Title: A 3-Part, Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-925 in Healthy Volunteers and Patients with Narcolepsy

NCT Number: NCT03748979

Protocol Approve Date: 12-JUN-2019

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

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

TAKEDA PHARMACEUTICALS

PROTOCOL

A 3-Part, Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-925 in Healthy Volunteers and Patients with Narcolepsy

Study Identifier: TAK-925-1003

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

Date: 12 June 2019

Version/Amendment Number: Amendment 3

Amendment History:

Date	Amendment Number	Region
10 Oct 2018	Initial Version	All sites
05 Nov 2018	Amendment 1	All sites
18 Jan 2019	Amendment 2	All sites
12 Jun 2019	Amendment 3	All sites

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-925
Study Identifier: TAK-925-1003	**Phase: 1**

Protocol Title: A 3-Part, Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-925 in Healthy Volunteers and Patients with Narcolepsy

Trial Design:

This study will consist of three parts. Part A is a randomized, double-blind, placebo-controlled, multiple rising dose (MRD) study to assess safety, tolerability, and pharmacokinetics (PK) of TAK-925 administered via intravenous (IV) infusion in healthy subjects. Part B is a randomized, double-blind, placebo-controlled MRD study to assess the safety, tolerability, PK and pharmacodynamics (PD) of TAK-925 administered via IV infusion in patients with narcolepsy type 1 (NT1). Part C is a randomized, double-blind, placebo-controlled, parallel group, multiple repeat dose study to assess the safety, tolerability, PK and PD of one or more dose levels of TAK-925 vs. placebo in patients with narcolepsy type 2 (NT2). Part A' is an open-label single oral dose study to assess PK, safety and tolerability of TAK-925 administered orally in healthy subjects. Parts A - A' may be conducted in parallel, rather than sequentially, depending on the doses administered and emerging safety/tolerability data.

In general, considering the completion times of the prior studies, TAK-925-1001 and TAK-925-1002, Part A, Part B and Part A' are expected to begin in parallel. Part A will test safety and tolerability in healthy volunteers (HV) starting from the dose level associated with that was found to be safe and tolerable based on the preliminary blinded safety adverse event (AE) profiles in TAK-925-1001 study. Part B will test safety, tolerability and PD in NT1 patients, who will be administered a lower dose than subjects in Part A. The initial dose in Part B was found to be safe and tolerable based on the preliminary blinded safety AE profiles in NT1 patients in the TAK-925-1001 study. The initial dose in Part B is more than 10 times lower than the highest dose level tested in TAK-925-1001 HV cohorts. Results from the TAK-925-1001 study will also be available at the time of initiation of Part A and Part B. Part A' will assess the safety, tolerability and PK after oral administration of TAK-925 in healthy volunteers at a dose level that was found to be safe and tolerable after IV administration in TAK-925-1001 study and is anticipated to result in lower exposure of TAK-925 after oral administration, due to high first-pass metabolism expected from available nonclinical data. For Part C, the NT2 patient doses are expected to be similar to that in Part A, although recruitment of these cohorts will be slower. Initiation of Part A and Part C may also occur at the same time if the similar doses are studied. The initiation of cohorts in parallel with each other is contingent on Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, and if not approved, the cohorts will enroll as required, which may be sequentially or overlapping with each other. The NT1 and NT2 patients recruited are expected to be generally healthy other than having narcolepsy.

For more details, see Section 6.1.

Trial Primary Objective:

<All Parts>

To investigate the safety and tolerability of TAK-925 when administered to healthy subjects and NT1 and NT 2 patients.

Secondary Objectives:

<All parts>

To investigate the pharmacokinetics of TAK-925 when administered to healthy volunteers or narcolepsy patients

<Parts B and C>

To investigate the PD of TAK-925 after multiple doses, primarily with evaluation of sleep latency on maintenance of wakefulness test (MWT) when TAK-925 is administered to NT1 or NT2 patients.

Trial Subject Population: Healthy adults, healthy elderly volunteers and patients with NT1 and NT2.

Planned Number of Subjects:	**Planned Number of Sites:**
(1) Part A Healthy adults • Cohort A1: 8 subjects • Cohort A2: 8 subjects • Cohort A3 (optional): 8 subjects • Cohort A4 (optional): 8 subjects • Cohort A5 (optional): 8 subjects • Cohort A6 (optional healthy elderly): 8 subjects. (2) Part B NT1 patients • Cohort B1: 6 subjects • Cohort B2: 6 subjects • Cohort B3 (optional): 4-6 subjects from B1 or B2, or newly enrolled subjects. • Cohort B4 (optional): 4-6 subjects from B1 or B2 or newly enrolled subjects. (3) Part C NT2 patients • Cohort C1: 6 subjects • Cohort C2 (optional): 6 subjects Numbers for Part B and C show target number of subjects. (4) Part A' Healthy adults • Cohort A'1: 6 subjects • Cohort A'2 (optional): 6 subjects	3 sites
Dose Levels: Dose Regimens: Dosage: <Part A> Healthy adults and healthy elderly: TAK-925 or placebo is to be administered via IV infusion over 9 hours once daily up to 7 days. <Part B> NT1 patients: TAK-925 or placebo is to be administered via IV infusion over 9 hours or longer once daily up to 7 days. <Part C> NT2 patients: TAK-925 or placebo is to be administered via IV infusion over 9 hours once daily up to 7 days. <Part A'> Healthy adults: TAK-925 is to be administered as a single oral dose Administration: <Part A, B and C>	**Route of Administration:** <Part A, B and C> intravenous (IV) <Part A'> Oral

TAK-925 1.5 to 240 mg/9h is to be administered. The maximum dose cap in this study will be 240 mg/9h or dose levels which could be administered within equivalent infusion rate with 240 mg/9h when infusion time is longer. <Part A'> TAK-925 112 to 336 mg (given as oral solution) is to be administered in fasting condition.	
Duration of Treatment: <Part A, B and C> 7 days <Part A'> 1 day	**Planned Trial Duration:** <Part A> Screening period: Day -28 to Day -3 Check-in: Day -2 Treatment Period: Day 1 to 7 Follow up visit: Day 15 <Part B and C> Screening period: Day -42 to Day -3 Check-in: Day -2 Treatment Period: Day 1 to 7 Follow up visit: Day 15 Patients who will roll over from B1 or B2 to B3 or B4 could repeat the trial duration twice. <Part A'> Screening period: Day -28 to Day -2 Check-in: Day -1 Treatment Period: Day 1 Follow up phone call: Day 7

Main Criteria for Inclusion:

In order to be eligible for study participation, the following criteria must be satisfied:

1. The subject must understand the study procedures and agree to participate by providing written informed consent.
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be judged to be in good health by the investigator to participate in the study, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening Visit and prior to the first dose of study drug or first invasive procedure.
4. For a male subject who is nonsterilized and sexually active with a female partner of childbearing potential, the subject must meet the following birth control requirements:
   - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from the first dose of study drug until 92 days after the last dose of study drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1 year post bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
   - Is a male subject who agrees to not donate sperm from the first dose of study drug until 92 days after the last

dose of study drug.

Healthy adults (Part A and A') and elderly (Part A)

5. The subject must be male or female.
6. The subject must have a body mass index ≥18.5 and ≤30.0 kg/m^2 at the Screening Visit.
7. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months prior to the first dose of study drug or first invasive procedure.
8. CCI [redacted]
9. For a female subject, the subject must meet one of the following birth control requirements:

   Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or 6 months of spontaneous amenorrhea in females aged >45 years with serum follicle-stimulating hormone levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels is required.

   Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

   Had a tubal ligation with appropriate documentation of surgical procedure

   Has a congenital condition resulting in no uterus.

For the details specific to Part A, B, C and A', refer to the Section 7.1.

