influence the subject's participation in this study or study results. (For subjects enrolled in Part 2, the disease under study [narcolepsy] will be excluded.)
25. A subject who has abnormal laboratory values detected at Screening or on hospital admission (Day -1) that suggest a clinically significant underlying disease or ALT and/or AST of 1.5 times the ULN.
26. A subject who, in the opinion of the investigators, is unlikely to comply with the protocol or is unsuitable for other reasons.

Healthy Adults or the Healthy Elderly (Cohorts 1-4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort):

27. A subject unwilling to stop smoking during the study period.
28. A female subject of childbearing potential who is sexually active (premenopausal and nonsterilized).
29. A subject who has a clinically significant sleep disorder (including sleep apnea syndrome and insomnia).

Healthy Adults (only Cohort 4):

30. A subject whose CSF was collected within 14 days prior to hospitalization (Day -1).
31. A subject who has a known hypersensitivity to anesthetics, and medications used for CSF collection or lumbar puncture.
32. A subject who has clinically significant vertebral deformities (scoliosis or kyphosis) which, in the opinion of the investigators, may interfere with lumbar puncture.
33. A subject who has a clinically significant back pain and/or injury.
34. A subject who has a local infection at the puncture site.
35. A subject who has thrombocytopenia or bleeding tendencies before the beginnng of study procedures.
36. A subject who has signs and symptoms of radiculopathy including leg pain and paresthesia.
37. A subject who has focal neurological deficit that might suggest an increase in intracranial pressure.
38. A subject who has abnormal findings on ophthalmological examination /fundoscopy suggestive of raised intracranial pressure (eg, optic disc swelling/papilledema, uncontrolled hypertensive retinopathy).
39. A subject who suffers from moderate to severe headaches requiring analgesics.

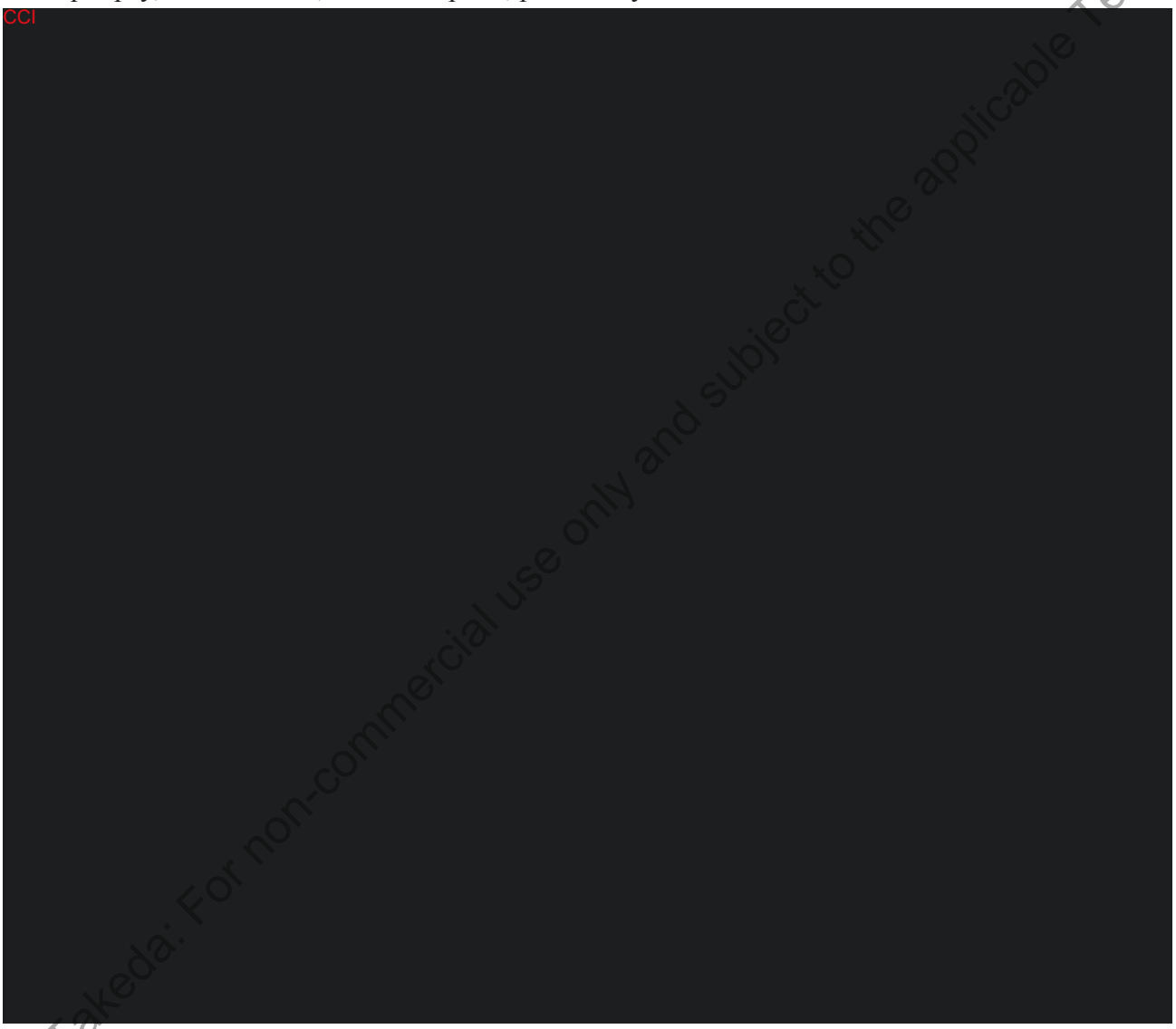
Patients with type 1 narcolepsy

40. A patient unwilling to quit smoking 40 minutes before the scheduled MWT and 1 hour before sleeping.
41. A patient who has sleep disorder(s) associated with excessive sleepiness (including sleep apnea syndrome) other than narcolepsy.
42. Excessive caffeine consumption (>400 mg/day) within seven days before hospital admission (Day -1).
43. Use of drugs with stimulating or sedating properties, anti-parkinson drugs or anti-convulsant drugs within 7 days before the start of study drug administration or 5 times the half life of each drug. For selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, there should be a washout period (at least 5 times the elimination half-life of each drug or for 7 days,

whichever is longer prior to the start of study drug adoministration), and the administration should be discontinued with gradual dose reductions (See Section 7.3).

44. A subject who has a disease requiring excluded medications, including anxiety, depression, epilepsy, heart disease, serious hepatic, pulmonary or renal disease.

CCI



7.3 Excluded Medications, Supplements, Dietary Products

(1) Part 1

Excluded medications, supplements and dietary products are listed in Table 7.a.

Subjects must be instructed not to take any medications including over-the-counter (OTC) drugs, other than prescribed medications, without prior consultation with the investigators.

Table 7.a Excluded Medications, Supplements, and Dietary Products (Part 1)

From 28 days prior to the start of study drug administration (Day 1) to the follow-up visit	From 7 days prior to the start of study drug administration (Day 1) to the follow-up visit	From 7 days prior to the start of study drug administration (Day 1) to the discharge from hospital	From 24 hours prior to the start of study drug administration (Day 1) to the discharge from hospital
Prescribed drugs[1)]	Grapefruit/Grapefruit juice	Vitamins	Caffeine-containing products
OTC drugs	Cruciferous vegetables (e.g., kale, broccoli, cress, collard greens, kohlrabi, brussels sprouts, mustard)	Alcohol-containing products	
Supplements (St. John's wort, ginseng, kava kava, Ginkgo biloba and melatonin)	Charcoal-grilled meats		
Chinese herbal medicine			
Vaccination/vaccine			
Nicotin-containing foods			

OTC drugs: over-the-counter drugs
Note: If medications are required to treat an AE, certain medications may be allowed by the investigators.
1) Coadministration of moderate to strong CYP3A4 inhibitors or inducers (see (18), Table 7.b) will be prohibited from 28 days prior to the start of administration (Day 1) or from at least 5 times the terminal half-life of each drug, whichever comes first, to the follow-up visit.

(2) Part 2

Excluded medications and dietary products are shown in Table 7.b. Administration of psychostimulants, hypnotics, anti-anxiety drugs, antipsychotics and anticonvulsants must be discontinued within a minimum of 7 days before the start of the study drug administration. The investigators should taper off the dose of each drug and discontinue within the washout period (at least 5 times the terminal half-life of the antidepressant), to ensure the appropriateness of the washout period. Administration of moderate to strong CYP3A4 inhibitors or inducers should also be discontinued. Any drugs must not be used from the period shown in Table 7.b until all tests planned on Day 4 have been completed. The investigator will review the concomitant medication use at screening, and determine the time of discontinuation for relevant drugs that should not be used anymore. At the discontinuation, the investigators shuold pay attention to the drugs of which gradual recuction of dose is required. Subjects will also be instructed not to take any medications including OTC drugs without prior consultation with the investigators.

Table 7.b Excluded Medications and Dietary Products (Part 2)

Excluded Medications and Dietary Products	At least 7 days prior to the start of study drug administration or 5 times the terminal half-life of each drug listed below, whichever is longer.
(1) Psychostimulants	Methylphenidate hydrochloride, modafinil, pemoline, methanphetamine hydrochloride
(2) Antipsychotics	As for depot formulation of antipsychotics, they should be determined appropriately in consideration of the period to disappearance.
(3) Antianxiety drugs (Tranquilizers)	Including benzodiazepine
(4) Antidepressants	The doses of drugs used to control cataplexy, such as tricyclic antidepressants, SSRIs and serotonin-noradrenaline reuptake inhibitors (SNRIs) must be stepwisely reduced with caution.
(5) Mood stabilizers	-
(6) Anticonvulsants	-
(7) Hypnotics	Including Chinese herbal medicine (*Yokukansan, Yokukansankachinpihange*) used for insomnia.
(8) Antiparkinson drugs	-
(9) Corticosteroids	Only for systemic use.
(10) Interferon, interleukin preparation	-
(11) Muscle-relaxants	-
(12) Antihistamines	Oral administration only. OTC drugs and pharmaceutic adjuvants are also included.
(13) Central nervous system-acting β-blockers	-
(14) Central nervous system -acting antitussives	-
(15) Central nervous system -acting antiemetics	-
(16) Narcotic analgesics and non-narcotic analgesics (opioid analgesics and pregabalin only)	-
(17) St. John's Wort, health foods containing melatonin	-
(18) Moderate to strong CYP3A4 inhibitors or inducers 1) Strong CYP3A4 inhibitors: Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir, ritonavir, elvitegravir, indinavir, saquinavir, idelalisib, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, telaprevir, tipranavir, troleandomycin, voriconazole 2) Moderate CYP3A4 inhibitors: Amprenavir, aprepitant, atazanavir,	-

casopitant, cimetidine, ciprofloxacin, diltiazem, clotrimazole, miconazole, crizotinib, cyclosporine, dronadarone, erythromycin, fluconazole, fosamprenavir, fluvoxamine, imatinib, istradefylline, tofisopam, verapamil 3) Strong CYP3A4 inducers: Carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin 4) Moderate CYP3A4 inducers: Bosentan, efavirenz, etravirine, modafinil	

Note: If medications are required to treat an AE, certain medications may be allowed by the investigators.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Meals and drinks (except water) prior to the laboratory tests must be taken 8 hours prior to the tests.

Dinner on the day before laboratory tests must be taken by 21:00.

Prescribed meals must be taken during hospitalization and intake of other foods is prohibited.

After discharge, excessive eating or drinking should be avoided until the follow-up period is finished.

7.4.2 Activity

Sleeping at non-specified time is prohibited.

Excessive exercise is prohibited during the study period.

Blood donation within at least 12 weeks (84 days) after the last examination in the study is prohibited.

If a subject visits another medical institution during the study period, the subject must report to the investigators in advance as far as possible. After the visit, the subject must report the background of the visit and the details of the treatment that the subject received, to the investigators. Then, the investigators will contact with the medical institution to inform that the subject is participating in the clinical trial.

In Part 1, smoking is prohibited during the study period. In Part 2, subjects who have a smoking habit will be allowed to smoke under limitation, to comply with the followings during confinement:

- Smoking will not be allowed from 40 minutes before when each MWT is performed. Smoking will be allowed after the study drug infusion, but up until 1 hour before sleeping.
- The subject must not interfere with any scheduled study procedures and tests by smoking during hospital stay.

In addition to the above, the following instructions will be given to subjects in Part 2

- CCI [redacted]
- Subjects will follow the notes shown in the manual for pharmacodynamic tests (CCI and MWT).
- In the washout period between Period 1 and Period 2, subjects will be instructed and monitored as much as possible that time of each daytime nap should be within 30 minutes and the number of daytime nap should be up to 5 times so as not to disturb night time sleep.

7.5 Record of Discontinuation or Withdrawal of a Subject before Study Drug Administration

The investigators are responsible for all subjects who signed the informed consent form. If a subject is withdrawn from the study before the first study drug administration, the investigators will complete the electronic case report form (eCRF) to record the details.

The primary reason for the withdrawal will be recorded in the eCRF using the following categories:

- Death.
- Adverse event (AE).
- Screen Failure (The subject did not meet the inclusion criteria or did meet the exclusion criteria.) <specify reason>.
- Protocol deviation.
- Lost to follow-up.
- Pregnancy
- Voluntary withdrawal <specify reason>.
- Termination of entire study by the sponsor.
- Sample size sufficient.
- Other <specify reason>.

The subject identification number assigned to the subject who withdrew from the study before the start of study drug administration should not be reused. However if a reserve subject is to participate in another Cohort, the same subject identification number may be used.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for withdrawal of subject from the study or discontinuation of study drug administration should be recorded in the eCRF using the following categories. For subjects who withdrew from the study before the start of study drug administration, refer to Section 7.5.

1. Death.

   A subject died during the study period.

   Note: If the subject died during the study period, the event will be treated as a serious adverse event (SAE). See Section 10.2.9.3 for the reporting procedures.

2. AE.

   A subject who has experienced an AE that requires early termination of the study because subject's continued participation imposes an unacceptable risk to his/her health or the subject is unwilling to continue the study because of the AE.

   If a situation that meets any of the following criteria occurs during the study treatment, the study drug should be discontinued immediately and an appropriate follow-up will be started (eg, Laboratory tests will be repeatedly performed until the subject's laboratory profile returns to the normal or baseline level. See Section 9.2.9):

   - Liver function test (LFT) abnormal
     - ALT or AST elevates over 8 times higher than the ULN, or
     - ALT or AST elevates over 5 times higher than the ULN and this elevation persists for more than 2 weeks, or
     - ALT or AST elevates over 3 times higher than the ULN and the total bilirubin elevates over 2 times higher than the ULN, or INR elevates over 1.5 times higher than the ULN, or
     - ALT or AST elevates over 3 times higher than the ULN, which is accompanied by fatigue, nausea, vomiting, right upper abdominal pain or tenderness, pyrexia, rash or eosinophilia (>5%).
   - Sustained elevation of blood pressure

   In non-clinical studies, CCI [redacted] assuming that BP elevation immediately after the start of infusion may drop down over time, the following instructions will be provided,

   - if:
     - SBP of 180 mmHg or higher is persisting
     - DBP of 110 mmHg or higher is persisting
     - 40 mmHg or higher increase in SBP from baseline prior to the start of infusion of TAK-925 is persisting

If measured BP meets one or more of the above criteria, the BP will be measured again 5 minutes after the first measurement for confirmation. If any cardiovascular or neurological related symptoms is observed, administration of the study drug should be discontinued immediately and an appropriate medical treatment should be provided (eg, lowering BP judged by the investigators), and an emergency test will be requested as needed. If any cardiovascular or neurological related symptoms are not observed, repeated measurements of BP should be performed every 15 minutes. The study drug will be discontinued immediately if SBP and DBP exceeds 200 mmHg and 120 mmHg, respectively. The study drug will be discontinued if SBP is between 180 and 200 mmHg, or if DBP is between 110 and 120 mmHg, or if 40 mmHg or higher increase in SBP from baseline has been continued over 1 hour, or if the investigators judged that it would be difficult to continue the study drug administration. If the BP does not decrease 30-60 minutes after the discontinuation of the study drug, an appropriate treatment should be provided at the discretion of the investigators.

The study drug will not be rechallenged including the case that the discontinuation of the study drug is discontinued due to an increase in BP.

3. Protocol deviation.

   If it becomes clear after the start of study drug administration that a subject failed to meet the inclusion criteria specified in the study protocol or did not adhere to the protocol, and the subject's continued participation in the study poses an unacceptable risk to his/her health.

4. Lost to follow-up.

   A subject did not return to the study site and attempts to contact the subject were all unsuccessful. These attempts to contact the subject must be recorded in the subject’s source documents.

5. Pregnancy.

   A subjects is found to be pregnant.

   Note: If a subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Appendix B

6. Voluntary withdrawal.

   A subject wishes to withdraw from the study. If the reason for withdrawal was found, it should be recorded in the eCRF.

   Note: Any attempts should be made to identify the underlying reason for the withdrawal, and where possible, the underlying reason should be recorded as the primary reason for withdrawal. (A withdrawal due to an AE should not be put into the “voluntary withdrawal” category).

7. Termination of entire study by the sponsor.

   The sponsor determined early termination of the study.

8. Other

   Note: The specific reason should be recorded in the eCRF.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigators must discontinue the study at any time during the study period if a subject meets the "Criteria for Discontinuation or Withdrawal of a Subject" described in Section 7.6. In addition, a subject can discontinue his or her participation in the study at any time during the study period without giving a reason for discontinuation. When subject's participation in the study is discontinued, the investigators should record the primary reason for discontinuation. In addition, all procedures for tests/observations/assessments to be performed when the study is discontinued should be performed as far as possible.

In the event that a subject discontinued his/her study, Section 9.3.1.1 should be referenced for PK sample collection.

7.8 Subject Replacement

When a subject discontinues the trial, an additional subject may be enrolled for replacement, if it is deemed appropriate by the investigator and the sponsor. The study site should contact the sponsor to report a medication ID number for the subject replaced. The number of subjects to be replaced by other subjects in the study will be a maximum of 4 per cohort in Cohorts 1 and 2 in Part 1, and a maximum of 8 each in Part 1 and Part 2. In Part 1, the cohort for the replacing subjects will be regarded as another cohort separate from the existing cohort.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

[Compound]

Code name: TAK-925

Dosage form and strength:

TAK-925 Injection consists of [redacted] TAK-925 Injection will be diluted in saline when used.

TAK-925 Placebo Injection will be supplied as commercially available saline. The saline to be administered to the study subjects will not be supplied by the sponsor. The TAK-925 Placebo Injection for blind use to be supplied by the sponsor will not be used.

[Manufacturing]

The drug substance of TAK-925 is manufactured by the Takeda Pharmaceutical Company Limited. (Osaka Japan).

[redacted].

8.1.1 Clinical Study Drug Labeling

Each vial of TAK-925 Injection or TAK-925 Placebo Injection for blind use is contained in a box. In the outer box, the following are indicated: the name of the study drug, the number of study drugs, storage condition, manufacturing number, expiration date, protocol number, the name and address of the sponsor, and the labeling of "for clinical use".

8.1.2 Clinical Study Drug Inventory and Storage

[redacted]

The study drug will be stored in an appropriate and safe place where an access is restricted until it is used or until it is returned to the sponsor or its designee for disposal. The study drug will be stored under the conditions described on the label until it is prepared. The temperature of the storage place should be recorded on every working day.

8.1.3 Randomization Code Creation and Storage

The personnel responsible for randomization (the sponsor's designee) will prepare the randomization table/schedule prior to the start of the study. The randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.4 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigator will stores the emergency key until at the time of emergency opening or until the completion of the study.

The blinding may be compromised by the results that should not be reported prior to the opening of the randomization code, such as the measurement results of study drug concentrations. In the case where these final measurement results are reported to the investigator prior to opening, a measure to maintain the blinding should be taken (eg, a medication ID number is replaced by another number so that a site staff in charge cannot identify the subject). For the details of the procedures for measuring drug concentrations, refer to a manual for measuring drug concentrations to be created separately.

Furthermore, the personnel who prepare the study drug (TAK-925 and placebo) or discard the vials used for the preparation may have a chance to know the randomization details. Therefore, the study site should identify such personnel prior to the start of study and prepare a list of the personnel. Since it is difficult for the personnel who may have a chance to know the randomization details to be kept blinded, observer blinding should be secured by the separately specified procedures.

The personnel who may have a chance to know the randomization details must not disclose the information to any third party until opening of all randomization codes, except to follow the procedures specified by the sponsor. Furthermore, in the process of preparation and administration of the study drug (including disposal of vials after study drug administration), measures should be taken so that the study drugs, their vials and so on are not exposed to subjects and study personnel other than those designated by the investigator.

In the case that blinding of the study drug is broken, the investigators can obtain study drug assignment /randomization information by opening the emergency key.

When the investigators breaks the blinding of the study drug, he/she should report it to the study sponsor as promptly as possible. In addition, the date of unblinding and the reason of unblinding should be specified in the record of emergency key opening. The same information (except the time) will be recorded in the eCRF.