Main Criteria for Exclusion:

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

1. The subject has participated in another investigational study within 4 weeks (or based on local regulations) prior to the Screening Visit. The 4-week window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the Screening Visit of the current study. This criterion is not applicable to patients who will participate in B3 or B4 after they completed B1 or B2.
2. The subject is an employee of the sponsor or study site or immediate family member (eg, spouse, parent, child, sibling) of the sponsor or study site.
3. The subject has a history of cancer (malignancy).
4. The subject has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
5. Has a known hypersensitivity to any component of the formulation of TAK-925 or related compounds.
6. The subject has a positive pregnancy test.
7. The subject is a lactating/nursing female.
8. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody/antigen, or serologic reactions for syphilis at the Screening Visit. Note: Subjects with positive hepatitis B virus or hepatitis C virus serology may be enrolled if quantitative polymerase chain reaction for hepatitis B virus or hepatitis C virus ribonucleic acid is negative.
9. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the Screening Visit.
10. The subject is unable to refrain from or anticipates using excluded medications (see Section 7.3) beginning approximately 7 days prior to administration of the first dose of study drug, throughout the study including washout intervals between treatment periods, until the Follow-up Visit.
11. The subject consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

12. The subject has a moderate to severe substance use disorder.
13. The subject's renal creatinine clearance (CCR) ≤50 mL/min at the time of screening and baseline
14. The subject has poor peripheral venous access.
15. The subject has undergone whole blood draw prior to the start of study drug administration as any of below:

    For both male and female subjects,

    ≥200 mL within 4 weeks (28 days)

    For male subjects,

    ≥400 mL within 12 weeks (84 days)

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

    For female subjects,

    ≥400 mL within 16 weeks (112 days)

    ≥400 mL in total within 52 weeks (364 days)
16. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of study drug administration.
17. The subject has a risk of suicide according to endorsement of item 4 or 5 with screening/baseline visit Columbia Suicide Severity Rating Scale (C-SSRS) or has made a suicide attempt in the previous 6 months.
18. CCI [redacted]
19. The subject has a lifetime history of major psychiatric disorder, such as bipolar disorder or schizophrenia. Subject who has history of major depressive disorder (MDD) may be include but a subject who has current active major depressive disorder or who has had active major depressive disorder in the past 6 months is excluded.
20. The subject has a clinically significant history of head injury and trauma.
21. The subject has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
22. The subject has known coronary artery disease, a history of myocardial infarction (MI), angina, cardiac rhythm abnormality, or heart failure.
23. The subject's screening ECG reveals a QT interval with Frederica correction method (QTcF) >450 ms (men) or >470 ms (women).
24. The subject has a resting PR outside of the range of 45 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes, at the Screening Visit or Check-in (Day -1).
25. The subject has medical condition (in case of Part B and C, narcolepsy is exceptional.) that would preclude enrollment in the view of the investigators, such as medically significant unstable cardiovascular, pulmonary, hepatic, renal, or Gastro-intestinal (GI) disease.
26. The subject has abnormal laboratory test values that suggest a clinically significant underlying disease at the Screening Visit or baseline or any subject with transaminase (Alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) >1.5 (Part A and A') or >2.0 (Part B and C)×upper limit of normal (ULN) at the Screening Visit (or baseline in Part A and A').
27. The subject experienced sleep wake cycle disturbance with external factors such as irregular work hours; routine night-shift work or travel with significant jet lag within 7 days before randomization
28. The subject who, in the opinion of the investigator or sub-investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

For the details specific to Part A, B, C and A', refer to Section 7.2.

Main Criteria for Evaluation and Analyses:

- The primary endpoint:

Safety and tolerability: number of subjects with AEs

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

<All parts>

- Pharmacokinetic parameters (C_{eoi}, AUC_{τ}, $R_{ac(AUC)}$) of TAK-925

<Part B and C>

- Change from baseline in Sleep latency in the MWT to Days 1 and 7

Statistical Considerations:

Safety Analysis:

All data analyses and summaries will be performed using the safety set separately for Part A, B, C and A' by treatment.

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 Medicines and Healthcare Products Regulatory Agency (MedDRA) dictionary and tabulated by the system organ class (SOC) and the Preferred Term (PT).

The observed values, the changes from baseline and change from time-matched baseline will be summarized for each scheduled sampling time using descriptive statistics.

PK Analysis:

All data analyses and summaries will be performed using the PK set separately for Part A, B, C and A' by treatment.

Plasma concentrations and pharmacokinetic parameters of TAK-925 and its metabolites (CCI) will be summarized for each scheduled sampling time using descriptive statistics. For Parts A, B and C, the relationship between TAK-925 exposure and safety will be explored graphically. CCI [redacted]

PD Analysis:

All data analyses and summaries will be performed using the PD set separately for Parts B and C.

The average sleep latency in the MWT will be summarized (N, mean, median, SD, minimum, and maximum) for baseline, post-dose, change from baseline and change from Day 1 to Day 7 by treatment. Percentage of the patients who recorded the average sleep latency in the MWT equal to or over 40 minutes in Day 1 and Day 7 will be provided by treatment group.

If applicable, the effect of TAK-925 will be evaluated with a linear mixed effects model. The response variable in the model will be the change from baseline in the average sleep latency in the MWT. The model will include treatment (each dose level of TAK-925 and placebo), day (as a categorical variable), the treatment-by-day as fixed effects, baseline average sleep latency in the MWT as a covariate, and subjects as a random effect.

Sample Size Justification:

The sample size in Part A (8 subjects per cohort: 6 active and 2 placebo), Part B and C (6 patients per cohort: 4 active and 2 placebo) and Part A' (open label, 6 subjects per cohort) is assumed to be sufficient for investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of TAK-925 when multiple doses of TAK-925 are administered intravenously in healthy adults, healthy elderly, and narcolepsy patients, or when a single dose of TAK-925 is administered orally in healthy adults. The sample size is not based on considerations of statistical power.

2.0 STUDY SCHEMATIC

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

Part	Cohort/Panel	Daily dose level (mg)	Dosing regimen	Randomization
Part A (Healthy adults)#	A1	44	IV infusion over 9 hours up to 7 days. Start time of infusion could be changed in optional cohorts A3 to A5.	8 subjects randomized 6:2 to TAK-925 vs. placebo in each cohort, double-blind
	A2	112 (TBD)		
	A3*	TBD		
	A4*	TBD		
	A5*	TBD		
	A6 (elderly)*	TBD		
Part B (NT1 patients)#	B1	11	IV infusion over 9 hours up to 7 days	6 subjects randomized 4: 2 to TAK-925 vs. placebo in each cohort, double-blind
	B2	44 (TBD)		
	B3*	TBD	IV infusion with longer (TBD) hours up to 7 days	4-6 subjects randomized (3:1, 4:1 or 5:1) to TAK-925 vs. placebo in each cohort, double-blind
	B4*	TBD	IV infusion over 9 hours up to 7 days, different, increasing dose from Day 1 to Day 7	
Part C (NT2 patients)#	C1	44 (TBD)	IV infusion over 9 hours up to 7 days	6 subjects randomized 4: 2 to TAK-925 vs. placebo in each cohort, double-blind
	C2*	TBD		
Part A' (Healthy adults)	A'1	112	Single oral administration	6 subjects per cohort (TAK-925 administration, open)
	A'2*	TBD		

Abbreviations: TBD, To Be Determined
Doses in subsequent cohorts in all parts will be determined based on the emerging safety/tolerability and PK (when available) and PD information and available safety/tolerability, and PK/PD data from previous cohorts as well as the ongoing TAK-925-1001 and TAK-925-1002 studies. Planned number of subjects in each cohort is shown.
All doses given by IV infusion over 9 hours daily for 7 days except B3
* Optional cohorts

3.0 SCHEDULE OF STUDY PROCEDURES

Part A (Healthy volunteers, Screening to Day 2)