When the investigators breaks the blinding of the study drug, he/she should immediately discontinue the administration of the study drug and withdraw the relevant subject from the study.

The investigators shall not change any evaluations of the subject after unblinding, except the case that the investigators is not informed of unblinding information (ie, when the sponsor breaks the blinding to perform an unblinding analysis).

8.1.5 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (a site's designee) will receive the pharmacy manual created by the sponsor, and follow the manual to appropriately store the sponsor-supplied drugs. The investigator will also receive the manual from the sponsor. The manual will contain instructions on ensuring appropriate receipt, handling, storage, management and prescription of the drugs and the return of those drugs to the sponsor or the destruction of unused drugs.

The on-site pharmacist (a site's designee) will immediately return the unused study drugs to the sponsor after the study is completed at the study site.

9.0 STUDY PROCEDURES

The investigators should collect the data according to the procedures described in the following sections. The tests/observations/assessments for each procedure are to be performed by the same investigator, subinvestigator or site's designee. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Each subject's consent to participate in the study must be obtained prior to the initiation of any study procedures. The requirements for obtaining subjects' consents are described in Section 13.2. A separate informed consent pertaining to the collection, storage and analysis of samples for pharmacogenomic research to be performed in this study must be obtained prior to collecting blood of samples for pharmacogenomic.

9.1.1.1 Assignment of Subject Identification Number

A unique subject identification (ID) number will be assigned to each subject at the time of explaining informed consent. This subject ID number will be used throughout the study.

9.1.1.2 Study Drug Assignment

In Cohorts 1-3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort (if it is added), subjects in each cohort will be assigned to each cohort the study drug in order of the medication ID number according to the randomization schedule (See Figure 9.a, Figure 9.b and Figure 9.c). In Cohort 4, eligible subjects will be assigned with the subject ID number. In Cohorts 5-7, subjects in each cohort will be assigned to the study drug in order of the medication ID number after the subject eligibility is confirmed (See Figure 9.d).

The assigned medication ID number or subject ID number will be used by a study site to distinguish each PK sample, and is the only code to identify each subject when a PK sample is collected from the subject. This number must be displayed on each sample vial that will be sent to the local/central laboratory for pharmacokinetic evaluation. The laboratory will report the measurement results using these numbers. These numbers will be used only for the purpose described in this section and will not be replaced by 7 digit subject identification numbers that are provided when a subject's consent to participate in the study is obtained, and are used to identify each subject in all other procedures to be performed during the study period. In the case that the study drug is to be administered to a reserve subject, the reserve subject will receive the study drug of which the medication ID number, which was assigned to the original subject (only in Cohorts 1 to 3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort). If a subject is replaced, the replacing subject will receive the study drug with a different medication ID number from the number assigned to the original subject who discontinued the study.

Figure 9.a Summary of Cohorts 1 and 2

Dose Level 1	
A	TAK-925 7 mg
B	TAK-925 7 mg
C	TAK-925 7 mg
D	Placebo

→

Dose Level 2	
E	TAK-925 14 mg
F	TAK-925 14 mg
G	TAK-925 14 mg
H	Placebo

→

Dose Level 3	
A	TAK-925 28 mg
B	TAK-925 28 mg
C	Placebo
D	TAK-925 28 mg

→

Dose Level 4	
E	TAK-925 56 mg
F	TAK-925 56 mg
G	Placebo
H	TAK-925 56 mg

→

Dose Level 5	
A	TAK-925 112 mg
B	Placebo
C	TAK-925 112 mg
D	TAK-925 112 mg

→

Dose Level 6	
E	TAK-925 134.4 mg
F	Placebo
G	TAK-925 134.4 mg
H	TAK-925 134.4 mg

1) Double-blind, crossover study. Each Cohort consists of 8 subjects, and each group consists of 2 subjects. Dose Levels 1, 3 and 5 will be investigated in the same subjects (Groups A-D in Cohort 1). Similarly, Dose Levels 2, 4 and 6 will be investigated in the other same subjects (Groups E-H in Cohort 2).
2) At Dose Level 1, firstly 2 subjects will be enrolled: one subject will be randomized to one of Groups A to C, and another subject to Group D. After confirming the safety and tolerability of TAK-925, 6 more subjects will be enrolled 2 hours after the start of infusion, and each of these subjects will be randomly assigned to one of Groups A to D, to evaluate the safety, tolerability and PK of TAK-925. Finally, two subjects each will be assigned to Groups A to D. The Doses after Dose Level 2 and subsequent doses will be determined based on the safety, tolerability and PK data obtained at previous dose levels.

Figure 9.b Summary of Cohort 3 and Cohort R1 (Healthy Elderly Supplement Cohort)

TAK-925 112 mg/TAK-925 TBD
Placebo

TBD: To be dterminied

1) Double-blind study. Cohort 3 and Cohort R1 consists of 8 subjects each: 6 subjects in the TAK-925 group and 2 subjects in the placebo group. Dose of Cohort 3 will be 112 mg, dose of Cohort R1 to be determined.

Figure 9.c Summary of Cohorts S1-S4 (Healthy Adult Supplement Cohorts)

TAK-925 TBD
Placebo

TBD: To be dterminied

1) In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohorts 1 and 2, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol.
2) Double-blind study. Each Cohort consists of 8 subjects: 6 subjects in the TAK-925 group and 2 subjects in the placebo group.
3) The dose can be determined for each Cohort.

Figure 9.d Summary of Cohorts 5-7

Cohort 5		
	Period 1	Period 2
I	TAK-925 TBD	Placebo
J	Placebo	TAK-925 TBD

Cohort transfer →

Cohort 6		
	Period 1	Period 2
K	TAK-925 TBD	Placebo
L	Placebo	TAK-925 TBD

Cohort transfer →

Cohort 7		
	Period 1	Period 2
M	TAK-925 TBD	Placebo
N	Placebo	TAK-925 TBD

TBD: To be dterminied

1) Double-blind (the sponsor is unblinded), 2x2 crossover study.
2) Cohorts 5 and 6 consist of 4 subjects each. Two subjects each will be assigned to each group (Groups I-L). Cohort 7 consists of a maximum of 12 subjects, and each group (Groups M and N) consists of a maximum 6 subjects.
3) Each Cohort will be investigated in different subjects.

9.1.2 Inclusion and Exclusion

Each subject will be assessed according to the inclusion/exclusion criteria described in Section 7.0. Moreover, C-SSRS will be adopted in order to evaluate the risk of suicide. Only the evaluator who has been certified on the C-SSRS will evaluate C-SSRS in this study.

9.1.3 Medical History/Demography

Demographic information to be obtained will include date of birth, sex, race (reported by the subject), height, weight, caffeine consumption, alcohol consumption, and smoking status of the subject.

Medical history to be obtained will include whether the subject has any clinically significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions or diseases will be considered concurrent medical conditions. Any conditions (ie, diagnoses) associated with clinically significant laboratory test values, ECG or physical examination abnormalities observed at screening/baseline should be described. Prior medications including any medications that the subject completed within 4 weeks (28 days) prior to signing the informed consent and medications related to the eligibility criteria and the safety evaluations will be investigated.

In Part 2, the following information will be investigated during the screening period.

Primary disease (narcolepsy): the age of onset, the date of diagnosis.

The number of symptoms associated with the primary disease within the past one month (based on a subject's self-assessment): The average number of falling asleep in a day, the average number of a sleep attacks (overwhelming sleepiness without awareness of falling asleep) in a day, the average number of awakenings during sleep in a day, the total number of sleep paralysis symptoms within 1 month, the total number of hypnagogic hallucinations within 1 month, the average number of cataplexy episodes within 1 week.

Investigation of biomarkers related to the primary disease: Information about a test for measuring the concentration of orexin in the CSF (test performed or not performed;, if the test is performed, the concentration of orexin in the CSF will be recorded.), information about the MSLT (Presence of information, if available, the mean sleep latency and the number of SOREM periods will be recorded.)

Status of the sleep-related lifestyle within the past one month: The average number of the naps in a day, the average hours of sleep in a day, the average time of wake-up/go to bed.

On Day -1 in Part 2, the investigators will interview whether the number of the above symptoms accompanied by the primary disease have changed within a week before the hospital visit when compared to that during the screening period. The number of each symptoms observed within a week will also be recorded based on the sleep diary and a subject's self-assessment.

9.1.4 Concomitant Medications

Concomitant medications are any drugs administered except the study drug. Concomitant medications include medicines prescribed by a physician or OTC drugs purchased by a subject. Concomitant medications do not include any drugs supplied by the sponsor. 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 the initial and final administrations and reasons for use must also be recorded in the eCRF.

9.1.5 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions. Subjects will be asked how likely they are to doze off or fall asleep in the eight different situations in daily life. Respondents will be asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sum of 8 item scores) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity (daytime sleepiness) in daily life. The total scores will be recorded.

The ESS will be performed on Day -1 in Part 2.

9.1.6 HLA-DQB1 *06:02 Typing Gene Analysis

HLA-DQB1 *06:02 typing will be performed only on subjects on whom the presence of HLA-DQB1 *06:02 was not confirmed by their backgrounds/medical records in Part 2. In almost all narcoleptic patients with cataplexy who also has HLA-DQB1 polymorphism, the concentration of orexin in the CSF was reportedly low. Hence, this genotyping is regarded as a biomarker to identify a patient with type 1 narcolepsy in an appropriate clinical setting.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

A physical examination will be performed on the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) skin; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. When a physical examination is performed on Day 2 and Day 4 in Part 2, the items described in Section 9.3.2.3 will be completed using subjects self assessment and recorded.

9.2.2 Height and Weight

Each subject's height and weight will be measured. 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 one decimal place.

9.2.3 BMI

BMI will be calculated using the following formula:

Rating index: BMI=weight (kg)/[height $(m)^2$]

The measured value should be rounded off to one decimal place. The inclusion criteria for BMI will be defined based on the values after rounding.

9.2.4 Columbia Suicide Severity Rating Scale (C-SSRS)

A risk of suicide will be assessed using the C-SSRS at time points specified in the Schedule of Study Procedures (On Day 2 in Part 1 and Day 4 in Part 2). Two versions of the C-SSRS (baseline /screening and since the last visit) will be used in this trial. Any suicidal ideation or suicidal behavior detected by the C-SSRS during the study period will be recorded as an adverse event.

9.2.5 Vital Signs

Vital signs will include body temperature (tympanic temperature), respiratory rate,SBP and DBP in sitting, lying and standing positions (BP will be measured, except as otherwise noted, after the subject is lying in a bed with the head of the bed up to 30 degrees and takes a rest for more than 5 minutes, using the same arm each time), and pulse rate (heart beats per minute).

The same method (eg, the same and appropriately sized cuff, auscultatory method or manometer) must be used for all BP measurements for each subject. All measurement values will be recorded in the source documents and the eCRF.

When measurement of vital signs is scheduled at the same time as blood sampling, blood sampling should be performed first, then vital signs measurement will be performed within an acceptable time window (see Appendix C).

In the event that significantly elevated BP is observed after the stat of infusion of the study drug, the investigator should monitor the BP carefully and record the subject's status before and after the elevation in BP and a possible cause in the source documents.

9.2.6 12-Lead ECG

Measurements performed using a standard 12-lead ECG will be recorded. Subjects should take a rest in a recumbent position at least 5 minutes before each ECG measurement. The investigators (or a specialist working at the study site) will judge the ECG finding as "within normal limit" or "abnormal". If the investigators (or a specialist working at the study site) judged "abnormal", he/she will assess whether the abnormality is clinically significant. The time when the ECG was performed will be recorded. The following parameters will be recorded in the eCRF from the subject’s ECG trace: HR, RR interval, PR interval, QT interval, QRS interval, and QTcF.

When 12-lead ECG measurements are scheduled at the same time as blood sampling, blood sampling should be performed first, then 12-lead ECG will be measured within an acceptable time window (see Appendix C).

9.2.7 Study Drug Administration

The study drug will be intravenously administered to subjects over 9 hours on Day 1 in Part 1 and Day 1 and Day3 in Part 2 (TAK-925 will be administered to each subject only once in Part 2). The times of the start and the end of study drug administrations will be recorded. The infusion rate where the C_{max} (C_{ss}) becomes lower than the minimum pharmacologically active concentration will be calculated from the nonclinical data and used. Based on the pharmacokinetic data obtained from Cohort 1 Dose Level 1 and subsequent dose levels, the infusion rate will be adjusted to reach the steady-state concentration in 2 hours in the subsequent dose levels. This adjustment is essential to allow the infusion rate to reach the steady state when the first MWT is performed in Part 2.

Regaridng the possible occurrence of interruption or discontinuation of study drug administration, whether it occured or not occured, the time of interruption or discontinuation (if it was found) and the time of re-administration should be recorded in the eCRF.

9.2.8 AE Monitoring

AE monitoring must be commenced after obtaining the consent form signed by the subject. The details of AE collection and the procedures are provided in Section 10.2.

9.2.9 Laboratory Procedures and Assessments

All samples will be collected in accordance with the acceptable laboratory test procedures. Laboratory test samples will be collected after at least 8 hour-fasting on the days specified in the Schedule of Study Procedures (Section 3.0).

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following panels:

Red blood cell (RBC)	White blood cell (WBC) and differential (%)
Hemoglobin	Mean cell hemoglobin (MCH)
Hematocrit	Mean cell hemoglobin concentration (MCHC)
Platelet	Mean cell volume (MCV)

Serum Chemistry

Serum chemistry will consist of the following standard chemistry panels:

Albumin	Potassium
Alkaline phosphatase	Total protein
ALT	Sodium
AST	C-reactive protein
Total bilirubin	Total cholesterol
Blood urea nitrogen	Lactate dehydrogenase
Calcium	Magnesium
Chloride	Phosphorus
Creatinine	Triglycerides
γ-GTP	Uric acid
Glucose	

Urinalysis

Urinalysis will consist of the following panels:

Protein	Ketone bodies	Microscopy
Glucose	pH	RBC
Occult blood	Specific gravity	WBC
Nitrite	Urobilinogen	Squamous epithelial cell

Other

Tests to be performed at the same time of eligibility judgement:	
Serum	**Urine**
Immunology test Hepatitis screen (HBsAg and HCV antibody) HIV antigen-antibody detection assay Syphilis serum reaction test	Drug screen (phencyclidines, benzodiazepines, cocaines, stimulants, cannabinoids, morphines, barbiturates, and tricyclic antidepressants) Cotinine screen(a) Alcohol screen (urine test or breath test)(a) Pregnancy Test(b)

Note: The investigators will directly report the results of immunology test, urine drug screen, cotinine screen and alcohol screen to the subjects. The sponsor will confirm the overall test results ("Positive" or "All negative") and will not obtain detailed results for the subjects (including reserve subjects) who will be selected to be given the study drug. If a subject is positive for a drug screen performed in Part 2, the details should be reviewed to judge the subject eligibility.

(a) Part 1 only.
(b) Only for female subjects of childbearing potential in Part 2.

Hematology, serum chemistry and urinalysis will be performed at each study site. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

Ccr will be estimated using the Cockcroft-Gault Equation.

Cockcroft-Gault Equation

Male subjects: Ccr = [(140-Age) x Body Weight (kg)]/[72 x Serum Creatinine Level (mg/dL)]

Female subjects: Ccr = 0.85 x [(140-Age) x Body Weight (kg)]/[72 x Serum Creatinine Level (mg/dL)]

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-GTP and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormal value was detected. (Refer to Section 7.6 and Section 10.2.9.5 for the appropriate guidance on reporting abnormal liver function tests.)

The investigator will store a copy of the reference ranges for the laboratory test values.

9.3 PK, PD, and PGx, Samples

Samples for PK, PD, and pharmacogenomics (PGx) analyses will be collected as specified in the Schedule of Study Procedures (Section 3.0). Refer to the separately created manual for the detail of collection and handling of samples and the shipment of samples to the central laboratory. The actual time of sample collection for PK and PD analyses will be recorded in the source documents and the eCRF. Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Sample Collections

Sample Name	Primary Sampling	Primary Sampling Fraction	Purpose of Use	Sample Collection
Plasma sample for PK	Plasma	-	PK analysis	Mandatory
Urine sample for PK (a)	Urine	-	PK analysis	Mandatory
CSF sample for PK (b)	CSF	-	PK analysis	Mandatory
Blood sample for DNA PGx	Blood	DNA	PGx analysis	Optional

DNA: deoxyribonucleic acid.
(a) Only Part 1
(b) Only Cohort 4 in Part 1

9.3.1 PK Measurements

Pharmacokinetic parameters of TAK-925 and its metabolites ([redacted]) will be calculated from the concentration-time profile in all evaluable subjects. For all calculations, not the scheduled sampling times, but the actual sampling times will be used.

(1) Part 1

Unless otherwise specified, the following pharmacokinetic parameters will be calculated from the plasma concentrations of TAK-925 and its metabolites (CCI [redacted]):

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity
C_{max}	Maximum observed concentration
C_{eoi}	Concentration at the end of infusion
t_{max}	Time of first occurrence of Concentration
$t_{1/2z}$	Terminal disposition phase half-life
CCI [redacted]	
V_{ss}	Volume of distribution at state after intravenous administration (only for TAK-925)
V_z	Apparent volume of distribution during the terminal phase (only for TAK-925)
CL	Total clearance after intravenous administration (only for TAK-925)

Unless otherwise specified, the following urinary pharmacokinetic parameters were calculated from the urine concentrations of TAK-925 and its metabolites (CCI [redacted]):

Symbol/Term	Definition
Urine	
Ae_{24}	Amount of drug excreted in urine from time 0 to time 24
fe_{24}	Fraction of administered dose of drug excreted in urine from time 0 to time 24.
CL_R	Renal clearance

Unless otherwise specified, the following pharmacokinetic parameters will be calculated from the CSF concentrations of TAK-925 and its metabolites (CCI [redacted]):

Symbol/Term	Definition
CSF	
$R_{CSF/Plasma, ss}$	CSF/Plasma drug concentration at steady state

(2) Part 2

Unless otherwise specified, the following pharmacokinetic parameters will be calculated from the plasma concentrations of TAK-925 and its metabolites (CCI [redacted]):

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity
C_{max}	Maximum observed concentration
C_{eoi}	Concentration at end of infusion
t_{max}	Time of first occurrence of Concentration
$t_{1/2z}$	Terminal disposition phase half-life
CCI [redacted]	
V_{ss}	Volume of distribution at state after intravenous administration (only for TAK-925)
V_z	Apparent volume of distribution during the terminal phase (only for TAK-925)
CL	Total clearance after intravenous administration (only for TAK-925)

9.3.1.1 Plasma Samples for PK Measurements

The timing of PK blood samples may be changed if emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK of TAK-925. To reflect the plasma exposure more precisely, blood samples will be collected from the arm opposite to the one on which intravenous (IV) infusion is performed. If the opposite arm is not available, blood samples should be collected at the site as distant to the infusion site as possible, and the site of the blood sampling should be documented.

The blood sampling times, times of the start and the end of infusions should be recorded accurately, and particularly care should be given when recording the blood sampling times during the infusion and around the time close to the infusion.

The details of the preparation, handling, and shipping of samples are provided in the Study and Laboratory Manuals.

The blood samples used for pharmacokinetic analysis of TAK-925 and its metabolites (CCI [redacted]) (3 mL/time in Part 1 and 3-6 mL/time in Part 2) will be collected into a blood sampling tube containing an anticoagulant, ethylenediaminetetraacetic acid dipotassium (EDTA-2K).

Blood samples used for pharmacokinetic analysis of TAK-925 and its metabolites (CCI [redacted]) will be collected according to Table 9.b and Table 9.c.

(1) Part 1

Table 9.b Collection of Blood Samples for Pharmacokinetic Analysis (Part 1)

Analyte	Sample	Analysis date	Blood sampling time
TAK-925 and its metabolites (CCI [redacted])	Plasma	Day 1-2	Before infusion, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 9 hours after the start of infusion, and 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6,10[1)] and 15 hours after the end of infusion

1) Dose Level 1 and 2 of Cohorts 1 and 2 will be excluded at 10 hours after the end of infusion.

(2) Part 2

Table 9.c Collection of Blood Samples for Pharmacokinetic Analysis (Part 2)

Analyte	Sample	Analysis date	Blood sampling time
TAK-925 and its metabolites (CCI [redacted])	Plasma	Day 1-4	Before infusion[1)], 1, 2[1)], 4[1)], 6[1)] and 9[1)] hours after the start of infusion and 0.17, 0.5, 1, 2[1)] and 15[1)] hours after the end of infusion, at bedtime[1)] and right after wake-up.

1) Blood sampling will be 6 mL. For the other sampling times, 3 mL will be collected.

Blood samples collected for the placebo groups will not be analyzed.

In the case that a subject prematurely discontinues the study between the time from the start of study drug administration to the completion of procedures on Day 2 in Part 1 and on Day 4 in Part 2, the last blood samples to be used for pharmacokinetic analysis will be collected from the subject during his/her hospital stay.