	MRD																																		
	Day		Day-1 scheduled time								Day 1 scheduled time																										Day
	-28 to -3	-2	Hours								Hours																										2
												After start of infusion													After end of infusion										
	Screening	Check-in	-23	-22	-20	-18	-15	-14	-13	-11	Pre dose	0 5	1	1 5	2	3	4	5	6	7	8	9	0 17	0 33	0 5	0 75	1	1 5	2	3	4	6	10	15
Administrative Procedures																																			
Informed Consent	X																																		
Informed Consent {retained samples, pharmacogenomics}	X																																		
Inclusion/Exclusion Criteria/Demographics	X		X								X																								
Medical History	X		X																																
Concomitant Medication Review	X----------Continuous monitoring----------X																																		
Clinical Procedures/ Assessments																																			
Full Physical Examination	X										X [a]																								X [a]
Height	X																																		
Weight	X										X [a]																								
BMI	X																																		
CCI																																			
TAK-925/Placebo Administration												9-hour continuous IV infusion																							X
Continuous BP			X----------Continuous monitoring----------X																																	
CCI																																			
C-SSRS	X		X																																
CCI																																			
AE monitoring	X----------Continuous monitoring----------X																																		

Footnotes are on the next page

MRD																																						
	Day		Day-1 scheduled time								Day 1 scheduled time																												Day
	-28 to -3	-2	Hours								Hours																												2
											Pre dose	After start of infusion															After end of infusion												
	Screening	Check-in	-23	-22	-20	-18	-15	-14	-13	-11		0 5	1	1 5	2	3	4	5	6	7	8	9	0 17	0 33	0 5	0 75	1	1 5	2	3	4	6	10	15						
CCI [redacted]																																							
PK Evaluations																																							
Plasma sample for TAK-925 and/or Metabolites assay [g]											X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X		X	X	X				
PGx Evaluations																																							
Blood sample for DNA PGx																																							X
Other																																							
Standard Meals [h]			X								X						X										X											X
Confinement			X----------Continuous ----------X																																				

Abbreviations: AE, adverse event; BMI, body mass index; C-SSRS, BP, blood pressure; Columbia Suicide Severity Rating Scale; DBP, diastolic blood pressure; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; IV, intravenous; PR, pulse rate; MRD, multiple rising dose; CCI [redacted]; PD, pharmacodynamic(s); PGx, pharmacogenomic(s); PK, pharmacokinetic(s); CCI [redacted]; SBP, systolic blood pressure; CCI [redacted]

a Day 1 predose physical examination and weight may be done within approximately 24 hours prior to study drug administration For Days 2, 3, 5 and 7, physical examination will occur predose on each day

b CCI [redacted]

c CCI [redacted]

d CCI [redacted]

e CCI [redacted]

f CCI [redacted]

g Blood collection for plasma TAK-925 concentration and its metabolites will be collected:
Day 1 and 7: Predose, 0 5, 1, 1 5, 2, 4, 6, 8, 9 hours after start of infusion, 0 17, 0 33, 0 5, 0 75, 1, 1 5, 2, 3, 6, 10 and 15 hours after end of infusion
Day 5 and 6: Predose, 9 hours after start of infusion

h Standardized meals (approximately 30% fat content relative to total calories) will be administered during confinement The time will be adjusted approximately the same time from Day 1 through Day 7 Day 8 and Day 15 are option The meals on Day 1 and Day 7 should be the same

Part A (Healthy volunteers, Day 3 to Day 15)

MRD																														
	Day				Day 7 Scheduled time																								Day		
	3	4	5	6	Hours																								8	-	15
						After start of infusion											After end of infusion														
					Pre dose	0 5	1	1 5	2	3	4	5	6	7	8	9	0 17	0 33	0 5	0 75	1	1 5	2	3	4	6	10	15	ET	Follow up
Administrative Procedures																														
Informed Consent																														
Informed Consent {retained samples, pharmacogenomics}																														
Inclusion/Exclusion Criteria/Demographics																														
Medical History																														
Concomitant Medication Review	X----------Continuous monitoring----------X																													
Clinical Procedures/Assessments																														
Full Physical Examination	X [a]		X [a]		X [a]																						X	X	X	
Height																														
Weight																											X	X		
BMI																														
CCI [redacted]																														
TAK-925/Placebo Administration	X	X	X	X		9-hour continuous IV infusion																								
CCI [redacted]																														
C-SSRS																											X	X		
CCI [redacted]																														
AE monitoring	X----------Continuous monitoring----------X																													

Footnotes are on the next page

MRD																													
	Day				Day 7 Scheduled time																							Day		
	3	4	5	6	Hours																							8	-	15
					Pre dose	After start of infusion											After end of infusion													
						0 5	1	1 5	2	3	4	5	6	7	8	9	0 17	0 33	0 5	0 75	1	1 5	2	3	4	6	10	15	ET	Follow up
CCI [redacted]																													
PK Evaluations																													
Plasma sample for TAK-925 and/or Metabolites assay [g]			X	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X		X	X	X	X	
PGx Evaluations																													
Blood sample for DNA PGx																													
Other																													
Standard Meals [h]	X	X	X	X	X						X										X								
Confinement	X----------Continuous ----------X																												

Abbreviations: AE, adverse event; BP, Blood pressure; BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; DBP, diastolic blood pressure; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; PR, pulse rate; MRD, multiple rising dose; CCI [redacted]; PGx, pharmacogenomic(s); PK, pharmacokinetic(s); CCI [redacted] SBP, systolic blood pressure; CCI [redacted]

a Day 1 predose physical examination and weight may be done within approximately 24 hours prior to study drug administration. For Days 2, 3, 5 and 7, physical examination will occur predose on each day

b CCI [redacted]

c CCI [redacted]

d CCI [redacted]

e CCI [redacted]

f CCI [redacted]

g Blood collection for plasma TAK-925 concentration and its metabolites will be collected:
Day 1 and 7: Predose, 0 5, 1, 1 5, 2, 4, 6, 8, 9 hours after start of infusion, 0 17, 0 33, 0 5, 0 75, 1, 1 5, 2, 3, 6, 10 and 15 hours after end of infusion
Day 5 and 6: Predose, 9 hours after start of infusion

h Standardized meals (approximately 30% fat content relative to total calories) will be administered during confinement. The time will be adjusted approximately the same time from Day 1 through Day 7. The meals on Day 1 and Day 7 should be the same

Part B (NT1 patients, B1, B2, B3, B4) and C (NT2 patients) (Screening to Day 1)

	MRD																
	Day		Day-1 scheduled time	Day 1 scheduled time													
	-42 to -3	-2	Hours	Hours													
					After start of infusion									After end of infusion			
	Screening	Check-in		Predose	1	2	3	4	5	6	7	8	9	1	2	3	4	Postdose night
Administrative Procedures																		
Informed Consent	X																	
Informed Consent {retained samples, pharmacogenomics}	X																	
Inclusion/Exclusion Criteria/Demographics	X [a]		X	X														
Medical History	X		X															
HLA DQB1 06:02 typing [c]	X																	
Concomitant Medication Review	X----------Continuous monitoring----------X																	
Clinical Procedures/Assessments																		
Full Physical Examination	X			X [d]														
Height	X																	
Weight [d]	X			X [d]														
BMI	X																	
CCI																		
TAK-925/Placebo Administration					9-hour (may be longer in B3) continuous IV infusion													
CCI																		
C-SSRS	X		X															
CCI																		
AE monitoring	X----------Continuous monitoring----------X																	

Footnotes are on the next page.