If there is a need to interrupt or slow the IV infusion, the sponsor will be contacted to consider to replace the subject. If the IV infusion is interrupted, 2 additional PK samples (one will be collected when the infusion is stopped and another will be collected when the infusion is restarted) may be collected. The date and time of each additional sample collection and the times of the start and interruption of the infusion should be recorded accurately.

In the case of premature discontinuation during the period from Day 2 to the follow-up in Part 1, and during the period from Day 4 to the follow-up in Part 2, blood samples for pharmacokinetic analysis will not be collected from the subject who visits the hospital as an outpatient.

9.3.1.2 Urine samples for PK Measurements

Urine samples used for pharmacokinetic analysis of TAK-925 and its metabolites (CCI [redacted]) (Part 1 only) will be collected sampled according to Table 9.d.

Table 9.d Collection of Urine Samples for Pharmacokinetic Analysis

Analyte	Sample	Analysis date	Urine sampling time
TAK-925 and its metabolites (CCI [redacted])	Urine	Day 1-2	Before infution, 0-9 hours after the start of infusion, and 0-3, 3-6 and 6-15 hours after end of infusion

Urine samples collected for the placebo group will not be analyzed.

9.3.1.3 CSF for PK Measurements

CSF samples used for pharmacokinetic analysis of TAK-925 (Cohort 4 only, 2.5 mL/time) will be collected according to Table 9.e.

Table 9.e. Collection of CSF Samples for Pharmacokinetic Analysis

Analyte	Sample	Analysis date	CSF sampling time
TAK-925 and its metabolites (CCI)	CSF	Day 1	6 hours after the start of infusion

9.3.1.4 Bioanalytical Methods

Plasma, urine and CSF concentrations of TAK-925 and its metabolites (CCI) will be measured using CCI . Moreover, residual samples after measurements may be used for the purpose of exploring unidentified metabolites or biomarkers if needed.

9.3.2 PD Measurements

9.3.2.1 Maintenance of Wakefulness Test (MWT)

In Part 2, the MWT will be conducted to evaluate the subject's daytime sleepiness objectively in patients with narcolepsy.

One session of MWT will be completed in 40 minutes.

One session of 40-minute MWT will be conducted on Day -1 in Part 2 while saline is intravenously infused to each subject so that they may become familiar with the MWT. The MWT will be conducted 4 times each (at 10:00, 12:00, 14:00 and 16:00) on Day 1 and Day 3, respectively. For the MWT on Day -1, sleep latency will be recorded as much as possible. On Day 1 and Day 3, sleep latency will be recorded in each session. In addition, REM sleep latency, the number of wakefulness/N1 to stage REM transitions, time in stage REM sleep without atonia will be recorded in each session.

As an exploratory evaluation, additional analysis using electroencephalogram data obtained by MWT may be performed after breaking the randomization code.

See the manual for pharmacodynamic tests (CCI and MWT) for details.

9.3.2.2 CCI

CCI

9.3.2.3 CCI [redacted]

CCI [redacted]

9.3.2.4 CCI [redacted]

CCI [redacted]

9.3.2.5 CCI [redacted]

CCI [redacted]

9.3.3 PGx Measurements

9.3.3.1 Blood Sample for DNA PGx Measurements

If whole blood samples are to be collected for PGx analysis, subjects must sign a consent form to agree to the sampling, storage and analysis of their blood for PGx research. Although the PGx research is part of this study, subject's participation in the research shall be optional.

On Day 1 (Part 1) or Day 3 (Part 2), 5-mL of whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected [redacted] after the start of study drug administration.

Samples for PGx should be collected from subjects who signed the consent form and had received the study drug at least once, after the start of study drug administration. The participation of study subjects in PGx sample collection is optional.

PGx analysis may be conducted to evaluate a potential contribution of polymorphism to a drug response, ie, the PK, safety/tolerability and PD of TAK-925. As PGx is a developing area, many genes and their functions are not yet fully understood at present. Future data may suggest a role of some of these genes in drug response, which may allow to conduct an additional hypothesis-generating exploratory research using the stored samples.

9.3.3.2 Blood Sample for RNA PGx Measurements

Not applicable.

9.3.4 Confinement

(1) Part 1

Subjects will be hospitalized in a hospital during the period from Day -1 to Day 2 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 2, and confirmed by the investigators. Hospitalization from Day -2 may be allowed for Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort as needed.

(2) Part 2

Subjects will be hospitalized in a hospital during the period from Day -1 to Day 4 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 4, and confirmed by the investigators.

In addition, hospitalization during the washout period prior to Day -1 may be allowed in each cohort as needed, to ensure the subject safety during the washout period. Rebound cataplexy may occur during the washout period of drugs used for the treatment of cataplexy. The investigators must be careful for frequent occurrence of cataplexy episodes and ensure the subject's safety in the most appropriate way.

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.

An AE can therefore be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is considered related to the medicinal product.

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 ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

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

Pre-existing conditions:

- 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. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) 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). The Investigator 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, the investigator or the subinvestigator 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, the 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 medication, the worsening or complication should be recorded as a new AE. The investigator 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 informed consent form 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.
- Serious adverse events (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 that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was 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
CCI

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

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The intensity/severity of an AE is categorized as:

Mild: The event is transient and easily tolerated by the subject

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities

Severe: The event makes daily activities impossible.

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, i.e., 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 investigators 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 (Number)

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 and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and abnormal LFTs) will be commenced when a subject signs the informed consent form, and continued until the follow-up period ends.

10.2.9.2 Reporting AEs

At each study visit, the investigators 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 investigational product 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 investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, 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 investigators concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end dates and times.
- Number.
- Severity/Intensity.
- The investigator's or subinvestigator's opinion on the causal relationship between the event and administration of study drug(s) (Related/Not Related).

- The investigator's or subinvestigator's opinion on 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 for the study drug.
- Outcome.
- Seriousness.
- Timing of occurrence (after administration of 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:

At the first onset or notification of the SAE occurred, the investigators must report the SAE to the sponsor with relevant information within 1 business day. The investigator must also submit a detailed SAE report to the sponsor within 10 calendar days. The report must contain all information about the SAE as much as possible, including at least the following:

- A brief description of the event and the reason why the event was categorized as serious.
- Subject identification number.
- Name of the investigators or subinvestigators.
- Name of the study medication(s).
- Causality assessment.

Any SAE spontaneously reported to the investigators 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 investigators should complete a copy of the follow-up SAE form or provide other written documentation and submit it immediately within 24 hours of receipt to the sponsor. Copies of any relevant data from the hospital notes (eg, ECGs, 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.

10.2.9.4 The Adverse Event Related CCI [redacted]

In an acute single-dose intravenous dose-escalation toxicity study in monkeys, CCI [redacted] [24] or those events that resulted in the discontinuation of study drug administration were

observed, the investigators must monitor these events continuously and report them to the sponsor immediately.

Further investigation may be needed for these events to establish their diagnosis. The same reporting method and reporting period as the SAE reporting will be used when the investigator reports the events to the sponsor (Refer to Section 10.2.9.3).

10.2.9.5 Reporting of Abnormal LFTs

When elevated ALT or AST elevates over 3 times higher than the ULN and the elevated total bilirubin over 2 times higher than the ULN, and these abnormal LFT values cannot be explained by other factors, these values will be recorded as SAEs and reported according to Section 10.2.9.3. In addition, the investigators will report these SAEs to the clinical research associates (CRAs) and investigate the cause other than the study drug(s) (possible occurrence of acute viral hepatitis A or B, or other acute hepatic diseases, past/current medical history).The follow-up laboratory tests described in Section 9.2.9 must also be performed.

10.2.10 Safety 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 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 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 an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational 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 by the analysis personnel prior to database lock. This document will provide further details regarding the definitions of analysis variables, and analysis methodologies to address all study objectives.

11.1.1 Analysis Sets

In this study, three analysis sets will be used: the safety analysis set, the PK analysis set, and the PD analysis set. The definition of each analysis set will be described in the SAP.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. If necessary, the SAP will be supplemented with new handling rules that were not discussed at the planning stage. The SAP must be finalized prior to database lock.

11.1.1.1 Safety Analysis Set

The safety analysis set will be defined as all subjects who received at least one 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 one dose of study drug and whose plasma or CSF concentration can be measured at least once or whose cumulative urinary excretion can be calculated.

11.1.1.3 PD Analysis Set

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

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the safety analysis set, the PK analysis set and the PD analysis set.

11.1.3 PK Analysis

(1) Endpoints and analysis methodologies

[Endpoints]

Plasma concentrations and pharmacokinetic parameters of TAK-925 and its metabolites (CCI [redacted]).

Urine pharmacokinetic parameters of TAK-925 and its metabolites (CCI [redacted]).

CSF concentrations and pharmacokinetic parameters of TAK-925 and its metabolites (CCI [redacted]).

[Analysis methodologies]

The following analysis will be performed using the PK analysis set in Cohorts 1-2 and Healthy Adult Supplement Cohort, and Cohorts 3 and Healthy Elderly Supplement Cohort, Cohort 4 and Part 2 by dose level.

Plasma and CSF concentrations of TAK-925 and its metabolites (CCI) will be summarized for each scheduled sampling time using descriptive statistics.

Descriptive statistics will be summarized for plasma, urine and CSF pharmacokinetic parameters of TAK-925 and its metabolites (CCI) summarized.

The details will be described in the SAP.

11.1.4 PD Analysis

(1) Endpoints and analysis methodologies

[Endpoints]

The average sleep latency in the MWT, sleep-related parameters in the MWT (sleep latency in each session, REM sleep latency, the number of wake/sleep stage 1(N1)-to-REM sleep transitions total time of REM sleep without atonia), assessment of daytime sleepiness using the KSS, assessment by the CCI , assessment of sleep-related symptoms of cataplexy and narcolepsy using a daily dairy for collecting cataplexy and sleep-related symptoms.

[Analysis methodologies]

The following analysis will be performed using the PD analysis set:

For the average sleep latency in MWT in Part 2, descriptive statistics for the observed values will be provided by dose level. An analysis of variance (ANOVA) for crossover design with the observed value as a response, the dose level, the group and the period as factors will be conducted. The differences in the least square means between each dose level of TAK-925 and placebo (each dose level of TAK-925 – the placebo) and two-sided confidence intervals will be provided. Bayesian posterior probabilities that the mean differences are greater than the value (specified in the SAP) will be provided based on the Bayesian posterior distributions for the mean differences between each dose level of TAK-925 and the placebo (each dose level of TAK-925 – the placebo).

The details for endpoints other than the average sleep latency in the MWT will be described in the SAP.

11.1.5 Safety Analysis

(1) Endpoints and analysis methodologies

[Endpoints]

AEs, Clinical Laboratory Tests, Vital Signs, Weight and 12-Lead ECG

[Analysis methodologies]

The following analysis will be performed using the safety analysis set in Cohorts 1-2 and Healthy Adult Supplement Cohorts, Cohorts 3 and Healthy Elderly Supplement Cohort, Cohort 4 and Part 2 by dose level.

11.1.5.1 AEs

A treatment emergent adverse event (TEAE) is defined as an AE that occurs on or after the start of study drug administration. The analyses of TEAEs will be conducted for the followings. TEAEs will be coded using the MedDRA dictionary and tabulated by the system organ class (SOC) and the Preferred Term (PT).

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

11.1.5.2 Clinical Laboratory Evaluation

For continuous variables, the observed values and changes from baseline will be summarized for each scheduled sampling time using descriptive statistics. Case plots will also be presented for the observed values. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled sampling time will be provided.

11.1.5.3 Vital Signs, Weight

The observed values and the changes from baseline will be summarized for each scheduled sampling time using descriptive statistics. Case plots will also be presented for the observed values.

11.1.5.4 Other Safety Parameters

12-Lead ECG parameters will be summarized as follows: For continuous variables, the observed values and the changes from baseline will be summarized for each scheduled sampling time using descriptive statistics. Case plots will also be presented for the observed values. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled sampling time will be provided. The details for other endpoints will be described in the SAP.

11.2 The Conversion Method of Data, and Handling of Lack of Data

For plasma and CSF concentrations as well as laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. The details will be provided in the SAP.

11.3 Committees Set Up for This Study

In this study, a central review of data from the MWT and the CCI will be performed.

The central reviewer must be a specialist who has an appropriate experience of evaluating endpoints. Upon request from the sponsor, the reviewer will perform consistent evaluation of the MWT and the CCI of which the results were reported by each study site.

The independent reviewer will review the MWT and CCI results submitted by the investigators. The details will be described in the manuals for pharmacodynamic tests (CCI and MWT) and for assessment of the CCI and MWT.

The results of review by the independent reviewer will be reported to each site.

11.4 Interim Data Review and Criteria for Premature Termination

The sponsor's unblinded team will review unblinded data. This team will review the effects on the safety tolerability, PK and the average sleep latency in the MWT to recommend a dose level in Cohort 6. The dose selected will be reported to the site pharmacist. All other site staff will remain blinded. A similar review will be performed for the dose level and the number of subjects in Cohort 7. Reviews of each cohort and the dose escalation after completion of each dose level will be provided in Section 6.2. Criteria for study termination or interruption are described in Section 6.5.4.

11.5 Determination of Sample Size

In Cohort 1-3 in Part 1, 8 subjects (6 in the TAK-925 group and 2 in the placebo group) was selected as the sample size to evaluate the safety, tolerability and PK of TAK-925 when a single dose of TAK-925 is administered intravenously to healthy adults and the healthy elderly. In the event that further investigation on the safety, tolerability and PK in healthy adults is needed after completion of Cohorts 1-2, a maximum of 4 additional cohorts (a total of 32 healthy adult subjects; 8 subjects [6 in TAK-925 group, 2 in placebo group] for each cohort) may be enrolled. If further investigation on the safety, tolerability and PK in healthy elderly is needed after completion of Cohort 3, a maximum of 1 additional cohort (a total of 8 healthy elderly subjects [6 in TAK-925 group, 2 in placebo group] per cohort) may be enrolled.

For Cohort 4 in Part 1, 4 subjects will be enrolled to evaluate the safety, tolerability, PK s of TAK-925 including the concentration of TAK-925 in the CSF when a single dose of TAK-925 is administered intravenously to healthy adults.

For Part 2, 4 patients each in Cohort 5, 6 and a maximum of 12 patients in Cohort 7 will be enrolled to evaluate the safety, tolerability, PK and pharmacodynamic effects of TAK-925 when a single dose of TAK-925 is administered to patients with type 1 narcolepsy.

These sample sizes are not based on any effect size obtained by the MWT or statistical evidence.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

The sponsor or a designee (Contract Research Organization) will visit study sites for periodic monitoring during the study period 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 the original documents, data and records. The investigator and the head of study site guarantee that the sponsor or its designee and the IRB/IEC have access to the source documents.

The sponsor or its designee (as long as blinding is not jeopardized) will review the records including the Investigator's Binder, study drugs, subjects' medical records, informed consent forms to confirm that all aspects of the study are appropriately conducted in accordance with the protocol. The consistency between the eCRF and the source documents related to the eCRF should also be reviewed. When a monitoring visit is performed at a study site, the investigator, subinvestigator and other study personnel must spare time to support that the monitoring is proceeded appropriately.

12.2 Protocol Deviations

The investigators can deviate from or change the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from the IRB or IEC. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and an approval from the IRB should be obtained.

The investigators should document all the protocol deviations.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or its designee. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the Medicines and Healthcare products Regulatory Agency in the U.K. [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] in Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the study site guarantee that the auditor can have access to all study documents 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 Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and Appendix A.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local rules of each participating region. The sponsor or its designee will need to obtain a document containing all names and titles of IRB or IEC members. If a member of the IRB or IEC is directly participating in this study, a written document regarding his or her abstinence from voting must also be obtained.

The sponsor or its designee will submit study-related documents to the IRB or IEC for review and approval of the protocol In addition to the protocol, the investigator's brochure, a copy of the informed consent forms, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to the central or local IRB or IEC for approval. The sponsor or its designee must obtain a written approval for the protocol and informed consent forms from the IRB or IEC before the commencement of the study. The documents approved by the IRB or IEC must contain the exact protocol title, protocol number, date of creation/amendment; and also edition number and date of approval of other documents reviewed (eg, informed consent forms). The sponsor will notify to each site after he/she confirmed the appropriateness of the site's regulation documents. Until the site receives the notification, no protocol procedures, including screening, will be commenced.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include amendments of protocol, informed consent form and subject recruitment materials, and local safety reporting requirements, update report of the study at the IRB/IEC-specified intervals, submission of the End of Study report, etc. The sponsor or its designee must obtain all the above documents approved by the IRB/IEC and relevant documents.

Incentives for subjects should not exert undue influence on their participations. Payments to subjects must be approved by the IRB or IEC and the sponsor.

Regarding a pharmacogenomic research using collected and stored samples, analysis will be carried out when the details are determined. A pharmacogenomic research plan will also be created.

13.2 Subject Information, Informed Consent, and Subject Authorization

An informed consent form will contain the detailed elements of the Declaration of Helsinki and the ICH Harmonised Tripartite Guideline for GCP and all applicable laws and regulations. The informed consent form also contains the planned and permitted usage, transfers, and disclosures of the subject's personal information and health information for the purpose of conducting this study. The form further explains the nature of the study, study objectives, and potential risks and benefits,

as well as the date of signature of informed consent form. The form will detail the requirements of the participant and the fact that he or she is free to withdraw from the study at any time during the study 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. The informed consent form must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigators to explain the detailed elements of the informed consent form 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.

The investigators must give must give the subject ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject determines that he or she will participate in the study, the subject must sign and date the informed consent form. The subject should be instructed to sign his/her legal name, not nickname, using blue or black ballpoint pen. The investigators must also sign and date the informed consent form at the time of consent and prior to the subject's enrollment in the study.

The investigators must store the signed original informed consent form, and also record the date the subject signed in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

If the consent form is revised, the investigators must obtain a signature from the subject again, in the same manner as the original informed consent was obtained. The new date of signature should be recorded in the subject's medical record, and a copy of the revised informed consent form should be given to the subject.

Subjects who consented to provide their DNA samples for a PGx research can withdraw their consent and request disposal of stored samples at any time prior to analysis. If a subject withdrew his/her consent, the sponsor must be informed of the 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. In this study, the subject's source data will only be linked to the sponsor's clinical study database or documents via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to identify the subject and confirm the accuracy of the subject's unique identification number.

To ensure that the study is being conducted according to the protocol and the ICH-GCP guidelines, the sponsor, CRAs, sponsor's designees, representatives of each regulatory authorities (eg, FDA, MHRA, PMDA), sponsor-designated auditors and the IRBs/IECs can require the investigator to permit them to have access to the original documents (source data or documents), including, but not limited to, laboratory test results, ECG measurements, admission and discharge records during the subject's study participation, and autopsy results. The investigators must obtain authorization

from the subject when CRAs, representatives of the regulatory authorities, etc. have access to the subject's original medical record as part of the informed consent process (see Section 13.2).

When a copy of the subject's source documents is provided to the sponsor, personally identifiable information (eg, subject's name, address, and other identifiers not recorded in the subject's eCRF) must be removed.

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with all test results and data derived by the study. During and after the study, only the sponsor can disclose the study information to other investigators or regulatory authorities, unless otherwise specified by law Any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor, unless otherwise agreed in the study site agreement.

The sponsor may publish any data and information obtained from the study (including data and information provided by the investigator) without consent of the investigator. The investigator and subinvestigator must obtain a prior written approval from the sponsor when externally publishing any information obtained from the study to a specific academic society, etc.

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, Takeda will, at a minimum, register all interventional clinical trials it sponsor's anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of the study, as stipulated in the Takeda Policy/Standard. Takeda contact information, along with the name, city, state (only for the U.S.), country of each medical institution that will conduct a clinical trial and the subject recruiting status will be registered and available for public viewing.

13.4.3 Clinical Trial Results Disclosure

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

13.5 Insurance and Compensation for Injury

Each subject participating 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 needed, the sponsor or the 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, contact the sponsor or the 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
Ae	amount of drug excreted in urine
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
BP	Blood pressure
BSES	betadex sulfobutyl ether sodium
C_{6h}	observed concentration at 6 hours after starting dose
Ccr	Creatinine clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CRA	clinical research associate
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ESS	Epworth Sleepiness Scale
FDA	U.S. Food and Drug Administration
fe	fraction of administered dose of drug excreted in urine
FIH	first-in-human
GCP	Good Clinical Practice
γ-GTP	gamma-glutamyl transferase

Term	Definition
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HED	human equivalence dose
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSD-3	International Classification of Sleep Disorders, third edition
IEC	independent ethics committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
KSS	Karolinska Sleepiness Scale
CCI [redacted]	CCI [redacted]
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	The Medicines and Healthcare Products Regulatory Agency
MHW	The Ministry of Health and Welfare
MRSD	maximum recommended starting dose
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
NOAEL	no observed adverse effect level
OX	orexin
OX1R	orexin type 1 receptor
OX2R	orexin type 2 receptor
OTC	over-the-counter
PD	pharmacodynamics
PGx	pharmacogenomics
PK	pharmacokinetics
PT	Preferred Term
PMDA	The Pharmaceuticals and Medical Devices Agency
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
QOL	quality of life
QTcF	corrected QT with Frederica correction method
RBC	red blood cell
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan

Term	Definition
SBP	systolic blood pressure
SOREM	sleep-onset rapid eye movement
SSRIs	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
$t_{1/2}$	half-life period
ULN	upper limit of normal
V_z	volume of distribution
WBC	white blood cell

15.0 DATA HANDLING AND RECORDKEEPING

The details of procedures for data management will be documented in the Data Management Plan. AEs, and past and current medical history will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 eCRFs

An eCRF is prepared for each subject who signed the informed consent form.

The sponsor or its designee will allow all study sites to have access to eCRFs. The sponsor will teach appropriate site staff how to use and complete the eCRF. The eCRF is used to transmit the information collected from the study to the sponsor and the regulatory authorities. The eCRF must be completed in English. When an eCRF is prepared, data are entered directly into the eCRF.

After all data are entered, a logic check will be performed by computer to detect incorrect dates, missing data, questionable values, etc. If the sponsor (or its designee) asks the study site a guestion about the entered data, the study site will answer the question.

A change or the correction of eCRF will be recorded as the audit trail that recorded an information before and after a changer or the correction, change or reviser, change or correction day and the reason.

The principal investigator must review the eCRF for completeness and accuracy and provide his/her electronic signature in an appropriate page. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered in the eCRFs.

The following data will not be recorded in the eCRF:

- Pharmacogenomic analysis results
- Laboratory results
- Drug concentration measurement results

If the investigators modifies or corrects the data in the eCRF or adds new information to the data after the clinical study database is locked, such modification or correction should be made using the modification and correction record of the eCRF. The principal investigator must review the modification and correction record of the eCRF for completeness and accuracy, and then provide his/her electronic signature within the eCRF.

The sponsor or its designee must review all eCRFs for completeness and accuracy during his/her periodic visits to the study site. The sponsor or its designee will also review study-related subjects' medical and hospital records to ensure the accuracy of those subjects' eCRFs. The completed eCRFs are the sole property of the sponsor, and the investigators must not disclose the information to any third parties, except authorized representatives of the regulatory authorities, without written permission of the sponsor.

15.2 Record Retention

For the purpose of investigation or audit by the regulatory authorities, the sponsor or its designee, the investigator or the head of the study site must keep the records stipulated in Section 15.1 and the documents including the study-specific documents, subject identification log, medical records, original signed and dated informed consent forms, electronic copies of eCRFs including their audit trails, and drug accountability log. The investigator and the head of the study site must retain essential documents until the following 1 or 2, whichever comes later. However, if the sponsor needs to retain those documents longer than the day, the head of the study site and the sponsor should discuss how long and how they will be retained.

1. The day when a marketing approval of the study drug was obtained (or the day 3 years after the notification of early termination of the study)
2. The day 3 years after the date of early termination or completion of the study

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

16.0 REFERENCES

[1] American Academy of Sleep Medicine. The International Classification of Sleep Disorders, Third edition.Darien, IL: American Academy of Sleep Medicine; 2014.

[2] Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, et al. Reduced number of hypocretin neurons in human narcolepsy. Neuron. 2000;27(3):469-74.

[3] Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med. 2000;6(9):991-7.

[4] Sakurai T. New treatment of sleep disorders. Orexin and sleep-wake regulation system. Brain 21. 2015;18(2):53-60.

[5] Guidelines on the Diagnosis and Management of Narcolepsy. The Japanese Society of Sleep Research.

[6] Kornum BR, Knudsen S,Ollila HM, Pizza F, Jennum PJ, Dauvilliers Y, et al. Narcolepsy. Nat Rev Dis Primers. 2017;3:Article 16100.

[7] Moresco M, Riccardi LN, Pizza F, Zenesini C, Caporali L, Plazzi G, et al. Pharmacogenetics and treatment response in narcolepsy type 1: Relevance of the polymorphisms of the drug transporter gene ABCB1. Clin Neuropharmacol. 2016;39:18-23.

[8] Lammers GJ. Treatment of Narcolepsy. In: Baumann CR, Bassetti CL, Scammell TE, editors. Narcolepsy: Pathophysiology, diagnosis, and treatment. New York: Springer; 2011. p. 401-9.

[9] Sakurai T. Function of orexin and mechanism of action of orexin receptor antagonist . Nippon rinsho. 2015; 73(6): 1023-30

[10] Xu TR, Yang Y, Ward R, Gao L, Liu Y. Orexin receptors: multi-functional therapeutic targets for sleeping disorders, eating disorders, drug addiction, cancers and other physiological disorders. Cell Signal. 2013;25(12):2413-23.

[11] Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. Neuron. 2001;30(2):345-54.

[12] Huang SC, Dai YW, Lee YH, Chiou LC, Hwang LL. Orexins depolarize rostral ventrolateral medulla neurons and increase arterial pressure and heart rate in rats mainly via orexin 2 receptors. J Pharmacol Exp Ther. 2010;334(2):522-9.

[13] U.S. Food and Drug Administration [Internet]. Pharmacology/Toxicology, Below is a sortable table of Pharm/Tox guidances [updated 2005 Jul 28]. Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers; 2005 Jul [about 30p]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm.

[14] VFEND for Intravenous use 200 mg, Package leaflet Pfizer Inc. January, 2018 revision (the 19th edition)

[15] CARNEXIV[prescribing information] Deerfield, IL, USA:Lundbeck, 2016 October.

[16] Modiodal 100 mg tablet, Package leaflet The Mitsubishi Tanabe Pharma Corp. April, 2015 revision (the 8th edition)

[17] Xyrem[prescribing information]. Palo Alto, CA, USA:Jazz Pharmaceuticals, Inc. 2014 April.

[18] Xyrem[Summary of product characteristics]. United Kingdom, UCB Pharma Ltd. 2010 October.

[19] Wakix[Summary of product characteristics]. France, Bioprojet Pharma. 2017 February.

[20] Guidelines for clinical evaluation method of a medicament for use in the elderly, Yaku-shin104, Notification of the First Evaluation and Registration Division Chief, Pharmaceutical Affairs Bureau, MHW (2 Dec, 1993).

[21] Journal of Japan Society for the Study of Obesity. Obesity diagnostic criteria 2011. Obesity research. 2011;10 (extra edition).

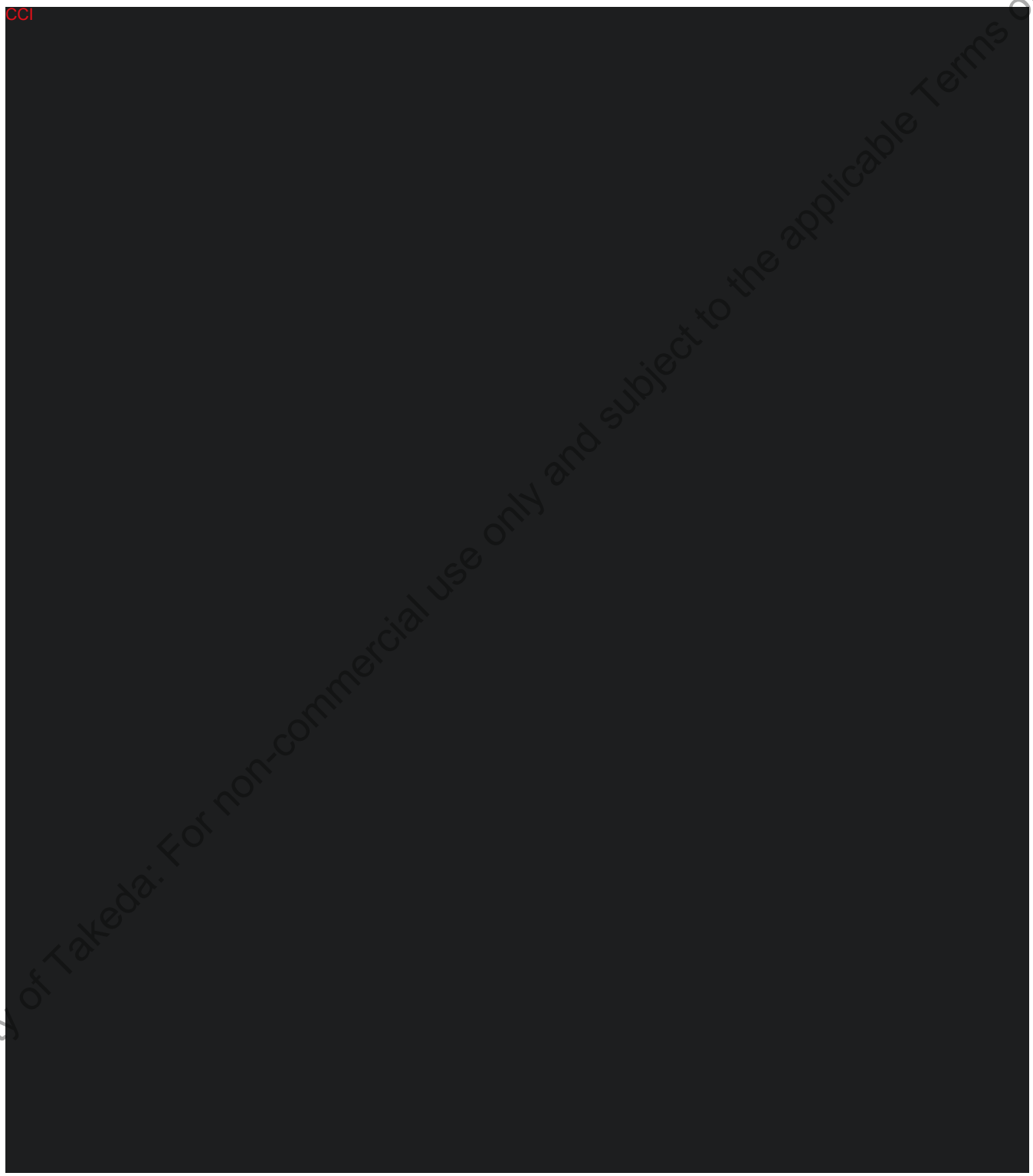
[22] Legal Performance Regulations Regarding Security of Safe Supply of Safe Blood Formulas(Ordinance of the Ministry of Health and Welfare No.22 of 1956).

[23] General Considerations for Clinical Trials (21 Apr, 1998 Iyaku-shin 380).

[24] The Ministry of Health, Labour and Welfare, The manual for each disease of serious adverse events, seizure and epilepsy, in May, 2009 (http://www.info.pmda.go.jp/juutoku/file/jfm0905004.pdf) (access date: 24 July, 2017)

17.0 APPENDICES

CCI



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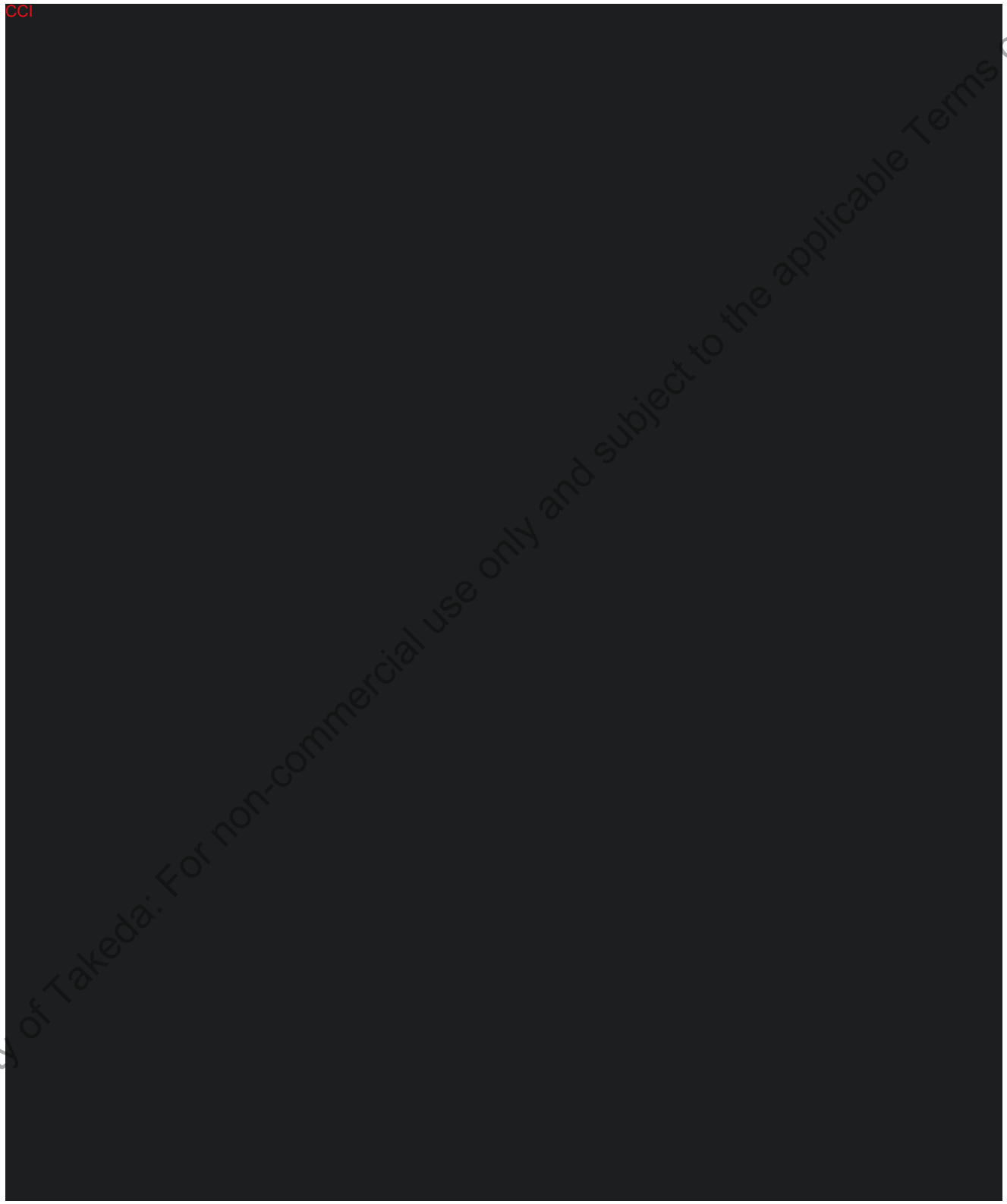

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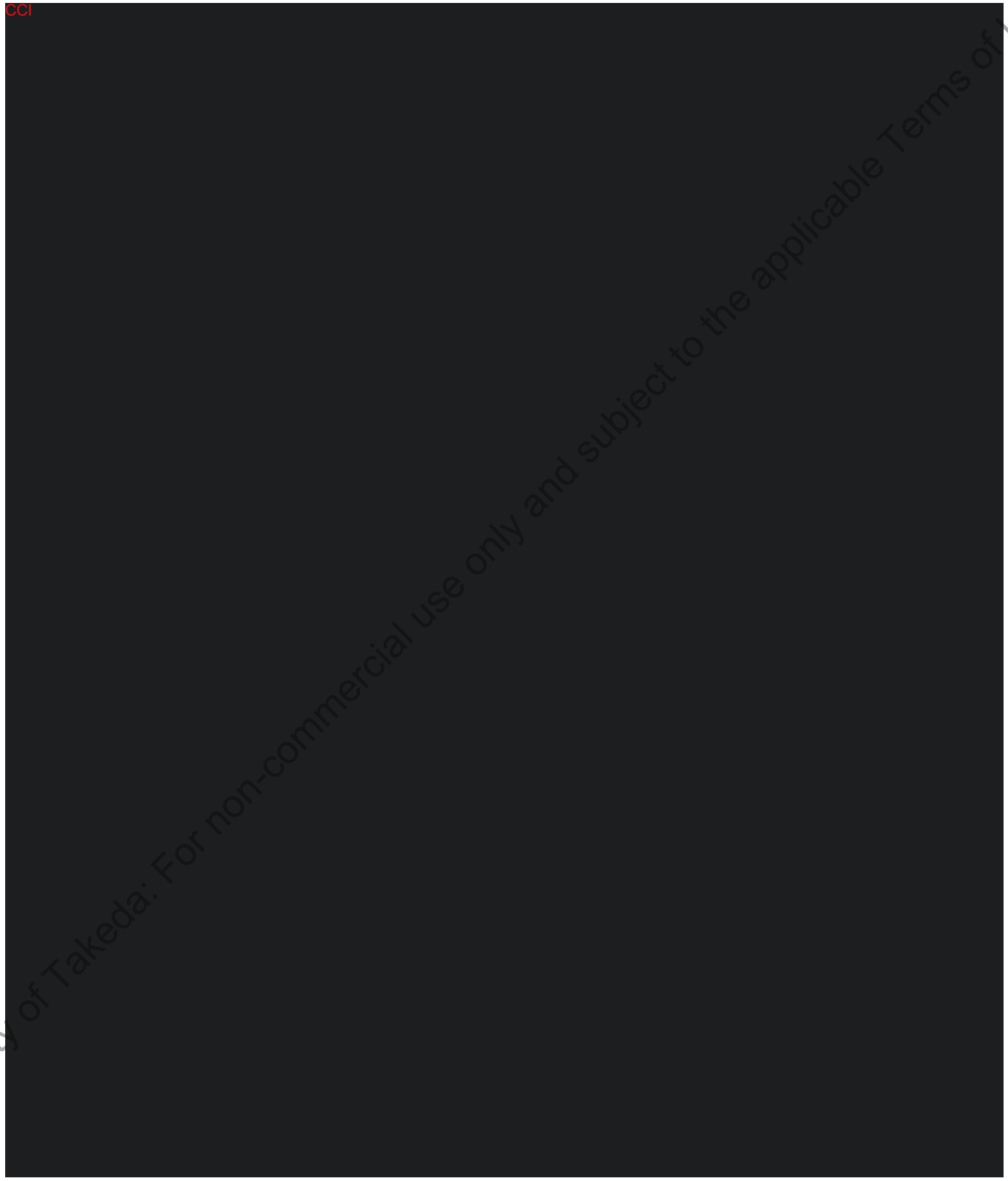

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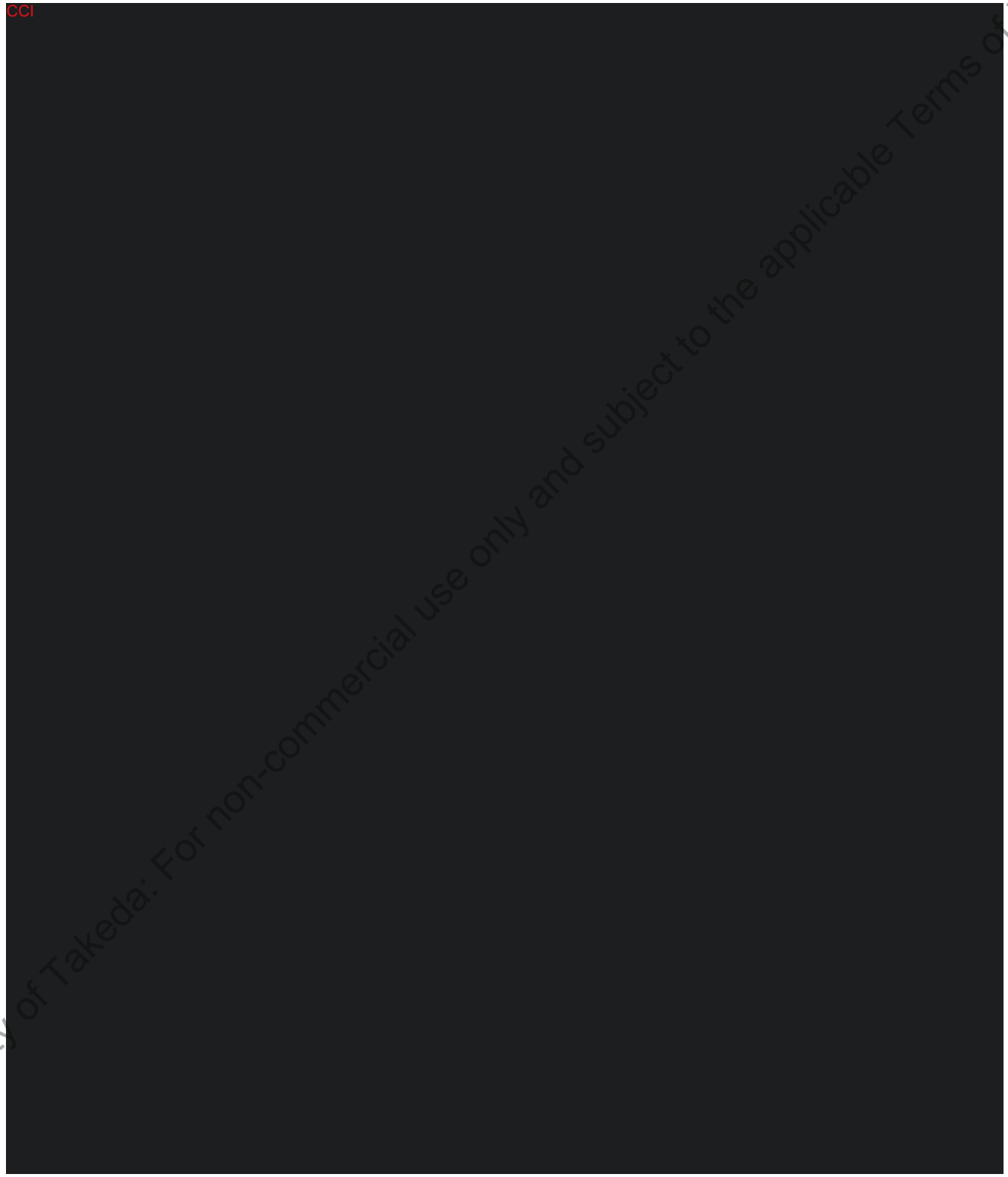