	MRD																
	Day		Day-1	Day 1 scheduled time													
	-42 to -3	-2		Hours													
					After start of infusion									After end of infusion			
	Screening	Check-in		Predose	1	2	3	4	5	6	7	8	9	1	2	3	4	Postdose night
CCI																		
PK Evaluations																		
Plasma sample for TAK-925 and/or Metabolites assay [i]				(X) [i]	(X) [i] ----------(X) [i]													
PD Evaluation																		
MWT [j]			X			X		X		X		X						
CCI																		
ESS	X		X															
KSS [l]			X	X	X		X		X		X		X	X	X	X	X	X
CCI																		
PGx Evaluation																		
Blood sample for DNA PGx																		
Other																		
Standard Meals [o]			X	X				X							X			
Confinement			X----------Continuous----------X															

Abbreviations: AE, adverse event; β-hCG, beta-human chorionic gonadotropin; BMI, body mass index; C-SSRS, Columbia Suicide Severity Rating Scale; DBP, diastolic blood pressure; ECG, electrocardiogram; EEG, electroencephalogram; ESS, Epworth Sleepiness Scale; ET, early termination; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; HLA DQB1, human leukocyte antigen DQB; IV, intravenous; PR, pulse rate; KSS, Karolinska Sleepiness Scale; MRD, multiple rising dose; MWT, maintenance of wakefulness test; CCI ; PD, pharmacodynamic(s); CCI ; PGx, pharmacogenomic(s); PK, pharmacokinetic(s); CCI ; CCI ; SBP, systolic blood pressure

a. To confirm eligibility of patients, CCI , maintenance of wakefulness test (MWT), and/or CCI orexin examination could be done as a study procedure(s) during the screening period, if necessary. Patients with no PSG data within 3 years before screening needs to be verified for clinically significant obstructive sleep apnea (OSA)/ restless legs syndrome (RLS) with appropriate questionnaires. Subjects with their ages over 45 year old are

essentially recommended to have PSG assessment during screening period if they don't have PSG data within past 3 years. Further confirmation may be requested to sleep specialists based on the result of questionnaires.

b. The subject who directly move on to Cohort B3, B4 could skip Day 8 assessment marked and follow up visit and move into Day -2 in B3 and B4 schedule without serum β-hCG and urine drug screen on Day -2.
c. Not required for patients with previously confirmed HLA medical record data
d. Day 1 Predose physical examination and weight may be done within approximately 24 hours prior to study drug administration. On Days 2, 4 and 7, full physical examination will occur predose on each day.
e. CCI [redacted]
f. CCI [redacted]
g. Predose hematology, serum chemistry, urinalysis may be done within approximately 24 hours prior to study drug administration on Day 1.
h. CCI [redacted]
i. Blood collection for plasma TAK-925 concentration and its metabolites will be collected: Refer to Table 9.c for the details.
j. MWT will be conducted on Day -1, Day 1 and Day 7 at approximately 10, 12, 14 and 16 o'clock of the day. For Cohort B4, MWT will also be conducted on Day 4 at approximately 10, 12, 14 and 16 o'clock of the day.
k. CCI [redacted]
l. CCI [redacted]
m. CCI [redacted]
n. CCI [redacted]
o. Standardized meals will be administered during confinement. The time will be adjusted approximately the same time from Day 1 through Day 7, light lunch will be served on Day -1, Day 1 and Day 7 (and Day 4 for cohort B4) between 2nd and 3rd session of MWT. Day 8 and Day 15 are option. The meals on Day 1 and Day 7 (and Day 4 for cohort B4) should be the same.

Part B (NT1 patients, B1, B2, B3, B4) and C (NT2 patients), (Day 2 to Day 15)

	MRD																						
	Day					Day 7 Scheduled time															Day		
	2	3	4	5	6	Hours															8 [b]	-	15
							After start of infusion									After end of infusion							
						Predose	1	2	3	4	5	6	7	8	9	1	2	3	4	Postdose night		ET	Follow up [b]
Administrative Procedures																							
Informed Consent																							
Informed Consent {retained samples, pharmacogenomics}																							
Inclusion/Exclusion Criteria/ Demographics																							
Medical History																							
HLA DQB1 06:02 typing [c]																							
Concomitant Medication Review	X----------Continuous monitoring----------X																						
Clinical Procedures/Assessments																							
Full Physical Examination	X [d]		X [d]			X [d]															X	X	X
Height																							
Weight																					X [b]	X	
BMI																							
CCI																							
TAK-925/Placebo Administration	X	X	X	X	X		9-hour (may be longer in B3) continuous IV infusion																
CCI																							
CCI																							
C-SSRS																					X [b]	X	
CCI																							
AE monitoring	X----------Continuous monitoring----------X																						

Footnotes are on the next page.

	MRD																						
	Day					Day 7 Scheduled time															Day		
	2	3	4	5	6	Hours															8 [b]	-	15
							After start of infusion								After end of infusion								
						Predose	1	2	3	4	5	6	7	8	9	1	2	3	4	Postdose night		ET	Follow up [b]
CCI																							
PK Evaluations																							
Plasma sample for TAK-925 and/or Metabolites assay [i]	(X) [i]	(X) [i]	(X) [i]	(X) [i]	(X) [i]	(X) [i]	(X) [i] ----------(X) [i]														(X) [i]	(X) [i]	
PD Evaluation																							
MWT [j]			(X) [j]					X		X		X		X									
CCI																							
PGx Evaluation																							
Blood sample for DNA PGx	X																						
Other																							
Standard Meals [o]	X	X	X	X	X	X				X						X							
Confinement	X----------Continuous monitoring----------X																						

Abbreviations: AE, adverse event; β-hCG, beta-human chorionic gonadotropin; BMI, body mass index; BP, blood pressure; C-SSRS, Columbia Suicide Severity Rating Scale; DBP, diastolic blood pressure; ECG, electrocardiogram; EEG, electroencephalogram; CCI ; ET, early termination; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; HLA DQB1 ,human leukocyte antigen DQB; IV, intravenous;PR, pulse rate; CCI ; MRD, multiple rising dose; MWT, maintenance of wakefulness test; CCI ; PD, pharmacodynamic(s); CCI ; PGx, pharmacogenomic(s); PK, pharmacokinetic(s); CCI ; CCI ; SBP, systolic blood pressure

a. To confirm eligibility of patients, CCI orexin examination could be done as a study procedure(s) during the screening period, if necessary. CCI Subjects with their ages over 45 year old are essentially recommended to have CCI

[redacted]. Further confirmation may be requested to sleep specialists based on the result of questionnaires.

b. The subject who directly move on to Cohort B3, B4 could skip Day 8 assessment marked and follow up visit and move into Day-2 in B3 and B4 schedule without serum β-hCG and urine drug screen on Day -2.
c. Not required for patients with previously confirmed HLA medical record data
d. Day 1 predose physical examination may be done within approximately 24 hours prior to study drug administration. On Days 2, 4 and 7, physical examination will occur predose on each day.
e. [redacted]
f. [redacted]
g. [redacted]
h. [redacted]
i. Blood collection for plasma TAK-925 concentration and its metabolites will be collected: Refer to Table 9-c for the details.
j. MWT will be conducted on Day -1, Day 1 and Day 7 at approximately 10, 12, 14 and 16 o'clock of the day. For Cohort B4, MWT will also be conducted on Day 4 at approximately 10, 12, 14 and 16 o'clock of the day.
k. [redacted]
l. [redacted]
m. [redacted]
n. [redacted]
o. Standardized meals will be administered during confinement. The time will be adjusted approximately the same time from Day 1 through Day 7, but light lunch will be served on Day-1, Day 1 and Day 7 (and Day 4 for cohort B4) between 2nd and 3rd session of MWT. Day 8 and Day 15 are option. The meals on Day 1 and Day 7 (and Day 4 for cohort B4) should be the same.

Part A' (Healthy volunteers)

	Day	Day	Day 1 scheduled time												Day	Day	
	-28 to -2	-1	Hours												2		7
	Screening	Check in	Predose	0	0.25	0.5	1	1.5	2	3	4	6	8	12	24	ET	Follow up[f]
Administrative Procedures																	
Informed Consent	X																
Informed Consent {retained samples, pharmacogenomics}	X																
Inclusion/Exclusion Criteria/Demographics	X	X	X														
Medical History	X	X															
Concomitant Medication Review	X----------Continuous monitoring----------X																
Clinical Procedures/ Assessments																	
Full Physical Examination	X		X[a]												X	X	(X)
Height	X																
Weight	X		X[a]														
BMI	X																
CCI [redacted]																	
TAK-925 Administration				X													
CCI [redacted]																	
C-SSRS	X	X													X	X	
AE monitoring	X----------Continuous monitoring----------X																
CCI [redacted]																	

Footnotes are on the next page.