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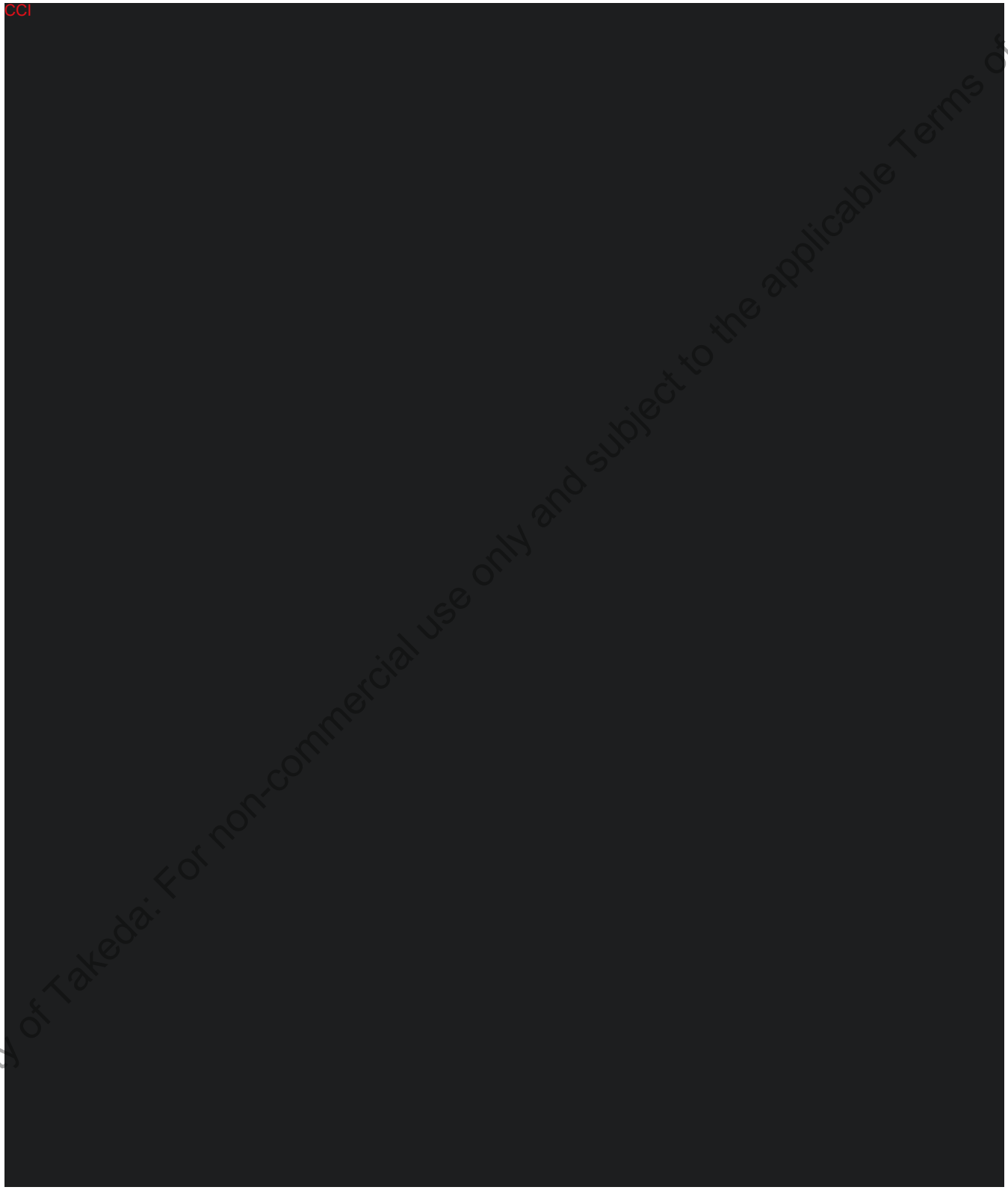

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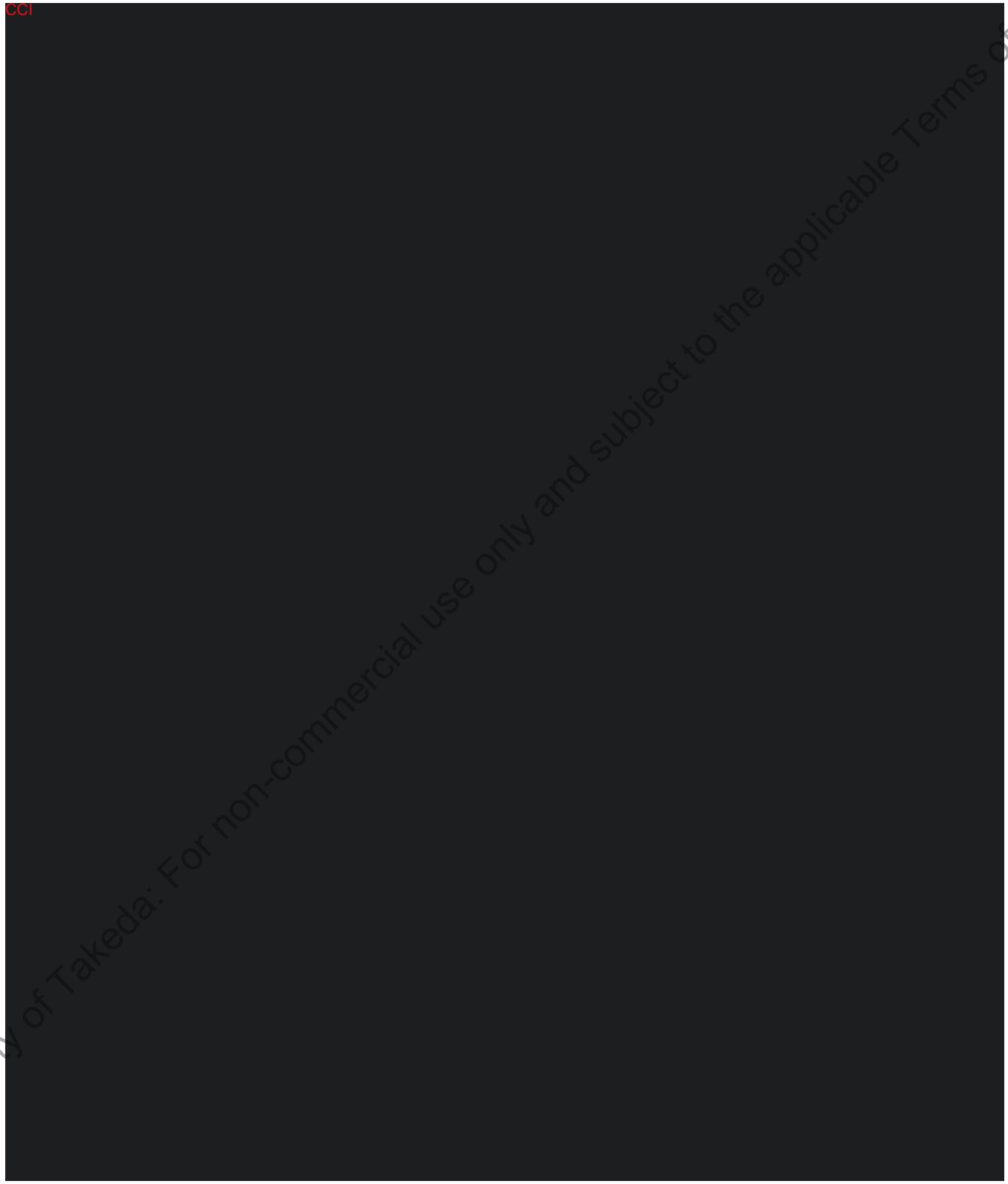

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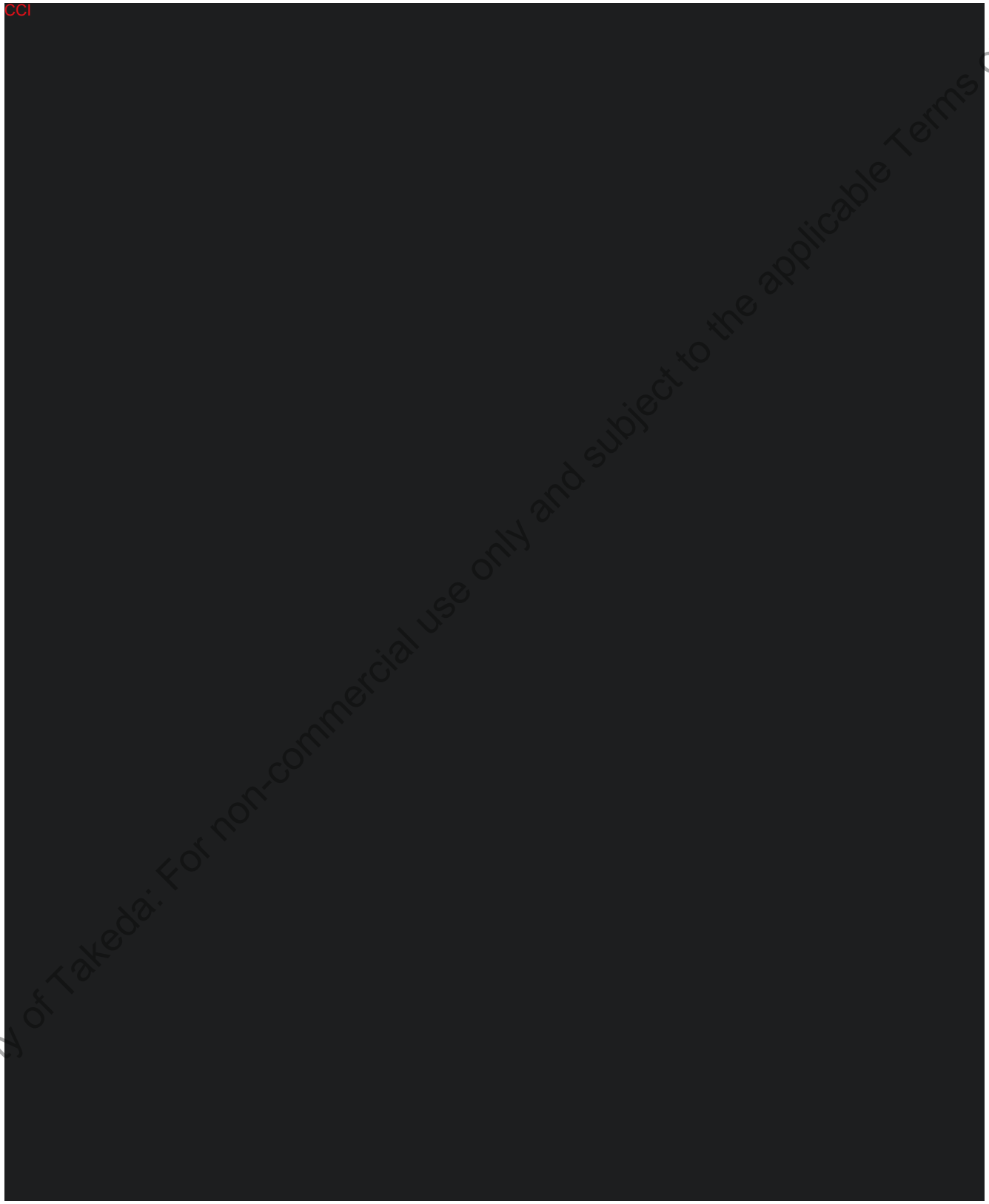

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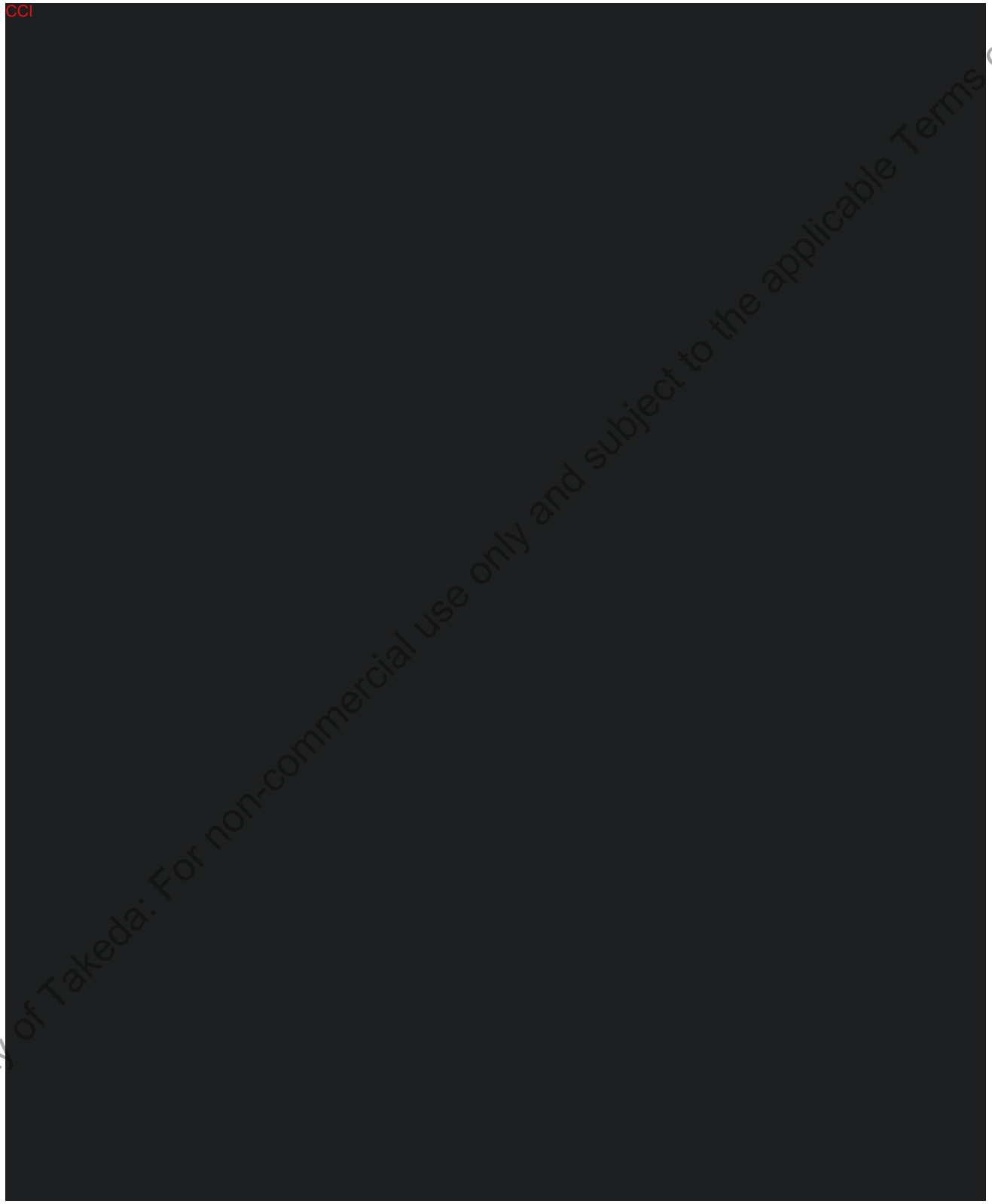

Page Edited (3rd version)		Existing Text Amendment 1: 22 Jan 2018	Revised Text Amendment 2: 06 Mar 2018	Rationale for Amendment
Page	Item			
p.8-9	1.0 STUDY SUMMARY	Trial Design: ・・・ (1) Part 1 In Cohort 3 and Healthy Adult Supplement Cohort following Cohort 2. ・・・ In Cohort 3, 8 healthy elderly will be enrolled. Of these 8 subjects, 6 will be randomly assigned to the TAK-925 group and 2 to the placebo group. This cohort will be initiated after started with the dose of which the safety and tolerability has been established in healthy adults. ・・・ Cohorts 3 and 4 may be started at the discretion of the sponsor, considering the status of Cohorts 1, 2 and Healthy Adult Supplement Cohort.	Trial Design: ・・・ (1) Part 1 In Cohort 3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort (in the event that a cohort is added) following Cohort 2. ・・・ In Cohort 3, 8 healthy elderly will be enrolled. Of these 8 subjects, six will be randomly assigned to the TAK-925 group and 2 to the placebo group. This cohort will be initiated after started with the dose of which the safety and tolerability has been established in healthy adults. In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 3, a maximum of 1 additional cohorts for Healthy Elderly Supplement Cohorts that enrollse 8 healthy elderly per cohort will be commenced without amendment of the protocol. The cohort name of R1 will be assigned for the Healthy Elderly Supplement Cohort. Six subjects will be randomly assigned to the TAK-925 group and 2 subjects to the placebo group, to evaluate the safety, tolerability and PK. In the Healthy Elderly Supplement Cohort, the dose may be higher orlower than or the same to that of prior cohort dose levels, or an intermediate dose between two prior doses. ・・・ Cohort 3, Healthy Elderly Supplement Cohort and Cohort 4 may be started at the discretion of the sponsor, considering the status of Cohorts 1, 2 and Healthy Adult Supplement Cohort.	Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higer dose. Clerical corrections
p.10	1.0 STUDY SUMMARY	Planned Number of Subjects: (1) Part 1 ・・・ ・ Cohort 4: 4 subjects In the event that a cohort is added, a maximum of 4 cohorts (32 additional subjects) can be enrolled.	Planned Number of Subjects: (1) Part 1 ・・・ ・ Cohort 4: 4 subjects In the event that a cohort is added, a maximum of 5 cohorts (40 additional subjects) can be enrolled.	
p.11	1.0 STUDY SUMMARY	Planned Trial Duration: (1) Part 1 Screening period (Cohort 1 Dose Level 1, Cohort 2 Dose Level 2, Cohorts 3 and 4 and Healthy Adult Supplement Cohort) Days -28 to -2	Planned Trial Duration: (1) Part 1 Screening period (Cohort 1 Dose Level 1, Cohort 2 Dose Level 2, Cohorts 3 and 4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort) Days -28 to -2	
p.11	1.0 STUDY SUMMARY	Main Criteria for Inclusion: ・・・ The Healthy Elderly (Cohort 3)	Main Criteria for Inclusion: ・・・ The Healthy Elderly (Cohort 3 and Healthy Elderly Supplement Cohort)	

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p.12	1.0 STUDY SUMMARY	Main Criteria for Exclusion: ・・・ Healthy Adult and The Healthy Elderly (Cohorts 1-4 and Healthy Adult Supplement Cohort)	Main Criteria for Exclusion: All Subjects ・・・ Healthy Adult and The Healthy Elderly (Cohorts 1-4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort)	Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higher dose.
p.13	1.0 STUDY SUMMARY	Statistical Considerations: PK: For Cohorts 1-2 in Part 1, Healthy Adult Supplement Cohort and Part 2, the following analyses will be performed for each dose level using the PK analysis set. For the other cohorts, the analyses will be performed for each cohort and each dose level using PK analysis set.	Statistical Considerations: PK: For Cohorts 1-2 and Healthy Adult Supplement Cohort, Cohort 3 and Healthy Elderly Supplement Cohort, Cohort 4, Part 2, the following analyses will be performed for each dose level using the PK analysis set. Plasma and CSF concentrations of TAK-925・・・.	
p.14	1.0 STUDY SUMMARY	Sample Size Justification: ・・・ If further investigation on the safety, tolerability and PK is needed after completion of Cohorts 1-2, a maximum of 4 additional cohorts (a total of 32 healthy adult subjects; 8 subjects [6 in TAK-925 group, 2 in placebo group] per cohort) may be enrolled. Randomized toTAK-925:6 subject, placebo: 2 subjects for a maximum of 32 additional subjects. For Cohort 4 in Part 1, 4 subjects will be enrolled to evaluate the safety, tolerability, PK of TAK-925 including the concentration of TAK-925 in the CSF when a single dose of TAK-925 is administered intravenously to healthy adults.	Sample Size Justification: ・・・ If further investigation on the safety, tolerability and PK in healthy adults is needed after completion of Cohorts 1-2, a maximum of 4 additional cohorts (a total of 32 healthy adult subjects; 8 subjects [6 in TAK-925 group, 2 in placebo group] per cohort) may be enrolled. If further investigation of safety, tolerability and PK in healthy elderly is needed after completion of Cohort 3, a maximum of 1 additional cohort (a total of 8 healthy elderly subjects [6 in TAK-925 group, 2 in placebo group] per cohort) may be enrolled. For Cohort 4 in Part 1, 4 subjects will be enrolled to evaluate the safety, tolerability, PK of TAK-925 including the concentration of TAK-925 in the CSF when a single dose of TAK-925 is administered intravenously to healthy adults.	

<table>
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<tr><td>p.15</td><td>2.0 STUDY SCHEMATIC</td><td>Figure 2.a Summsry of the Study Design
<Part 1>
1. Cohorts 1 and 2 (Healthy Adults) and Cohorts S1-S4 (Healthy Adult Supplement Cohorts)
<table><tr><td></td><td colspan="6">Dose Level</td></tr><tr><td>Cohort</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr><tr><td>1</td><td></td><td>TBD</td><td></td><td>TBD</td><td></td></tr><tr><td>2</td><td>TBD</td><td></td><td>TBD</td><td></td><td>TBD</td></tr></table>・・・
2) The doses should be determined in consideration of the following target plasma level: Dose Level 1: 20 ng/mL, Dose Level 2: 40 ng/mL, Dose Level 3: 80 ng/mL, Dose Level 4: 150 ng/mL, Dose Level 5: 300 ng/mL, Dose Level 6: 600 ng/mL. The steady-state concentration (C_{ss}) of TAK-925 is estimated to be 21.3 ng/mL when 7 mg is administered as Dose level 1
・・・</td><td>Figure 2.a Summsry of the Study Design
<Part 1>
1. Cohorts 1 and 2 (Healthy Adults) and Cohorts S1-S4 (Healthy Adult Supplement Cohorts)
<table><tr><td></td><td colspan="6">Dose Level</td></tr><tr><td>Cohort</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr><tr><td>1</td><td></td><td>28 mg</td><td></td><td>112 mg</td><td></td></tr><tr><td>2</td><td>14 mg</td><td></td><td>56 mg</td><td></td><td>134.4 mg</td></tr></table>・・・
2) The doses of Dose Levels 7-10 are planned as follows. However based on the available the safety, tolerability and PK data, there is a possibility that the dose may be appropriately increased or decreased within the range not exceeding 420 mg. Dose Level 7: 180 mg, Dose Level 8: 240 mg, Dose Level 9: 320 mg, Dose Level 10: 420 mg
・・・</td><td rowspan="3">Specified the dose at completed Dose Level
Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1.
With the above, It was possible to investigate in healthy elderly at higher dose.</td></tr>
<tr><td>p.15</td><td>2.0 STUDY SCHEMATIC</td><td>Figure 2.a Summsry of the Study Design
<Part 1>
・・・
2. Cohort 3 (The healthy elderly)
<table><tr><td>Cohort 3</td></tr><tr><td>TAK-925 TBD</td></tr><tr><td>Placebo</td></tr></table></td><td>Figure 2.a Summsry of the Study Design
<Part 1>
・・・
2. Cohort 3 (The healthy elderly) and Cohort R1 (The Healthy Elderly Supplement Cohort)
<table><tr><td>Cohort 3/Cohort R1</td></tr><tr><td>112 mg/TAK-925 TBD</td></tr><tr><td>Placebo</td></tr></table></td></tr>
<tr><td>p.15</td><td>2.0 STUDY SCHEMATIC</td><td>Figure 2.a Summsry of the Study Design
<Part 1>
・・・
3. Cohort 4 (Healthy adults)
<table><tr><td>Cohort 4</td></tr><tr><td>TAK-925 TBD</td></tr></table></td><td>Figure 2.a Summsry of the Study Design
<Part 1>
・・・
3. Cohort 4 (Healthy adults)
<table><tr><td>Cohort 4</td></tr><tr><td>112 mg</td></tr></table></td></tr>
</table>

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<tr><td>p.16-18</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td>Part1 (Cohorts 1-4 and Healthy Adult Supplement Cohort)
<table>
<tr><th></th><th>Day -1</th><th>Predose Day 1</th><th>Day 1</th><th>Day 2/Early Termination</th></tr>
<tr><td>Vital Signs (respiratory rate, temperature) (d)</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Blood Sample Collection for Preservation and Pharmacogenomic Research</td><td></td><td></td><td>X (a)</td><td></td></tr>
<tr><td>Hospitalization</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table>
Abbreviations: C-SSRS=The Columbia Suicide Severity Rating Scale; HIV= human immunodeficiency virus, CSF= cerebrospinal fluid・・・
(c)・・・
Day -1: Measurements will be performed at 15:00 and 19:00, totally 2 times.
Day1: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours postdose
・・・
Orthostatic BP (1 and 5 minutes after standing up) will also be measured after the above vital signs were measured 1, 2 and 4 hours after the start of infusion.
・・・</td><td>Part1 (Cohorts 1-4 and Healthy Adult Supplement Cohort)
<table>
<tr><th></th><th>Day -1</th><th>Predose Day 1</th><th>Day 1</th><th>Day 2/Early Termination</th></tr>
<tr><td>Vital Signs (respiratory rate, body temperature) (d)</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Blood Collection for Retained Samples and Pharmacogenomic Research</td><td></td><td></td><td>X (a)</td><td></td></tr>
<tr><td>Hospitalization</td><td>X (i)</td><td>X</td><td>X</td><td>X</td></tr>
</table>
Abbreviations: BMI=body mass index, C-SSRS=The Columbia Suicide Severity Rating Scale, HIV= human immunodeficiency virus, CSF= cerebrospinal fluid・・・
(c)・・・
Day -1: Measurements will be performed at 15:00 and 19:00, totally 2 times. (No Measurement in Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort)
Day1: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours after the start of infusion
On Day -1 and Day 1 in Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort, measurement will be performed at following the same time point.
Day -1: -24, -23.75, -23.5, -23.25, -23, -22.5, -22, -21.5, -21, -20.5, -20, -19, -18, -17, -16, -15, -14, -13 and -12 hours after the start of infusion.
Day 1: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after the start of infusion.
On Day 1, Measurement at well as 24 hours after the start of infusion will also be performed.
・・・
Orthostatic BP (1 and 5 minutes after standing up) will also be measured after the above vital signs were measured 1, 2 and 4 hours after the start of infusion (only on Day 1).
・・・
i) Hospitalization from Day -2 may be allowed for Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort as needed.</td><td>Decided to evaluate vital signs in more detail in Healthy adult Supplement Cohort and Healthy Elderly Supplement Cohort based on the result of Cohort 2 Dose Level 6 of Part 1.</td></tr>
</table>

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<tr><td>p.27-28</td><td>6.1 Trial Design</td><td>(1) Part 1
・・・
In Cohort 2 Dose Level 2 and subsequent dose levels in Cohorts 1 and 2, Cohort 3 and Healthy Adult Supplemental receive TAK-925 or placebo simultaneously. (such that 4 subjects will be dosed at first, and if there are no safety issues, the remaining 4 subjects may be dosed about 1 hour later.)
・・・This cohort will be initiated after started with the dose of which the safety and tolerability has been established in healthy adults.
・・・
Cohort 3 and 4 may be started at the discretion of the sponsor, considering the status of Cohorts 1, 2 and the Healthy Adult Supplement Cohort. (Cohorts 3 and 4 may be implemented in parallel with Cohorts 1 and 2. The doses to be used in Cohorts 3 and 4 will be determined based on the available safety, tolerability and PK data, and nonclinical study results.)</td><td>(1) Part 1
・・・
In Cohort 2 Dose Level 2 and subsequent dose levels in Cohorts 1 and 2, Cohort 3, Healthy Adult Supplemental Cohort and Healthy Elderly Supplement Cohort (in the event that the cohort is actually added) receive TAK-925 or placebo simultaneously. (such that 4 subjects will be dosed at first, and if there are no safety issues, the remaining 4 subjects may be dosed about 1 hour later.).
・・・This cohort will be initiated after s started with the dose of which the safety and tolerability has been established in healthy adults. In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 3, a maximum of 1 additional cohorts for Healthy Elderly Supplement Cohort that enrolls 8 healthy elderly per cohort will be commenced without amendment of the protocol. The cohort name of R1 will be assigned for the Healthy Elderly Supplement Cohort. Six subjects will be randomly assigned to the TAK-925 group and 2 subjects to the placebo group, to evaluate the safety, tolerability and PK. In the Healthy Elderly Supplement Cohort, the dose may be higher or lower than or the same to that of prior cohort dose levels, or an intermediate dose between two prior doses.
・・・
Cohort 3, Healthy Elderly Supplement Cohort and Cohort 4 may be started at the discretion of the sponsor, considering the status of Cohorts 1, 2 and Healthy Adult Supplement Cohort. (Cohorts 3 and 4 may be implemented in parallel with Cohorts 1 and 2. The doses to be used in Cohorts 3 and 4 will be determined based on the available safety, tolerability and PK data, and nonclinical study results.)</td><td>Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1.
Along with the above, It was enabled to investigate in healthy elderly at higher dose.</td></tr>
<tr><td>p.30</td><td>6.1 Trial Design</td><td>Table 6.a Summary of Cohorts
<table>
<tr><th>Part</th><th>Cohort</th><th>Dosage</th></tr>
<tr><td rowspan="10">1[1)]</td><td>1[2)]</td><td>TAK-925 7 mg (Dose Level 1) or placebo</td></tr>
<tr><td>2</td><td>TAK-925 TBD mg (Dose Level 2) or placebo</td></tr>
<tr><td>1</td><td>TAK-925 TBD mg (Dose Level 3) or placebo</td></tr>
<tr><td>2</td><td>TAK-925 TBD mg (Dose Level 4) or placebo</td></tr>
<tr><td>1</td><td>TAK-925 TBD mg (Dose Level 5) or placebo</td></tr>
<tr><td>2</td><td>TAK-925 TBD mg (Dose Level 6) or placebo</td></tr>
<tr><td>S1 – S4[3)]</td><td>TAK-925 TBD mg or placebo</td></tr>
<tr><td>3</td><td>TAK-925 TBD mg or placebo</td></tr>
<tr><td>4</td><td>TAK-925 TBD mg</td></tr>
</table></td><td>Table 6.a Summary of Cohorts
<table>
<tr><th>Part</th><th>Cohort</th><th>Dosage</th></tr>
<tr><td rowspan="10">1[1)]</td><td>1[2)]</td><td>TAK-925 7 mg (Dose Level 1) or placebo</td></tr>
<tr><td>2</td><td>TAK-925 14 mg (Dose Level 2) or placebo</td></tr>
<tr><td>1</td><td>TAK-925 28 mg (Dose Level 3) or placebo</td></tr>
<tr><td>2</td><td>TAK-925 56 mg (Dose Level 4) or placebo</td></tr>
<tr><td>1</td><td>TAK-925 112 mg (Dose Level 5) or placebo</td></tr>
<tr><td>2</td><td>TAK-925 134.4 mg (Dose Level 6) or placebo</td></tr>
<tr><td>S1 – S4[3)]</td><td>TAK-925 TBD mg (Dose Level 7-10)[3)] or placebo</td></tr>
<tr><td>3</td><td>TAK-925 112 mg or placebo</td></tr>
<tr><td>4</td><td>TAK-925 112 mg</td></tr>
</table></td><td>Specified the dose at completed Dose Level</td></tr>
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<tr><td>p.30</td><td>6.1 Trial Design</td><td>Table 6.a Summary of Cohorts
・・・</td><td>Table 6.a Summary of Cohorts
<table>
<tr><th>Part</th><th>Cohort</th><th>Subjects Sample Size</th><th>Study Design</th><th>Dosage</th><th>Randomization</th></tr>
<tr><td>1[1)]</td><td>R1[4)]</td><td>Healthy elderly n=8</td><td>Double-blind, parallel group</td><td>TAK-925 TBD mg or placebo</td><td>TAK-925: 6 subjects, Placebo: 2 subjects</td></tr>
</table></td><td rowspan="2">Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1.
Along with the above, It was enabled to investigate in healthy elderly at higher dose.</td></tr>
<tr><td>p.30</td><td>6.1 Trial Design</td><td>Table 6.a Summary of Cohorts
1) In Part 1, Dose Levels 1, 3 and 5 will be tested in the same set of, and similaly, Dose Levels 2, 4 and 6 will be evaluated in the different set of the same subjects. In Part 2, different subjects will be used in each Cohort. The target plasma level totake into consideration as a standard is as follows. Dose Level 1: 20 ng/mL, Dose Level 2: 40 ng/mL, Dose Level 3: 80 ng/mL, Dose Level 4: 150 ng/mL, Dose Level 5: 300 ng/mL, Dose Level 6: 600 ng/mL. The steady-state concentration (C_{ss}) of TAK-925 is estimated to be 21.3 ng/mL when 7 mg is administered as Dose level 1.
・・・
3) In the event that further investigation on the safety, tolerability and PK of TAK-025 is needed after completion of Cohorts 1 and 2, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol.
4) In Part 2, the dose level to be used in Cohort 5 should be equal or less than one-third of the maximum dose of TAK-925 of which the safety and tolerability has been already confirmed.</td><td>Table 6.a Summary of Cohorts
1) In Part 1, Dose Levels 1, 3 and 5 will be tested in the same set of subjects, and similarly, Dose Levels 2, 4 and 6 will be evaluated in the different set of the same subjects. In Part 2, different subjects will be used in each Cohort.
・・・
3) In the event that further investigation on the safety, tolerability and PK of TAK-925 is needed after completion of Cohorts 1 and 2, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol. The Dose Levels 7-10 are planned as follows. However based on the available safety, tolerability and PK data, there is a possibility that the dose may be appropriately increased or decreased within the range not exceeding 420 mg. Dose Level 7: 180 mg, Dose Level 8: 240 mg, Dose Level 9: 320 mg, Dose Level 10: 420 mg.
4) In the event that further investigation on the safety, tolerability and PK of TAK-925 is needed after completion of Cohort 3, up to 1 additional cohorts that include 8 healthy elderly can be commenced without amendment of the protocol.
5) In Part 2, the dose level to be used in Cohort 5 should be equal or less than one-third of the maximum dose of TAK-925 of which the safety and tolerability has been already confirmed in Part 1.</td></tr>
<tr><td>p.31</td><td>6.1 Trial Design</td><td>Figure 6.a. Overview of the Trial Schedulee</td><td>Figure 6.a. Overview of the Trial Schedules</td><td>Correction of errors</td></tr>
</table>

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p.32	6.2 Cohort transition/Dose Escalation	・・・ The inclusion criteria for patients with type 1 narcolepsy includes those aged 18-80, but subjects aged 56 years or older will be enrolled based on the assessments of the safety results and PK data of Chohort 3 in Part 1.	・・・ The inclusion criteria for patients with type 1 narcolepsy in Part 2 includes those aged 18-80, but subjects aged 56 years or older will be enrolled based on the assessments of the safety results and PK data of Cohort 3 (and the Healthy Elderly Supplement Cohort) in Part 1.	Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higher dose. Correction of description
p.33	6.3.1 Rationale of population	(1) Part 1 ・・・with type 1 narcolepsy is enrolled in Part 2. In Cohort 4, healthy adults・・・	(1) Part 1 ・・・with type 1 narcolepsy will be is enrolled in Part 2. Also, considering the possibility of performing Part 2 at high doses, the Healthy Elderly Supplement Cohort will be added. In Cohort 4, healthy adults・・・	
p.34	6.3.2 Rationale of Trial Design	(1) Part 1 ・・・ After Cohort 2 Dose Level 2 and subsequent dose levels in Cohorts 1 and 2, Cohort 3 and Healthy Adult Supplement Cohort. (4 subjects will be dosed first, and if there are no safety issues, the remaining 4 subjects will be dosed approximately about 1 hour later.)	(1) Part 1 ・・・ After Cohort 2 Dose Level 2 , dosing will not be started simultaneously in all subjects in Cohort 3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort (in the event that a cohort is added). (4 subjects will be dosed first, and if there are no safety issues, the remaining 4 subjects will be dosed approximately 1 hour later.)	

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p.35-36	6.3.3 Rationale for Dose	(2) Maximum Dose/Exposure for This Trial Based on the NOAEL in rats of which the sensitivity was the highest among animals used in the two-week, nonclinical, repeat-dose, toxicity studies, and the clinical dose of betadex sulfobutyl ether sodium (BSES), which is an excipient contained in the study drug, the acceptable upper limits of C_{max} and AUC and the maximum dose of TAK-925 in this study were set to be CCI [redacted] For example, "VFEND IV 200 MG", approved, contains BSES, an excipient contained in the study drug. When VFEND is administered to a weighing 60 kg, the maximum dose of BSES per dose as the maintenance dose on and after Day 2 will be 3840 mg (VFEND IV 200 MG is given twice a day).The dose of BSES to be used in this study was set to be 3840 mg by using this calculation as reference. Since TAK-925 used as a study drug contains 100 mg of BSES as an excipient per 3.5 mg of TAK-925, the maximum dose of TAK-925 to be used in this study will be 134.4 mg.	(2) Maximum Dose/Exposure for This Trial Based on the NOAEL in rats of which the sensitivity was the highest among animals used in the two-week, nonclinical, repeat-dose, toxicity studies, and the clinical dose of betadex sulfobutyl ether sodium (BSES), which is an excipient contained in the study drug, the acceptable upper limits of C_{max} and AUC and the maximum dose of TAK-925 in this study were set to be CCI [redacted]. Meanwhile, in Cohort 2 Dose Level 6 CCI [redacted] of Part 1 in this study, C_{max} and AUC of TAK-925 were CCI [redacted] (preliminary result), respectively, and were safe and well-tolerated. These exposure levels of C_{max} and AUC are CCI [redacted] lower than the acceptable C_{max} and AUC of TAK-925 in this study, respectively. CCI [redacted] Thus, it was judged possible to investigate at higher doses, and the maximum dose (the upper limit) was set to be CCI [redacted] For example, "VFEND IV 200 MG", approved in Japan, contains BSES, an excipient contained in the study drug. Referring to the dosage of VFEND [14], the maximum amount of BSES per dose was set to be 3840 mg (when VFEND is administered to a human weighing 60 kg, as the maintenance dose on and after Day 2) in the protocol (first version and amendment 1). On the other hand, based on the result of Cohort 2 Dose Level 6 (134.4 mg) of Part 1 of this study and referring to the dosage of CARNEXIV [15] already approved in the United States, the maximum dose of BSES per dose was set to 12000 mg in the study protocol (amendment 2), within in the range of the amount of BSES, to be possibly administered within 9 hours as CARNNEXIV (CARNEXIV is infused every 6 hours, so this amount corresponds to 2 doses of CARNNEXIV). Since TAK-925 used as a study drug contains 100 mg of BSES as an excipient per 3.5 mg of TAK-925, 420 mg of TAK-925 contains 12000 mg of BSES.	Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higher dose.

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p.39	6.4 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters	・・・In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 1 and Cohort 2 Dose Level 6, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol. In the event that a long-term washout period is needed on the basis of the pharmacokinetic or safety evaluation results in Part 1, the dosing order of TAK-925 and placebo and Part 2 may be changed to a single-blind (only subjects are blinded), fixed-sequence approach (TAK-925 will be given after a placebo is given to all subjects).	・・・In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohort 1 and Cohort 2 Dose Level 6, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol. In the event that further investigation on the safety, tolerability and PK of TAK-925 is needed after completion of Cohort 3, up to 1 additional cohort that includes 8 healthy elderly can be commenced without amendment of the protocol. In the event that a long-term washout period is needed on the basis of the pharmacokinetic or safety evaluation results in Part 1, the dosing order of TAK-925 and placebo and Part 2 may be changed to a single-blind (only subjects are blinded), fixed-sequence approach (TAK-925 will be given after a placebo is given to all subjects).	Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higher dose.
p.46	7.2 Exclusion Criteria	Healthy Adults or the Healthy Elderlys (Cohorts 1-4 and Healthy Adult Supplement Cohorts):	Healthy Adults or the Healthy Elderly (Cohorts 1-4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort):	
p.58	9.1.1.2 Study Drug Assignment	In Cohorts 1-3 and Healthy Adult Supplement Cohort (if it will be added), subjects in each cohort will be assigned to each cohort the study drug in order of the medication ID number (See Figure 9.a, Figure 9.b and Figure 9.c). ・・・ In the case that the study drug is to be administered to a reserve subject, the reserve subject will receive the study drug of which the medication ID number was assigned to the original subject only in Cohorts 1 to 3, Healthy Adult Supplement Cohort) a subject is replaced, the replacing subject will receive the study drug with a different medication ID number from the number assigned to the original subject who discontinued the study.	In Cohorts 1-3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort (if it is added), subjects in each cohort will be assigned to each cohort the study drug in order of the medication ID number according to the randomization schedule (See Figure 9.a, Figure 9.b and Figure 9.c). ・・・ In the case that the study drug is to be administered to a reserve subject, the reserve subject will receive the study drug of which the medication ID number was assigned to the original subject only in Cohorts 1 to 3, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort) a subject is replaced, the replacing subject will receive the study drug with a different medication ID number from the number assigned to the original subject who discontinued the study.	