PK Evaluations																	
Plasma sample for TAK-925 and/or Metabolites assay[d]			X		X	X	X	X	X	X	X	X	X	X	X	X	
PGx Evaluations																	
Blood sample for DNA PGx					X												
Other																	
Standard Meals [e]		X									X		X				
Confinement		X----------Continuous ----------X															

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; C-SSRS, Columbia Suicide Severity Rating Scale; DBP, diastolic blood pressure; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; PR, pulse rate; PGx, pharmacogenomic(s); PK, pharmacokinetic(s); SBP, systolic blood pressure

a Day 1 predose physical examination and weight may be done within approximately 24 hours prior to study drug administration.

b CCI

c CCI

d Blood collection for plasma TAK-925 concentration and its metabolites will be collected:
Day 1: Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours postdose

e Standardized meals (approximately 30% fat content relative to total calories) will be administered during confinement, except on Day 1 when oral dosing in the morning will be under fasting conditions. Day2 is optional.

f Follow up phone call: If any AEs were reported by a subject at phone call, investigations shown in parenthesis (X) but not limited if necessary may be executed based on the investigator's discretion at the earliest convenience.

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 is greatly needed.

4.1.1 Orexin

Orexin is a neuropeptide and the orexinergic system is a major wake-promoting system of the brain. Two orexinergic neuropeptides, OX-A and OX-B, have been identified to date. The orexins exert effects via 2 types of receptors, the orexin type-1 receptor (OX1R) and the orexin type-2 receptor (OX2R). OX-A has a high affinity to OX1R and OX2R, and OX-B has a high affinity to

OX2R. These two orexin receptors make distinct contributions to the regulation of arousal. OX2R in the tuberomammillary nucleus (TMN) are essential for the maintenance of wakefulness, whereas both receptor types are required for the inhibition of rapid eye movement (REM) sleep [9].

The pathological loss of orexinergic neurons is associated with the development of narcolepsy type 1 (NT1) [10]. Narcolepsy with cataplexy, or NT1, has been defined by International Classification of Sleep Disorders, third edition (ICSD-3) criteria as having low levels of orexin in cerebrospinal fluid (CSF) (<110 pg/mL; <30% of normal levels), coming from the nearly complete loss of orexin producing neurons [1]. The pathophysiology of NT1 has a presumed, though unproven, autoimmune basis in individuals with a specific genetic predisposition, the most common of which is the human leukocyte antigen (HLA) DQB1*06:02 [11][12], which is notably estimated to be around 5-fold more prevalent in Japanese subjects. The etiology of NT2 is not known, but orexin levels in this condition are within 30 to 100 % of normal levels.

4.1.2 TAK-925

TAK-925 is a first-in-class OX2R-selective agonist. TAK-925 has a half-maximal effective concentration (EC50) of 5.5 nM in OX2R–CHO (Chinese hamster ovary) cells, versus >30 uM in OX1R–CHO cells, indicating over 5,000-fold selectivity for OX2R. Increase of wakefulness time and rescue of cataplexy which is the other core symptom of narcolepsy mice model were observed by TAK-925. TAK-925 showed sustained effects on wakefulness and cataplexy in orexin deficient narcolepsy mice model over 14 days of dosing. In addition, the arousal effect of TAK-925 after single dosing was confirmed in studies done during the normal sleep phase in three different species of wild type animals without orexin deficiency, including mice, cynomolgus monkeys and marmosets. These preclinical studies suggest that TAK-925 should show arousal effects in hypersomnolent states, whether or not there are due to orexin deficiency.

CCI

[redacted]

CCI

The first-in-human (FIH) phase 1 study (TAK-925-1001), is currently being conducted in Japan. This study is designed to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single, ascending doses of TAK-925 when administered via a 9-hour IV infusion to healthy adult and elderly adult subjects (aged ≥65 years old) and patients with NT1. Based on preliminary blinded safety data, single doses ranging from 7 to 240 mg in healthy subjects (approximately 8 subjects per cohort), and single doses of 11.2 and 44.8 mg tested in NT1 patients (4 subjects per cohort), have been safe and well tolerated with no severe or serious adverse events. All adverse events except influenza (considered as moderate) were mild in intensity. All cardiovascular related adverse events (blood pressure increased, pulse rate increased) were considered mild by the investigator. At dose levels less than 240 mg, the BP and PR effects were not clearly present for any one individual. Some BP and/or PR increase adverse events related to orthostatic position were also reported at the dose level of 134.4 mg or higher.

Following a single IV infusion, mean plasma systemic exposure of TAK-925 (C_{max}, observed plasma concentration at the end of infusion [C_{eoi}], and area under the plasma concentration-time curve from time 0 to infinity [AUC_{∞}]) increased approximately dose proportionally across dosing cohorts. On average, time to reach plateau was approximately 3 hours and the plasma terminal elimination $t_{1/2}$ ranged approximately from 3.8 to 5 hours across all doses. Further details can be found in the IB. TAK-925 exposure was increased by <30% in elderly subjects possibly due to decreased hepatic clearance.

In parallel with the FIH study described above, a proof of mechanism (POM) study in sleep-deprived healthy subjects is also ongoing in the US. This is a 4-period crossover study evaluating the PD effect on wakefulness, including maintenance of wakefulness test (MWT) sleep latency, of 2 single doses of TAK-925, 44 mg and 112 mg, each delivered as a 9-hour IV infusion, vs. modafinil 300 mg as an active comparator, and placebo. Results from this study will inform potential therapeutic use of TAK-925 in other patient populations with sleep disorders not associated with orexin deficiency, including patients with narcolepsy type 2 (NT2). Hence in this proposed multiple rising dose (MRD) study, both orexin deficient (NT1 patients) and normal orexin conditions (NT2 patients) will be evaluated.

4.2 Rationale for the Proposed Study

The primary objective of the current study is to evaluate the safety, tolerability, PK, efficacy and other PD of TAK-925 after repeated administration to CCI [redacted] The available nonclinical pharmacology, PK, and toxicology data and the preliminary clinical data from the FIH trial (TAK-925-1001) and a POM trial (TAK-925-1002) support the current trial design. The safety, tolerability, PK, efficacy and PD data obtained from the proposed MRD study will inform the design of and dosing regimen selection for subsequent studies with TAK-925.

CCI [redacted]

4.3 Benefit/Risk Profile

TAK-925 is a first-in-class OX2R-selective agonist. Preclinical pharmacology studies demonstrated that TAK-925 had arousal effects in hypersomnolent states both in animals with orexin deficiency (mice) and animals without orexin deficiency (mice, cynomolgus monkeys and marmosets). To explore potential effects in human, the ongoing TAK-925-1001 (first-in-human, FIH) and TAK-925-1002 (POM) studies include, in addition to healthy subjects, narcolepsy patients with orexin deficiency (NT1) and sleep-deprived healthy subjects. In this proposed MRD study, NT1 patients (orexin deficient) and NT2 patients (normal to somewhat reduced orexin levels) will both be evaluated. The results may provide early clues on whether TAK-925 has sustained effects in both NT1 and NT2 patients.

Safety information is limited to the data from nonclinical studies and blinded single rising dose (SRD) (TAK-925-1001) clinical studies available in healthy subjects and small number of NT1

patients (data will be unblinded at the time of conduct of this study). CCI [redacted]

CCI [redacted] In current clinical studies, TAK-925 is infused at low rate over 9 hours. At dose levels up to 240 mg, the C_{max} was lower than that of monkey's in which a CCI [redacted] was observed. No CCI [redacted] have occurred to date in the TAK-925-1001 and TAK-925 -1002 studies.

CCI [redacted]

CCI [redacted], would be expected to result in rapid resolution of increased blood pressure.

Clinical data from the ongoing SRD studies demonstrate TAK-925 is safe and well tolerated at dose levels up to 240 mg (preliminary blinded data). Review of available nonclinical and clinical drug safety data, when viewed in context of the potential benefit for patients with narcolepsy, supports a favorable benefit/risk ratio for TAK-925.

To date, the observed safety data for TAK-925, including mild and manageable adverse events, are acceptable considering the potential clinical benefit of TAK-925, and clinical study of TAK-925 should continue.

In the protocol amendment 2 (which primarily adds Part A' for oral dosing), CCI [redacted]

CCI [redacted] No toxicity that modifies the clinical benefit/risk profiles of TAK-925 was found.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed based on the following hypothesis:

5.1.1 Primary Hypothesis

<Part A and C>

One or more safe and well-tolerated multiple IV infusion TAK-925 dose levels will achieve a C_{eoi} (plasma concentration at the end of infusion) greater than or equal to the estimated concentration threshold required for efficacy in hypersomnia patients with normal CSF orexin level.

<Part B>

One or more safe and well-tolerated multiple IV infusion TAK-925 dose levels will achieve a C_{eoi} (plasma concentration at the end of infusion) greater than or equal to the estimated concentration threshold required for efficacy in hypersomnia patients with low CSF orexin level.

5.1.2 Secondary Hypothesis

At least 1 dose of TAK-925 shows a clinically meaningful difference (expected to be at least 3 minutes) from placebo for promoting wakefulness as measured by sleep latency using the MWT, after multiple dosing.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

<All Parts>

To investigate the safety and tolerability of TAK-925 when administered to healthy subjects and NT1 and NT2 patients.

5.2.2 Trial Secondary Objectives

<All parts>

To investigate the pharmacokinetics of TAK-925 when administered to healthy volunteers or narcolepsy patients

<Part B and C>

To investigate the PD of TAK-925 after multiple doses, primarily with evaluation of sleep latency on MWT when TAK-925 is administered to NT1 and NT2 patients.

5.2.3 CCI

CCI

[redacted]

5.3 Endpoints

5.3.1 Primary Endpoint

<All Parts>

- Safety and tolerability: number of subjects with AEs

5.3.2 Secondary Endpoints

<Parts A, B and C>

- Pharmacokinetic parameters (C_{eoi}, AUC_{τ}, $R_{ac(AUC)}$) of TAK-925

<Part B and C>

- Change from baseline in Sleep latency in the MWT to Days 1 and 7

5.3.3 CCI

CCI [redacted]

5.3.4 CCI

CCI [redacted]

CCI

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This study will consist of 3 parts. Part A is a randomized, double-blind, placebo-controlled, MRD study to assess safety, tolerability, and PK of TAK-925 administered via intravenous (IV) infusion in healthy subjects. Part B is a randomized, double-blind, placebo-controlled MRD study to assess the safety, tolerability, PK and PD of TAK-925 administered via IV infusion in patients with NT1. Part C is a randomized, double-blind, placebo-controlled, parallel group multiple repeat dose study to assess the safety, tolerability, PK and PD of one or more dose levels of TAK-925 vs. placebo in patients with NT2. Part A' is an open-label single oral dose study to assess PK, safety and tolerability of TAK-925 administered orally in healthy subjects. Parts A - A' may be conducted in parallel, rather than sequentially, depending on the doses administered and emerging safety/tolerability data.

In general, considering the completion times of the prior studies, TAK-925-1001 and TAK-925-1002, Part A, Part B and Part A' are expected to begin in parallel. Part A will test safety and tolerability in healthy volunteers (HV) starting from the dose level associated with that was found to be safe and tolerable based on the preliminary blinded safety adverse event (AE) profiles in TAK-925-1001 study. Part B will test safety, tolerability and PD in NT1 patients, who will be administered a lower dose than subjects in Part A. The initial dose in Part B was found to be safe and tolerable based on the preliminary blinded safety AE profiles in NT1 patients in the TAK-925-1001 study. The initial dose in Part B is more than 10 times lower than the highest dose level tested in TAK-925-1001 HV cohorts. Results from the TAK-925-1001 study will also be available at the time of initiation of Part A and Part B. Part A' will assess the safety, tolerability and CCI TAK-925 CCI [redacted] to healthy volunteers at a dose level that was found to be safe and tolerable after IV administration in TAK-925-1001 study and is anticipated to result in lower exposure of TAK-925 after oral administration, CCI [redacted] For Part C, the NT2 patient doses are expected to be similar to that in Part A, although recruitment of these cohorts will be slower. Initiation of Part A and Part C may also occur at the same time if the similar doses are studied. The initiation of cohorts in parallel with each other is contingent on Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, and if not approved, the cohorts will enroll as required, which may be sequentially or overlapping with each other. The NT1 and NT2 patients recruited are expected to be generally healthy other than having narcolepsy.

Part A – Multiple Rising Dose in Healthy Adults

Part A will have 2 dose cohorts as well as additional 4 optional cohorts. Each cohort of healthy adults will consist of 8 healthy subjects, randomized 6:2 active to placebo to TAK-925 vs. placebo (Table 6.a) in double-blinded fashion. The starting dose is selected based on the available preliminary safety, PK and PD data from the ongoing TAK-925-1001 study. Subsequent doses will be guided by safety, PK and PD data from previous cohorts as well as the TAK-925-1002 study (which is ongoing at the time of this protocol writing). TAK-925 or placebo will be administered as an IV infusion over 9 hours once daily for 7 days. Following review of emerging

safety and PK data (when available) in Cohort A1, the dose in Cohort A2 will be determined. Healthy adults may be recruited for up to 3 additional cohorts (A3 to A5) with 8 subjects each (randomized 6:2 active to placebo). The dose may be higher, lower or the same as that of prior cohort dose levels. Shifting the start time of infusion while keeping the dose the same as that previously studied may be considered in these optional cohorts [redacted]. The maximum dose and infusion rate in Part A shall not exceed the maximum dose or maximum infusion rate studied in healthy subjects in TAK-925-1001 study. The dose levels in subsequent cohorts will be optimized based on the recommendation of sponsor's unblinded team. The unblinded team will review available unblinded data including [redacted]

The safety and tolerability of the same or a lower dose than that of previous healthy adults cohorts may be studied in an optional cohort of healthy elderly subjects (N=8 subjects aged 65-80 years old, randomized 6:2 to TAK-925 vs. placebo) in Cohort A6. The healthy elderly optional cohort will be included as there are expected to be a few older patients in the Part B or Part C. It is expected that the healthy elderly cohort will provide data that supports the evaluation of TAK-925 in [redacted]

Part B – Multiple Rising Dose in Narcolepsy Type 1 (NT1) Patients

Part B will be conducted in NT1 patients. Two cohorts are planned, with optional cohorts allowed. For Cohorts B1 and B2, each cohort will consist of 6 subjects, randomized 4:2 to TAK-925 vs. placebo (Table 6.a) in double blinded fashion. TAK-925 or placebo will be administered as an IV infusion over 9 hours once daily for 7 days. Exploratory PD assessments will include evaluation of potential efficacy with [redacted]

The starting dose level in Part B will be selected based on preliminary data from the ongoing TAK-925-1001 study utilizing data regarding safety and tolerability, PK and results on the KSS and MWT in the NT1 cohorts, as well as the safety, tolerability and PK results in the healthy adult cohorts in TAK-925-1001 and Part A of this study (if available). The doses in the subsequent cohorts will be determined based on safety, tolerability, PD and available PK data from previous cohorts and/or from the prior studies with TAK-925. The dose level chosen in each of the subsequent cohorts will be determined by the sponsor's unblinded team composed of personnel who do not have subject contact or involvement with execution of the protocol at the site. The unblinded team will review unblinded safety, tolerability, and available PK and PD results from previous cohorts. The dose in the subsequent cohorts may be higher, the same as or lower than that used in the previous cohort(s).