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<tr><td>p.59</td><td>9.1.1.2 Study Drug Assignment</td><td>Figure 9.a Summary of Cohorts 1 and 2
<table><tr><th colspan="2">Dose Level 1</th></tr><tr><td>A</td><td>TAK-925 7 mg</td></tr><tr><td>B</td><td>TAK-925 7 mg</td></tr><tr><td>C</td><td>TAK-925 7 mg</td></tr><tr><td>D</td><td>Placebo</td></tr></table>
→
<table><tr><th colspan="2">Dose Level 2</th></tr><tr><td>E</td><td>TAK-925 TBD</td></tr><tr><td>F</td><td>TAK-925 TBD</td></tr><tr><td>G</td><td>TAK-925 TBD</td></tr><tr><td>H</td><td>Placebo</td></tr></table>
→
<table><tr><th colspan="2">Dose Level 3</th></tr><tr><td>A</td><td>TAK-925 TBD</td></tr><tr><td>B</td><td>TAK-925 TBD</td></tr><tr><td>C</td><td>Placebo</td></tr><tr><td>D</td><td>TAK-925 TBD</td></tr></table>
→
<table><tr><th colspan="2">Dose Level 4</th></tr><tr><td>E</td><td>TAK-925 TBD</td></tr><tr><td>F</td><td>TAK-925 TBD</td></tr><tr><td>G</td><td>Placebo</td></tr><tr><td>H</td><td>TAK-925 TBD</td></tr></table>
→
<table><tr><th colspan="2">Dose Level 5</th></tr><tr><td>A</td><td>TAK-925 TBD</td></tr><tr><td>B</td><td>Placebo</td></tr><tr><td>C</td><td>TAK-925 TBD</td></tr><tr><td>D</td><td>TAK-925 TBD</td></tr></table>
→
<table><tr><th colspan="2">Dose Level 6</th></tr><tr><td>E</td><td>TAK-925 TBD</td></tr><tr><td>F</td><td>Placebo</td></tr><tr><td>G</td><td>TAK-925 TBD</td></tr><tr><td>H</td><td>TAK-925 TBD</td></tr></table></td><td>Figure 9.a Summary of Cohorts 1 and 2
<table><tr><th colspan="2">Dose Level 1</th></tr><tr><td>A</td><td>TAK-925 7 mg</td></tr><tr><td>B</td><td>TAK-925 7 mg</td></tr><tr><td>C</td><td>TAK-925 7 mg</td></tr><tr><td>D</td><td>Placebo</td></tr></table>
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→
<table><tr><th colspan="2">Dose Level 3</th></tr><tr><td>A</td><td>TAK-925 <u>28 mg</u></td></tr><tr><td>B</td><td>TAK-925 <u>28 mg</u></td></tr><tr><td>C</td><td>Placebo</td></tr><tr><td>D</td><td>TAK-925 <u>28 mg</u></td></tr></table>
→
<table><tr><th colspan="2">Dose Level 4</th></tr><tr><td>E</td><td>TAK-925 <u>56 mg</u></td></tr><tr><td>F</td><td>TAK-925 <u>56 mg</u></td></tr><tr><td>G</td><td>Placebo</td></tr><tr><td>H</td><td>TAK-925 <u>56 mg</u></td></tr></table>
→
<table><tr><th colspan="2">Dose Level 5</th></tr><tr><td>A</td><td>TAK-925 <u>112 mg</u></td></tr><tr><td>B</td><td>Placebo</td></tr><tr><td>C</td><td>TAK-925 <u>112 mg</u></td></tr><tr><td>D</td><td>TAK-925 <u>112 mg</u></td></tr></table>
→
<table><tr><th colspan="2">Dose Level 6</th></tr><tr><td>E</td><td>TAK-925 <u>134.4 mg</u></td></tr><tr><td>F</td><td>Placebo</td></tr><tr><td>G</td><td>TAK-925 <u>134.4 mg</u></td></tr><tr><td>H</td><td>TAK-925 <u>134.4 mg</u></td></tr></table></td><td>Specified the dose at completed Dose Level
Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1.
Along with the above, It was enabled to investigate in healthy elderly at higher dose.
Decided to evaluate vital signs in more detail in Healthy adult Supplement Cohort and Healthy Elderly Supplement Cohort based on the result of Cohort 2 Dose Level 6 of Part 1</td></tr>
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p.59	9.1.1.2 Study Drug Assignment	Figure 9.b Summary of Cohort 3 TAK-925 TBD Placebo 1) Double-blind study. Cohort 3 consists of 8 subjects: 6 subjects in the TAK-925 group and 2 subjects in the placebo group.	Figure 9.b Summary of Cohort 3 and Cohort R1 (Healthy Elderly Supplement Cohort) TAK-925 112 mg/TAK-925 TBD Placebo 1) Double-blind study. Cohort 3 and Cohort R1 consists of 8 subjects: 6 subjects in the TAK-925 group and 2 subjects in the placebo group. Dose of Cohort 3 is 112 mg, dose of Cohort R1 to be determined.	Specified the dose at completed Dose Level Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higher dose. Decided to evaluate vital signs in more detail in Healthy adult Supplement Cohort and Healthy Elderly Supplement Cohort based on the result of Cohort 2 Dose Level 6 of Part 1
p.71	9.3.4 Confinement	(1) Part 1 Subjects will be hospitalized in a hospital during the period from Day -1 to Day 2 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 2, and confirmed by the investigators.	(1) Part 1 Subjects will be hospitalized in a hospital during the period from Day -1 to Day 2 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 2, and confirmed by the investigators. Hospitalization from Day -2 may be allowed for Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort as needed.	

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p.81	11.1.3 PK Analysis	(1) Endpoints and analysis methodologies [Analysis methodologies] The following analysis will be performed using the PK analysis set in Cohorts 1-2 and Cohorts S1-S4 (if additional Cohort is enrolled) in Part 1 and in Part 2 by dose level, and in the other cohorts by cohort and by dose level.・・・	(1) Endpoints and analysis methodologies [Analysis methodologies] The following analysis will be performed using the PK analysis set in Cohorts 1-2 and Healthy Adult Supplement Cohort, and Cohorts 3 and Healthy Elderly Supplement Cohort, Cohort 4 and Part 2 by dose level.	Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higher dose.
p.81	11.1.5 Safety Analysis	(1) Endpoints and analysis methodologies [Analysis methodologies] The following analysis will be performed using the Safety analysis set in Cohorts 1-2 and Cohorts S1-S4 (if additional Cohort is enrolled) in Part 1 and in Part 2 by dose level, and in the other cohorts by cohort and by dose level.	(1) Endpoints and analysis methodologies [Analysis methodologies] The following analysis will be performed using the safety analysis set in Cohorts 1-2 and Healthy Adult Supplement Cohorts, Cohorts 3 and Healthy Elderly Supplement Cohort, Cohort 4 and Part 2 by dose level.	
p.83	11.5 Determination of Sample Size	・・・In the event that further investigation on the safety, tolerability and PK is needed after completion of Cohorts 1-2, a maximum of 4 additional cohorts (a total of 32 healthy adult subjects; 8 subjects [6 in TAK-925 group, 2 in placebo group] for each cohort) may be enrolled. For Cohort 4 in Part 1, 4 subjects will be enrolled to evaluate the safety, tolerability, PK of TAK-925 including the concentration of TAK-925 in the CSF when a single dose of TAK-925 is administered intravenously to healthy adults.	・・・In the event that further investigation on the safety, tolerability and PK in healthy adults is needed after completion of Cohorts 1-2, a maximum of 4 additional cohorts (a total of 32 healthy adult subjects; 8 subjects [6 in TAK-925 group, 2 in placebo group] for each cohort) may be enrolled. If further investigation on the safety, tolerability and PK in healthy elderly is needed after completion of Cohort 3, a maximum of 1 additional cohort (a total of 8 healthy elderly subjects [6 in TAK-925 group, 2 in placebo group] per cohort) may be enrolled. For Cohort 4 in Part 1, 4 subjects will be enrolled to evaluate the safety, tolerability, PK of TAK-925 including the concentration of TAK-925 in the CSF when a single dose of TAK-925 is administered intravenously to healthy adults.	
p.93-94	16.0 REFERENCES	[13] U.S. Food and Drug Administration [Internet]. Pharmacology/Toxicology, Below is a sortable table of Pharm/Tox guidances [updated 2005 Jul 28]. Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers; 2005 Jul [about 30p]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm. [14] Modiodal 100 mg tablet, Package leaflet The Mitsubishi Tanabe Pharma Corp. April, 2015 revision (the 8th edition)・・・	[13] U.S. Fo1od and Drug Administration [Internet]. Pharmacology/Toxicology, Below is a sortable table of Pharm/Tox guidances [updated 2005 Jul 28]. Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers; 2005 Jul [about 30p]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm. [14] VFEND for Intravenous use 200 mg, Package leaflet Pfizer Inc. January, 2018 revision (the 19th edition) [15] CARNEXIV[prescribing information] Deerfield, IL, USA:Lundbeck, 2016 October. [16] Modiodal 100 mg tablet, Package leaflet The Mitsubishi Tanabe Pharma Corp. April, 2015 revision (the 8th edition)・・・	

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<td>p.98-99</td>
<td>Appendix C Acceptable Time Windows for Study Procedures</td>
<td>Part 1 (Cohorts 1-4 and Healthy Adult Supplement Cohort)
<table>
<tr><th>Item</th><th colspan="2">Operation Schedule (standard)</th><th>Allowance</th></tr>
<tr><td rowspan="6">Vital Signs (pulse rate, SBP and diastolic blood pressure)</td><td>Baseline</td><td>Day -1: once at 15:00 and 19:00 each, totally 2 times</td><td>12:00-17:00 and 19:00 to bedtime</td></tr>
<tr><td rowspan="5">Treatment period</td><td>Day 1: Predose</td><td>Right after waking up to just before dosing</td></tr>
<tr><td>Day 1: 0.25, 0.5, 0.75, 1.5, 2.5 and 3.5 hours after the start of infusion</td><td>Within ±10 minutes</td></tr>
<tr><td>Day 1: 1, 2, 3 and 4 hours after the start of infusion</td><td>Within ±15 minutes</td></tr>
<tr><td>Day1: 5, 6, 7, 8, 9, 10, 11 and 12 hours after the start of infusion</td><td>Within ±20 minutes</td></tr>
<tr><td>Day 2: 24 hours after the start of infusion</td><td>Within ±1 hour</td></tr>
</table>
…
(b) Will be performed after fasting for more than 8 hours.
(c) except dose level 1 and 2 of cohorts 1 and 2.</td>
<td>Part 1 (Cohorts 1-4 and Healthy Adult Supplement Cohort)
<table>
<tr><th>Item</th><th colspan="2">Operation Schedule (standard)</th><th>Allowance</th></tr>
<tr><td rowspan="10">Vital Signs (pulse rate, SBP and diastolic blood pressure)</td><td rowspan="5">Baseline</td><td>Day -1: once at 15:00 and 19:00 each, totally 2 times (c)</td><td>12:00-17:00 and 19:00 to bedtime</td></tr>
<tr><td>Day -1 (d) (e): 24 hours from the start of infusion.</td><td>-24.5 to -24 hours</td></tr>
<tr><td>Day -1 (d) (e): -23.75, -23.5, -23.25, -23, -22.5, -22, -21.5, -21, -20.5 and -20 hours after the start of infusion.</td><td>Within ±15 minutes</td></tr>
<tr><td>Day -1 (d) (e): -19, -18, -17, -16, -15, -14, -13 and -12 hours after the start of infusion.</td><td>Within ±20 minutes</td></tr>
<tr><td rowspan="5">Treatment period</td><td>Day 1 (e): Predose</td><td>Right after waking up to just before dosing (c) or -30 minutes to just before dosing (d)</td></tr>
<tr><td>Day 1 (e): 0.25, 0.5, 0.75, 1.5, 2.5 and 3.5 hours after the start of infusion</td><td>Within ±10 minutes</td></tr>
<tr><td>Day 1 (e): 1, 2, 3 and 4 hours after the start of infusion</td><td>Within ±15 minutes</td></tr>
<tr><td>Day1 (e): 5, 6, 7, 8, 9, 10, 11 and 12 hours after the start of infusion</td><td>Within ±20 minutes</td></tr>
<tr><td>Day 2 (e): 24 hours after the start of infusion</td><td>Within ±1 hour</td></tr>
</table>
…
(b) Will be performed after fasting for more than 8 hours.
(c) Not implemented or applied in in Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort
(d) Only in Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort
(e) In Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort, measurement will be porfromed at the same time period.
(f) Except dose level 1 and 2 of Cohorts 1 and 2.</td>
<td>Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1.
Along with the above, It was enabled to investigate in healthy elderly at higher dose.
Decided to evaluate vital signs in more detail in Healthy adult Supplement Cohort and Healthy Elderly Supplement Cohort based on the result of Cohort 2 Dose Level 6 of Part 1</td>
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p.102	Appendix C Acceptable Time Windows for Study Procedur	The total blood volume (rough estimate) to be collected from each subject is shown below. ・・・ Part 1 (Cohort 3-4 and Healthy Adult Supplement Cohort)	The total blood volume (rough estimate) to be collected from each subject is shown below. ・・・ Part 1 (Cohort 3-4, Healthy Adult Supplement Cohort and Healthy Elderly Supplement Cohort)	Judged to be possible to investigate at higher dose and changed maximum dose based on the result of Cohort 2 Dose Level 6 of Part 1. Along with the above, It was enabled to investigate in healthy elderly at higher dose.

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p.9	1.0 STUDY SUMMARY	Trial Design: (2) Part 2 ・・・ In Cohorts 5 and 6, 4 subjects each will be enrolled, and to give them TAK-925 or placebo will be intravenously infused for 9 hours on Day 1 and Day 2.	Trial Design: (2) Part 2 ・・・ In Cohorts 5 and 6, 4 subjects each will be enrolled, and TAK-925 or placebo will be intravenously infused for 9 hours on Day 1 and Day 3.	Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2.
p.10	1.0 STUDY SUMMARY	Dose Levels: ・・・ (2) Part 2 A single dose of TAK-925 or placebo will be administered intravenously for 9 hours on Day 2 alternately. If placebo is given on Day 1, TAK-925 is to be given on Day 2. If TAK-925 is given on Day 1, placebo is to be given on Day 2.	Dose Levels: ・・・ (2) Part 2 A single dose of TAK-925 or placebo will be administered intravenously for 9 hours on Day 1 and Day 3 alternately. If placebo is given on Day 1, TAK-925 is to be given on Day 3. If TAK-925 is given on Day 1, placebo is to be given on Day 3.	
p.10	1.0 STUDY SUMMARY	Duration of Treatment: ・・・ (2) Part 2 A single administration on Day 1 and Day 2 for each cohort (TAK-925 will be given only once)	Duration of Treatment: ・・・ (2) Part 2 A single administration on Day 1 and Day 3 for each cohort (TAK-925 will be given only once)	
p.11	1.0 STUDY SUMMARY	Planned Trial Duration: ・・・ (2) Part 2 Screening period: Days -42 to -2 Admission day: Day -1 Crossover period: Day 1 to 3	Planned Trial Duration: ・・・ (2) Part 2 Screening period: Days -42 to -2 Admission day: Day -1 Crossover period: Day 1 to 4	
p.12	1.0 STUDY SUMMARY	Main Criteria for Exclusion: Healthy Adults (Cohort 4 only) ・・・ ・ A subject who has clinically significant spinal deformities (scoliosis or kyphosis), which, in the opinion of the investigator, may interfere with lumbar puncture.	Main Criteria for Exclusion: Healthy Adults (Cohort 4 only) ・・・ ・ A subject who has clinically significant vertebral deformities (scoliosis or kyphosis), which, in the opinion of the investigator, may interfere with lumbar puncture.	Correction of errors
p.14	2.0 STUDY SCHEMATIC	Figure 2.a Summary of the Study Design ＜Part 2＞ ・・・ 3) Cohorts 5 and 6 consist of 4 subjects, each respectively. 2 subjects each in a group will be randomized to each sequence. On Days 1 and 2, TAK-925 or placebo will be administered intravenously to these subjects for 9 hours. Cohort 7 consists of a maximum of 12 subjects, and 6 subjects each at maximum in a group will receive TAK-925 or placebo intravenously for 9 hours on Days 1 and 2, TAK-925 or placebo will be administered intravenously to these subjects for 9 hours.	Figure 2.a Summary of the Study Design ＜Part 2＞ ・・・ 3) Cohorts 5 and 6 consist of 4 subjects, each respectively. 2 subjects each in a group will be randomized to each sequence. On Days 1 and 3, TAK-925 or placebo will be administered intravenously to these subjects for 9 hours. Cohort 7 consists of a maximum of 12 subjects, and 6 subjects each at maximum in a group will receive TAK-925 or placebo intravenously for 9 hours on Days 1 and 3, TAK-925 or placebo will be administered intravenously to these subjects for 9 hours.	Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2.