Two additional cohorts (B3 and B4) may be evaluated, with 4-6 subjects in each. With the intention of sequential panel design, NT1 patients in Cohort B1 or B2 may participate in Cohort B3 or B4 if feasible operationally. Patients in cohort B1 and B2 may participate in B3 or B4 after a sufficient washout period if and allowed by regulatory authorities and IRB/IEC. The subject who directly move on to cohort B3 or B4 could skip the Day 8 some assessments and follow up visit and move into Day-2 in B3 or B4. Cohort B3 or B4 will essentially consist of newly enrolled NT1 patients, but patients from B1/B2 who weigh over 50 kg could be also enrolled. There should be

sufficient intervals between the last dose in Cohort B1 or B2 and the first dose in Cohort B3 or B4 in order to make dose and dosing duration decisions for Cohorts B3 and B4. If there are fewer than 4 Cohort B1 or B2 subjects enrolled to Cohort B3 or B4, new patients with NT1 will be recruited. In Cohorts B3 and B4, TAK-925 will be administered in a blinded randomized manner (3:1, 4:1 or 5:1). The primary purpose of Cohort B3 is to evaluate the safety and tolerability and PD of longer infusion time, as well as to CCI [redacted] Otherwise, the design and procedures for B3 will be the same as the design of B1. The primary purpose of Cohort B4 is to assess the within-subject exposure-response relationship for PD/efficacy and safety of TAK-925 in NT1 patients. Patients in this cohort will receive different, increasing doses of TAK-925 daily over the 7 day period, the sequence of doses will be identical across patients. All subjects will receive the same dosing schedule. One subject within B3 and B4, respectively, will be randomized to placebo.

Part C – Multiple Doses in Narcolepsy Type 2 (NT2) patients

Narcolepsy type 2 patients will be evaluated in Cohorts C1 and C2. This part will start once TAK-925-1002 study data is available and once safety/tolerability information for the dose level to be tested in Part C is available from Part A. Conduct of the C2 cohort is optional. C1 and C2 cohorts will recruit 6 subjects each, randomized 4:2 to TAK-925 vs. placebo in double-blinded fashion, with study drug administered as a 9-hour intravenous infusion for 7 days (Table 6.a). The doses selected for Part C depend on the results from the TAK-925-1002 study, and data from other cohorts in this study may also be used. The same schedule of study assessments as in Part B will be executed CCI [redacted]

Part A' – Single Oral Doses in Healthy Adults

Part A' will investigate the pharmacokinetics of TAK-925 after oral administration in healthy subjects. Cohort A'1 will consist of 6 healthy subjects who will be administered a single dose of TAK-925 as an oral solution in an open-label fashion (Table 6.a). An oral dose of 112 mg is selected based on the safety and tolerability profiles in TAK-925-1001 study and available nonclinical data as a potential starting dose. CCI [redacted] (see Section 6.3.3). An optional Cohort A'2 is allowed based on the emerging information.

The study parts and planned dosing cohorts are outlined in Table 6.a.

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

Part	Cohort/Panel	Daily dose level (mg)	Dosing regimen	Randomization
Part A (Healthy adults)#	A1	44	IV infusion over 9 hours up to 7 days. Start time of infusion could be changed in optional cohorts A3 to A5.	8 subjects randomized 6:2 to TAK-925 vs. placebo in each cohort, double-blind
	A2	112 (TBD)		
	A3*	TBD		
	A4*	TBD		
	A5*	TBD		
	A6 (elderly)*	TBD		
Part B (NT1 patients)#	B1	11	IV infusion over 9 hours up to 7 days	6 subjects randomized 4: 2 to TAK-925 vs. placebo in each cohort, double blind
	B2	44 (TBD)		
	B3*	TBD	IV infusion with longer (TBD) hours up to 7 days	4-6 subjects randomized (3:1, 4:1 or 5:1 to TAK-925 vs. placebo in each cohort, double blind
	B4*	TBD	IV infusion over 9 hours up to 7 days, different, increasing dose from Day 1 to Day 7	
Part C (NT2 patients)#	C1	44 (TBD)	IV infusion over 9 hours up to 7 days	6 subjects randomized 4: 2 to TAK-925 vs. placebo in each cohort, double blind
	C2*	TBD		
Part A' (Healthy adults)	A'1	112	Single oral administration	6 subjects per cohort (TAK-925 administration, open)
	A'2*	TBD		

Doses in subsequent cohorts in all parts will be determined based on the emerging safety/tolerability and PK (when available) and PD information and available safety/tolerability, and PK/PD data from previous cohorts as well as the ongoing TAK-925-1001 and TAK-925-1002 studies. Planned number of subjects in each cohort is shown.
All doses given by IV infusion over 9 hours daily for 7 days except B3
* Optional cohorts

Study population

Healthy adults, healthy elderly volunteers and patients with NT1 and NT2.

Planned Number of Subjects:

(1) Part A Healthy adults

- Cohort A1: 8 subjects
- Cohort A2: 8 subjects
- Cohort A3 (optional): 8 subjects
- Cohort A4 (optional): 8 subjects
- Cohort A5 (optional): 8 subjects

- Cohort A6 (optional healthy elderly): 8 subjects

(2) Part B NT1 patients

- Cohort B1: 6 subjects
- Cohort B2: 6 subjects
- Cohort B3 (optional): 4-6 subjects from B1 or B2, or newly enrolled subjects
- Cohort B4 (optional): 4-6 subjects from B1 or B2 or newly enrolled subjects

(3) Part C NT2 patients

- Cohort C1: 6 subjects
- Cohort C2 (optional): 6 subjects

(4) Part A' Healthy adults

- Cohort A'1: 6 subjects
- Cohort A'2 (optional): 6 subjects

Numbers for Part B and C show target number of subjects.

Key Study Procedure Overview

<Part A>

After the screening visit, eligible participants will check-in on Day-2 to wear a [CCI redacted] and to ensure timely start of [CCI redacted] on Day -1, [CCI redacted] will be time matched to Day 1. On Day 1, eligible participants will be randomized 6: 2 to TAK-925 or placebo in double-blinded fashion, respectively. Study drug will be administered as a 9-hour IV infusion each day during Day 1 to Day 7. The subjects will be discharged on Day 8. Intensive PK sampling will be performed on Day 1 and Day 7. [CCI redacted] will also be collected on Day 1 and Day 7. [CCI redacted] will be collected throughout the inpatient stay as well as [CCI redacted] as an option on certain days if the data collected from cohorts suggests the need for this in addition to or replacing [CCI redacted]. A schedule of the events in this part is shown in Section 3.0.

<Part B and C>

After screening, eligible patients must discontinue their medication used for treatment of narcolepsy, including medications used for excessive daytime sleepiness and cataplexy. Medications must be discontinued for a minimum of 7 days or at least 5 half-lives for each medication, whichever is longer, before the first day of dosing (Day 1). For subjects for whom there are concerns over potential injury due to severe cataplexy, confinement may occur earlier than Day -2, based on principal investigator (PI) judgment. For Cohorts B1, B2, B3, B4, C1, and C2, participants will undergo [CCI redacted] on Day -2 and baseline of four MWT sessions will be conducted on Day -1 at approximately 1000, 1200, 1400 and 1600. IV dosing of study drug will start at approximately 0800. MWT will be conducted on Day 1 at approximately 1000, 1200, 1400

and 1600. Subjects will be allowed to take naps during the days without MWT assessment. CCI [redacted] On Day 7, subjects will have MWT performed at the same times as on Day -1. CCI [redacted] The subjects will be discharged on Day 8. Optional MWTs may be performed on Day 4 in all of these cohorts with the exception of B4, where it will be scheduled.