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<tr><td>p.16</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td><u>Part1(Cohorts 1-4 and Healthy Adult Supplement Cohort)</u>
・・・
(f) Blood samples for TAK-925 PK analysis will be collected: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 9 hours after the start of infusion, and 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 15 hours after the end of infusion.</td><td><u>Part1(Cohorts 1-4 and Healthy Adult Supplement Cohort)</u>
・・・
(f) Blood samples for TAK-925 PK analysis will be collected: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 9 hours after the start of infusion, and 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, <u>10 and</u> 15 hours after the end of infusion. <u>However, Dose Level 1 and 2 of Cohorts 1 and 2 will be excluded at 10 hours after the end of infusion.</u></td><td>Added pharmacokinetic sample to evaluate pharmacokinetic more accurately based on the pharmacokinetic data of Cohort 1 Dose Level 1.</td></tr>
<tr><td>p.18-19</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td><u>Part 2 – Patients with Narcolepsy</u>
<table><tr><td>Screening Day -42 to Day-2</td><td>Day -1</td><td>Predose Day 1, 2</td><td>Day 1, 2</td><td>Day 3/ Early Termination</td><td>Follow-Up Visit (a)</td></tr></table></td><td><u>Part 2 – Patients with Narcolepsy</u>
<table><tr><td>Screening Day -42 to Day-2</td><td>Day -1</td><td><u>Predose Day 1</u></td><td>Day 1</td><td><u>Day 2</u></td><td><u>Predose Day 3</u></td><td><u>Day 3</u></td><td>Day <u>4</u>/ Early Termination</td><td>Follow-Up Visit (a)</td></tr></table></td><td>Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2.</td></tr>
<tr><td>p.18</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td><u>Part 2 – Patients with Narcolepsy</u>
・・・
<table><tr><td>Clinical Procedures/Assessments</td><td>Day 1、2</td></tr><tr><td>CCI [redacted]</td><td>C</td></tr></table></td><td><u>Part 2 – Patients with Narcolepsy</u>
・・・
<table><tr><td>Clinical Procedures/Assessments</td><td>Day 1</td></tr><tr><td>CCI [redacted]</td><td></td></tr></table></td><td>Changed the schedule due to the change washout period of Part 2.</td></tr>
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<tr><td>p.18</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td>Part 2 – Patients with Narcolepsy
・・・</td><td>Part 2 – Patients with Narcolepsy
・・・
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<tr><td>Weight</td><td>X</td><td></td><td></td></tr>
<tr><td>BMI</td><td></td><td></td><td></td></tr>
<tr><td>Vital Signs (pulse rate, SBP and DBP) (f)</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Vital Signs (respiratory rate, body temperature) (g)</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>12-Lead Electrocardiogram (h)</td><td>X</td><td></td><td>X</td></tr>
<tr><td>C-SSRS</td><td></td><td></td><td></td></tr>
<tr><td>TAK-925/Placebo Administration</td><td></td><td></td><td>X</td></tr>
<tr><td>CCI</td><td colspan="3">CCI</td></tr>
<tr><td>MWT (Maintenance of Wakefulness Test) (i)</td><td></td><td></td><td>X</td></tr>
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<tr><td>CCI</td><td colspan="3">CCI</td></tr>
<tr><td>CCI</td><td colspan="3">CCI</td></tr>
<tr><td>Adverse Events</td><td colspan="3">Continuous Monitoring</td></tr>
</table></td><td>Changed the schedule due to the change washout period of Part 2.</td></tr>
<tr><td>p.19</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td>Part 2 – Patients with Narcolepsy
・・・
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<tr><th>Laboratory test/Assessments</th><th>Predose Day 1、2</th><th>Day 1、2</th></tr>
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<tr><td>Serum Chemistry</td><td>X(m)</td><td></td></tr>
<tr><td colspan="3">・・・</td></tr>
<tr><td>Blood Collection for Retained Samples and Pharmacogenomic Research</td><td></td><td>X(n)</td></tr>
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<tr><th>Laboratory test/Assessments</th><th>Predose Day 1</th><th>Day 1</th></tr>
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<tr><td>p.19</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td><u>Part 2 – Patients with Narcolepsy</u>
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<tr><td>p.19</td><td>3.0
SCHEDULE OF STUDY PROCEDURES</td><td><u>Part 2 – Patients with Narcolepsy</u>
・・・<table><tr><td>Laboratory test/Assessments</td><td>Day 3/Early Termination</td></tr><tr><td>Hematology</td><td>X</td></tr><tr><td>Urinalysis</td><td>X</td></tr><tr><td>Serum Chemistry</td><td>X</td></tr></table></td><td><u>Part 2 – Patients with Narcolepsy</u>
・・・<table><tr><td>Laboratory test/Assessments</td><td>Day <u>4</u>/Early Termination</td></tr><tr><td>Hematology</td><td><u>X(m)</u></td></tr><tr><td>Urinalysis</td><td><u>X(m)</u></td></tr><tr><td>Serum Chemistry</td><td><u>X(m)</u></td></tr></table></td></tr>
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p.19-20	3.0 SCHEDULE OF STUDY PROCEDURES	Part 2 – Patients with Narcolepsy ・・・ (f) Vital signs (pulse rate, SBP and DBP) will be measured: ・・・ Days 1 and 2: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after the start of the infusion. Day 2: 24 hours after the start of infusion ・・・ (g) Vital signs (respiratory rate, body temperature) will be measured during the screening period, within 1 hour predose on Day 1, at 5 hours after the start of infusion on Day 1 and Day2, and Day 3. (h) 12-Lead ECG will be measured during the screening period, on Day -1, between 2 and 9 hours after the start of infusion on Day 1 and Day 2, and Day 3 (i) MWT procedure will be conducted: Day -1: MWT procedures will be completed by 17:00. Day 1 and 2: MWT procedures will be conducted at 10:00, 12:00, 14:00 and 16:00 following the start of infusion dosing at 7:45. (j) CCI [redacted] ESS will be conducted on Day -1 only. CCI [redacted] (k) CCI [redacted] (l) CCI [redacted] (m) These tests will be conducted only before the start of infusion on Day 2. (n) Blood sampling will be performed only once for each subject after the start of infusion on Day 2. ・・・ (p) Blood samples for the PK evaluations of TAK-925 (and its metabolites) will be collected on Day 1, Day 2 and Day 3: Predose (Day 1 only), 1, 2, 4, 6 and 9 hours after the start of infusion, and 0.17 0.5, 1, 2 and 15 hours after end of infusion, and just before sleep.	Part 2 – Patients with Narcolepsy ・・・ (f) Vital signs (pulse rate, SBPc and DBP) will be measured: ・・・ Days 1 and 3: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after the start of the infusion. Day 2 and Day 4: 24 hours after the start of infusion ・・・ (g) Vital signs (respiratory rate, body temperature) will be measured during the screening period, within 1 hour predose on Day 1 and Day 3, at 5 hours after the start of infusion on Day 1 and Day 3, and at the same time period on Day 2 and Day 4. (h) 12-Lead ECG will be measured during the screening period, on Day -1, between 2 and 9 hours after the start of infusion on Day 1 and Day 3, and at the same time of the dayperiod on Day 2 and Day 4. (i) MWT procedures will be conducted: Day -1: MWT procedures will be completed by 17:00. Day 1 and 3: MWT procedures will be conducted at 10:00, 12:00, 14:00 and 16:00 following the start of infusion dosing at 7:45. (j) CCI [redacted] ESS will be conducted on Day -1 only. CCI [redacted] (k CCI [redacted] (l) CCI [redacted] (m) These tests will be conducted using the blood samples collected at the same timepoint on Day 2 and Day 4. (n)Blood sampling will be performed only once for each subject after the start of infusion on Day 3. ・・・ (p) Blood samples for the PK evaluations of TAK-925 (and its metabolites) will be collected on Day 1, Day 2, Day 3 and Day 4: Predose, 1, 2, 4, 6 and 9 hours after the start of infusion, and 0.17 0.5, 1, 2 and 15 hours after end of infusion, just before sleep and right after wake-up.	Changed the schedule due to the change washout period of Part 2.

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<tr><td>p.24</td><td>5.2.3 Trial Exploratory Objectives</td><td>CCI</td><td>CCI</td><td>CCI</td></tr>
<tr><td>p.25</td><td>5.3.3 Exploratory Endpoints</td><td>CCI</td><td>CCI</td><td></td></tr>
<tr><td>p.27</td><td>6.1 Trial Design</td><td>(2) Part 2
・・・
In Cohorts 5 and 6, 4 subjects each will be enrolled, and to be given TAK-925 will be intravenously infused for 9 hours on Day 1 and Day 2.</td><td>(2) Part 2
・・・
In Cohorts 5 and 6, 4 subjects each will be enrolled, and TAK-925 <u>or placebo</u> will be intravenously infused for 9 hours on Day 1 and Day <u>3</u>.</td><td>Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2.</td></tr>
<tr><td>p.30</td><td>6.1 Trial Design</td><td>Figure 6.a Overview of the Trial Schedules
・・・
<Part 2>
<table><tr><td rowspan="2">Screening</td><td>Baseline</td><td colspan="3">Treatment Period</td><td>Follow-up Period</td></tr><tr><td>MWT CCI</td><td>Study Drug Administration /Sampling/MWT/ CCI</td><td>Study Drug Administration /Sampling/MWT/ CCI</td><td>Sampling</td><td>Hospital Visit</td></tr><tr><td>Day -42--2*</td><td>Day -1</td><td>Day 1</td><td>Day 2</td><td>Day 3</td><td>Day 7</td></tr><tr><td></td><td colspan="4">← Hospitalization Period →</td><td></td></tr></table></td><td>Figure 6.a Overview of the Trial Schedules
・・・
<Part 2>
<table><tr><td rowspan="2">Screening</td><td>Baseline</td><td colspan="4"><u>Crossover period</u></td><td>Follow-up Period</td></tr><tr><td>MWT C CCI</td><td>Study Drug Administration /Sampling/MWT</td><td><u>Sampling/</u> CCI</td><td>Study Drug Administration /Sampling/MWT/</td><td>Sampling</td><td>Hospital Visit</td></tr><tr><td>Day -42--2*</td><td>Day -1</td><td>Day 1</td><td><u>Day 2</u></td><td>Day 3</td><td>Day 4</td><td>Day 7</td></tr><tr><td></td><td colspan="5">← Hospitalization Period →</td><td></td></tr></table></td><td>Changed the schedule due to the change washout period of Part 2. Clerical corrections</td></tr>
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p.30-31	6.2 Cohort transition / Dose Escalation	・・・The investigator will comprehensively investigate in a binded manner the safety and tolerability (adverse events, physical examination findings, vital signs, laboratory tests and 12-lead ECG findings) and available PK data of TAK-925 obtained in a blinded manner from the commencement of infusion at each Dose Level in Part 1 to 24 hours after the infusion (Day 2), or from the commencement of the final infusion at each Dose Level in Part 2 to 24 hours after the infusion (Day 3), and determine whether to proceed to the next dose level or next cohort after discussion(s) with the sponsor (and the medical expert, if necessary).・・・	・・・The investigator will comprehensively investigate in a binded manner the safety and tolerability (adverse events, physical examination findings, vital signs, laboratory tests and 12-lead ECG findings) of each Dose Level in Part 1 obtained, by 24 hours after the start of infusion (Day 2), or those of each Cohort in Part 2 obtained by 24 hours after the start of final infusion (Day 4), as well as available PK data obtained so far, then determine whether to proceed to the next dose level or next cohort after discussion(s) with the sponsor (and the medical expert, if necessary). ・・・	Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2.
p.33	6.3.2 Rationale of Trial Design	(2) Part 2 ・・・In each Cohort, the washout period to be set after the 2nd or subsequent infusions will be set 5 times the $t_{1/2}$ of TAK-925.	(2) Part 2 ・・・In each Cohort, the washout period to be set after the 2nd or subsequent infusions will be set 5 times the $t_{1/2}$ of TAK-925, as a guide, which is considered not to affect the PD effect.	
p.35	6.3.4.3 PD Endpoints	The PD endpoints will include MWT, CCI [redacted] ・・・	The PD endpoints will include MWT, CCI [redacted] ・・・	pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2. CCI [redacted]
p.37	6.4 Trial Design/Dosing/ Procedures Modifications Permitted Within Protocol Parameters	・ Prolongation of a washout period based on the safety and pharmacokinetic data obtained	・ Prolongation of a washout period based on the safety and pharmacokinetic data obtained. (In Part 2, infusion on Day 3 is changed to Day 4)	Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2.

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p.37	6.4 Trial Design/Dosing/ Procedures Modifications Permitted Within Protocol Parameters	・・・The total blood volume to be collected from a single subject will not exceed the maximum allowable volume (400 mL for subjects weighing 50 kg or more and 200 mL for a subject weighing less than 50kg) during this trial. The specified assessment time points of safety endpoints (eg, vital signs, ECG, laboratory tests) currently described in the protocol may be modified based on the newly obtained safety, tolerability, PK or PD/biomarker data (eg, to collect data at the time closer to the peak plasma concentrations achieved).・・・	・・・The total blood volume to be collected from a single subject will not exceed the maximum allowable volume (400 mL for subjects weighing 50 kg or more and 200 mL for a subject weighing less than 50kg) during this trial. The washout period between Period 1 and Period 2 in part 2 can be changed based on the newly obtained PK, safety and PD data. If this change occurs, the procedures and the schedule of study following CCI on the night on Day 2 will be shifted 1 day behind. (When the washout period is set to 2 days, refer to protocol Annex 3 in regard to the schedule, etc.) The specified assessment time points of safety endpoints (eg, vital signs, ECG, laboratory tests) currently described in the protocol may be modified based on the newly obtained safety, tolerability, PK or PD/biomarker data (eg, to collect data at the time closer to the peak plasma concentrations achieved).・・・	In order to enable to change the washout period of Part 2 without amendment of the protocol based on further pharmacokinetic data.
p.41	7.1 Inclusion Criteria	All Subjects ・・・ 5. A male subject who is nonsterilized and sexually active and has a female partner of childbearing potential agrees to use adequate contraception from the time of signing the consent form to 12 weeks (84 days) after the last dose of study drug. A female partner of the male subject should also be advised to use adequate contraception (See Appendix B).	All Subjects ・・・ 5. A male subject who is nonsterilized* and sexually active and has a female partner of childbearing potential agrees to use adequate contraception* from the time of signing the consent form to 12 weeks (84 days) after the last dose of study drug. A female partner of the male subject should also be advised to use adequate contraception* (See Appendix B).	Clerical corrections
p.45	7.2 Exclusion Criteria	All Subjects ・・・ 32. A subject who has clinically significant spinal deformities (scoliosis or kyphosis) which, in the opinion of the investigators, may interfere with lumbar puncture.	All Subjects ・・・ 32. A subject who has clinically significant vertebral deformities (scoliosis or kyphosis) which, in the opinion of the investigators, may interfere with lumbar puncture.	Clerical corrections

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p.47	7.3 Excluded Medications, Supplements, Dietary Products	(2) Part 2 ・・・Any drugs must not be used from the period shown in Table 7.b untill all tests planned on Day 3 have been completed.・・・	(2) Part 2 ・・・Any drugs must not be used from the period shown in Table 7.b untill all tests planned on Day 4 have been completed.・・・	Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2. Added a new subject management regulation in the washout period.
p.50	7.4.2 Activity	・・・ ・ CCI [redacted] ・ Subjects will follow the notes shown in the manual for pharmacodynamic tests (CCI [redacted] MWT).	・・・ ・ CCI [redacted] ・ Subjects will follow the notes shown in the manual for pharmacodynamic tests (CCI [redacted] MWT). ・ In the washout period between Period 1 and Period 2, subjects will be instructed and monitored as much as possible that time of each daytime nap should be within 30 minutes and the number of daytime nap should be up to 5 times so as not to disturb night time sleep.	
p.50	7.5 Record of Discontinuation or Withdrawal of a Subject before Study Drug Administration	・・・ ・ Lost to follow-up. ・ Voluntary withdrawal <specify reason>. ・・・	・・・ ・ Lost to follow-up. ・ Pregnancy ・ Voluntary withdrawal <specify reason>. ・・・	Due to omission
p.52-53	7.6 Criteria for Discontinuation or Withdrawal of a Subject	5. Voluntary withdrawal. ・・・ 6. Termination of entire study by the sponsor. ・・・ 7. Other ・・・	5. Pregnancy. A subjects is found to be pregnant. Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Appendix B 6. Voluntary withdrawal. ・・・ 7. Termination of entire study by the sponsor. ・・・ 8. Other ・・・	
p.57	9.1.1.2 Study Drug Assignment	In Cohorts 1-3 and Healthy Adult Supplement Cohort, subjects in each cohort will be assigned to each cohort the study drug in order of the medication ID number according to the randomization schedule (See Figure 9.a, Figure 9.b and Figure 9.c). In Cohorts 5-7,,・・・. The assigned medication ID number or subject ID number will to be・・・	In Cohorts 1-3 and Healthy Adult Supplement Cohort (if it will be added), subjects in each cohort will be assigned to each cohort the study drug in order of the medication ID number according to the randomization schedule (See Figure 9.a, Figure 9.b and Figure 9.c). In Cohort 4, eligible subjects will be assigned with the subject ID number. In Cohorts 5-7,・・・. The assigned medication ID number or subject ID number will to be used by・・・	In order to clarify the regulation on Cohort 4.

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p.60	9.2.1 Full Physical Exam	･･･When a physical examination is performed on Day 2 and Day 3 in Part 2,･･･.	･･･When a physical examination is performed on Day 2 and Day 4 in Part 2,･･･.	Changed the washout period of Part 2 based on the pharmacokinetic data of Cohort 1 Dose Level 1 and Cohort 2 Dose Level 2.
p.61	9.2.4 Columbia Suicide Severity Rating Scale (C-SSRS)	A risk of suicide will be assessed using the C-SSRS at time points specified in the Schedule of Study Procedures (On Day 2 in Part 1 and Day 3 in Part 2).	A risk of suicide will be assessed using the C-SSRS at time points specified in the Schedule of Study Procedures (On Day 2 in Part 1 and Day 4 in Part 2).	Changed the schedule due to the change washout period of Part 2.
p.62	9.2.7 Study Drug Administration	The study drug will be intravenously administered to subjects over 9 hours on Day 1 in Part 1 and Day 1 and Day 2 in Part 2 (TAK-925 will be administered to each subject only once in Part 2).	The study drug will be intravenously administered to subjects over 9 hours on Day 1 in Part 1 and Day 1 and Day 3 in Part 2 (TAK-925 will be administered to each subject only once in Part 2).	Changed the schedule due to the change washout period of Part 2.
p.66	9.3.1.1 Plasma Samples for PK Measurements	(1) Part 1 Table 9.b Collection of Blood Samples for Pharmacokinetic Analysis (Part 1) **Blood sampling time** Before infusion, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 9 hours after the start of infusion, and 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 15 hours after the end of infusion	(1) Part 1 Table 9.b Collection of Blood Samples for Pharmacokinetic Analysis (Part 1) **Blood sampling time** Before infusion, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 9 hours after the start of infusion, and 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 10[1)] and 15 hours after the end of infusion 1) Dose Level 1 and 2 of Cohorts 1 and 2 will be excluded at 10 hours after the end of infusion.	Added pharmacokinetic sample to evaluate pharmacokinetic more accurately based on the pharmacokinetic data of Cohort 1 Dose Level 1.
p.67	9.3.1.1 Plasma Samples for PK Measurements	(2) Part 2 Table 9.c Collection of Blood Samples for Pharmacokinetic Analysis (Part 2) **Analysis date** / **Blood sampling time** Day 1-3 / Before infusion[1, 2)], 1, 2[2)], 4[2)], 6[2)] and 9[2)] hours after the start of infusion and 0.17, 0.5, 1, 2[2)] and 15[2)] hours after the end of infusion, and at bedtime[2)]. 1) Since "before infusion" on Day 2 is the same time as "15 hours after the end of infusion" on Day 1, blood sampling is unnecessary. 2) Blood sampling will be 6 mL. For the other sampling times, 3 mL will be collected.	(2) Part 2 Table 9.c Collection of Blood Samples for Pharmacokinetic Analysis (Part 2) **Analysis date** / **Blood sampling time** Day 1-4 / Before infusion[1)], 1, 2[1)], 4[1)], 6[1)] and 9[1)] hours after the start of infusion and 0.17, 0.5, 1, 2[1)] and 15[1)] hours after the end of infusion, at bedtime and right after[1)] wake-up. 1) Blood sampling will be 6 mL. For the other sampling times, 3 mL will be collected.	Added pharmacokinetic sample to evaluate pharmacokinetic more accurately based on the pharmacokinetic data of Cohort 1 Dose Level 1.

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p.67	9.3.1.1 Plasma Samples for PK Measurements	(2) Part 2 ・・・ In the case that a subject prematurely discontinues the study between the time from the start of study drug administration to the completion of procedures on Day 2 in Part 1 and on Day 3 in Part 2,・・・ ・・・ In the case of premature discontinuation during the period from Day 2 to the follow-up in Part 1, and during the period from Day 3 to the follow-up in Part 2,・・・	(2) Part 2 ・・・ In the case that a subject prematurely discontinues the study between the time from the start of study drug administration to the completion of procedures on Day 2 in Part 1 and on Day 4 in Part 2,・・・ ・・・ In the case of premature discontinuation during the period from Day 2 to the follow-up in Part 1, and during the period from Day 4 to the follow-up in Part 2,・・・	Changed the schedule due to the change washout period of Part 2.
p.68	9.3.2.1 Maintenance of Wakefulness Test (MWT)	・・・The MWT will be conducted 4 times each (at 10:00, 12:00, 14:00 and 16:00) on Day 1 and Day 2, respectively. For the MWT on Day -1, sleep latency will be recorded as much as possible. On Day 1 and Day 2, sleep latency will be recorded in each session. In addition, REM sleep latency (RL), the number of wakefulness/N1 to stage REM transitions, time in stage REM sleep without atonia will be recorded in each session. See the manual for PD tests (CCI MWT) for details.	・・・The MWT will be conducted 4 times each (at 10:00, 12:00, 14:00 and 16:00) on Day 1 and Day 3, respectively. For the MWT on Day -1, sleep latency will be recorded as much as possible. On Day 1 and Day 3, sleep latency will be recorded in each session. In addition, REM sleep latency, the number of wakefulness/N1 to stage REM transitions, time in stage REM sleep without atonia will be recorded in each session. As an exploratory evaluation, additional analysis using electroencephalogram data obtained by MWT may be performed after breaking the randomization code. See the manual for PD tests (CCI MWT) for details.	In order to investigate electroencephalogram data obtained by MWT as an exploratory evaluation.
p.68	9.3.2.2 CCI	CCI	CCI	CCI
p. 69	9.3.2.3 CCI	CCI	CCI	
p.69	9.3.2.4 CCI	CCI	CCI	

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p.69	9.3.2.5 CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]
p.70	9.3.3.1 Blood Sample for DNA PGx Measurements	･･･ On Day 1 (Part 1) or Day 2 (Part 2), 5-mL of whole blood sample･･･	･･･ On Day 1 (Part 1) or Day 3 (Part 2), 5-mL of whole blood sample･･･	Changed the schedule due to the change washout period of Part 2.
p.70	9.3.4 Confinement	(2) Part 2 Subjects will be hospitalized in a hospital during the period from Day -1 to Day 3 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 3,･･･	(2) Part 2 Subjects will be hospitalized in a hospital during the period from Day -1 to Day 4 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 4,･･･	
p.80	11.1.4 PD Analysis	(1) Endpoints and analysis methodologies [Endpoints] The average sleep latency in the MWT, sleep-related parameters in the MWT (sleep latency in each session, REM sleep latency, the number of wake/sleep stage 1(N1)-to-REM sleep transition, total time of REM sleep without atonia), sleep-related parameters in the CCI [redacted] (wake time after sleep onset, the number of nocturnal awakenings, the number of arousal reactions, sleep latency, REM sleep latency, the number of REM sleep latency, wake/sleep stage 1(N1)-to-REM sleep transition, sleep-onset REM periods without atonia, apnea-hypopnea index, periodic limb movement arousal index in sleep, total sleep time, sleep efficiency, the incidence rate of each sleep stage), assessment of daytime sleepiness using the KSS, assessment by the CCI [redacted] assessment of sleep-related symptoms of cataplexy and narcolepsy using a daily dairy for collecting cataplexy and sleep-related symptoms.	(1) Endpoints and analysis methodologies [Endpoints] The average sleep latency in the MWT, sleep-related parameters in the MWT (sleep latency in each session, REM sleep latency, the number of wake/sleep stage 1(N1)-to-REM sleep transition, total time of REM sleep without atonia), assessment of daytime sleepiness using the KSS, assessment by the CCI [redacted] assessment of sleep-related symptoms of cataplexy and narcolepsy using a daily dairy for collecting cataplexy and sleep-related symptoms.	

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