For Cohorts B3 and B4, patients will check-in on Day-2 and CCI [redacted]. Study overview and key PD testing are illustrated in Figure 6.b and Figure 6.d, respectively. In Cohort B4, patients will receive increasing doses over the 7 day period, the dose levels tested within each individual will be at least 4, but could be as many as 7. However, the dosing sequence will be identical across all patients and the exact dose levels will be determined when results from TAK-925-1001 as well as cohorts prior to B4 in TAK-925-1002 become available.

<Part A'>

After the screening visit, eligible participants will check-in on Day -1. On Day 1 study drug will be administered orally to eligible participants. The subjects will be discharged on Day 2. CCI [redacted] sampling will be performed on Day 1 up to 24 hours postdose. CCI [redacted] Telephone call follow-up will be done on Day 7 and for any reported AEs, the subject will return for in-person evaluation. A schedule of the events in this part is shown in Section 3.0.

Figure 6.a Overview of the Trial Schedule (Part A healthy volunteers)

Screening Period	Check-in and Baseline	Treatment Period		Follow up visit
		Dose/Sample Collection	Sample Collection	
Days -28 to -3	Day -2 to Day-1 CCI [redacted] monitoring* CCI [redacted] CCI [redacted]	Day 1 to Day 7 Study drug administration/study assessment CCI [redacted], continuous CCI [redacted] monitoring per SOA/CCI [redacted]	Day 8 Study assessment	Day 15 or 7 days after early termination
	← Confinement →			

Abbreviations: BP, blood pressure; PR, pulse rate; SOA: schedule of activity
*Time-matched to Day 1 BP and PR data collection will be conducted from morning of Day-1.

Figure 6.b Overview of the Trial Schedule (Part B NT1 patients and Part C NT2 patients)

Screening Period	Check-in and Baseline	Treatment Period		Follow up visit
		Dose/Sample Collection	Sample Collection	
Days -42 to -3	Day -2 to Day-1 CCI /baseline MWT/ CCI monitoring* CCI	Day 1 to Day 7 Study drug administration/study assessment	Day 8 Study assessment	Day 15 or 7 days after early termination
	← Confinement →			

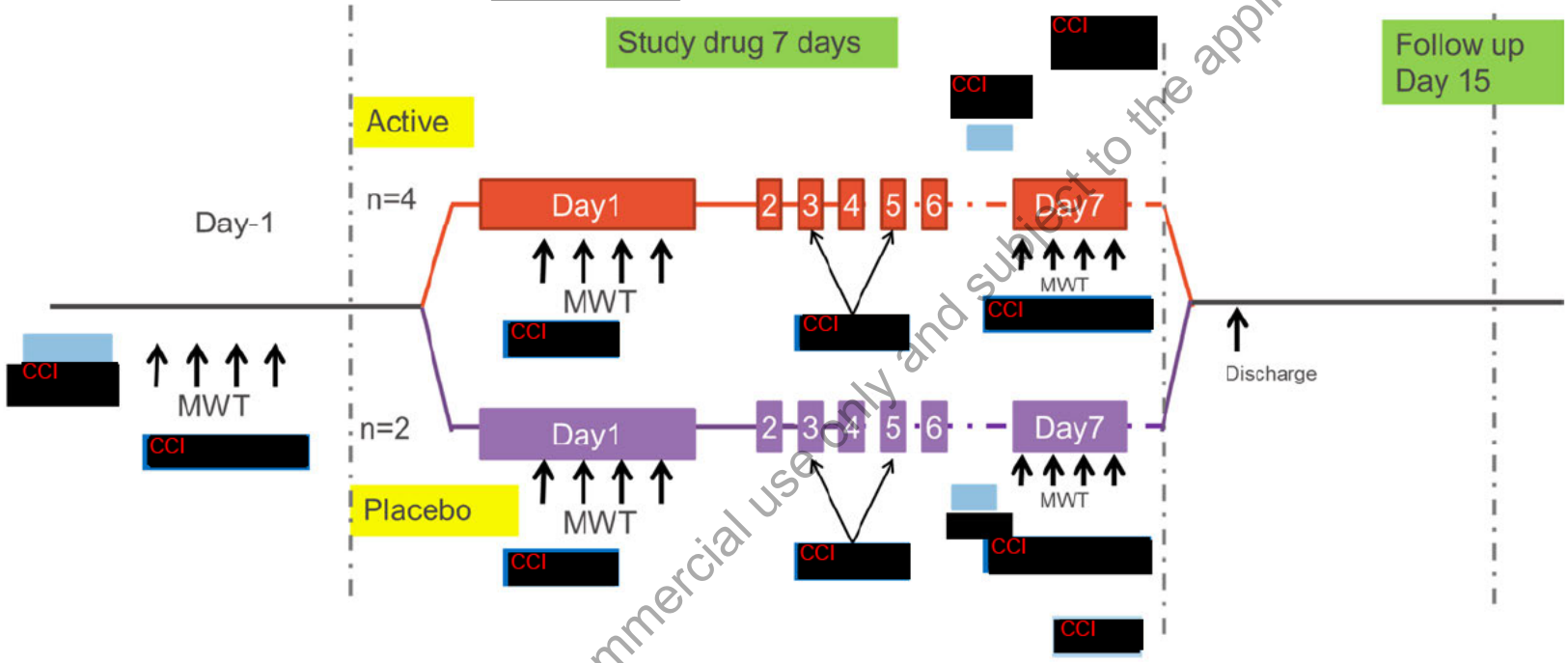
Abbreviations: BP, blood pressure; CCI ; PR, pulse rate; CCI

*Time-matched to Day 1 BP and PR data collection will be conducted from morning of Day-1. Baseline MWT and CCI will be conducted in B1, B2, B3, B4 and Part C. CCI

Figure 6.c Overview of the Trial Schedule (Part A' healthy volunteers)

Screening Period	Check-in and Baseline	Treatment Period		Follow up phone call
		Dose/Sample Collection	Sample Collection	
Days -28 to -2	Day-1	Day 1 Study drug administration/study assessment	Day 2 Study assessment	Day 7 AE assessment
	← Confinement →			

Figure 6.d Schedule of MWT and [CCI] for Part B and Part C



Abbreviations:EEG, electroencephalography; [CCI]; MWT, maintenance of wakefulness test;
[CCI] Cohort B4 will have an additional MWT on Day 4, and the dose administered will vary on different days.

6.2 Dose Escalation

Dose escalation in subsequent cohorts in all parts will be determined based on the available safety/tolerability and PK/PD data from previous cohorts as well as those from the ongoing TAK-925-1001 and TAK-925-1002 studies. Refer to the Section 6.3.3.1 for Starting Dose, the Section 6.3.3.2 for Maximum Dose and the Section 11.2 for Interim Data Review in an unblinded manner. The dose escalation process will be concluded with the agreement between the sponsor's blinded team and the investigator(s) based on the dose recommendation of the sponsor's unblinded team. Please also refer to the Section 6.4 for the situation when some cohorts might be run in sequential or in parallel without Interim Data Review by the sponsor.

CCI [redacted]

Dose escalation will not occur in event the following criteria are met in any dosage level cohort:

A serious adverse events occurs for which causative relationships can not be denied:

Two cases or more of severe adverse events for which causative relationships can not be denied during the treatment with a single cohort (from treatment initiation -to washout or at the time of completion of post-observation period)

Three or more cases of asymptomatic significantly increased blood pressure, as defined in Section 7.6.

In Part B and C, elderly patient aged over 65 may be allowed to be enrolled in a cohort where daily dose is more than 112 mg which the safety and tolerability was confirmed with elderly subjects in TAK-925-1001 study only after the safety and tolerability of TAK-925 in elderly subjects in Part A has been confirmed.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale for Study Population

(1) Part A and A' (healthy subjects)

The subjects included in Part A and Part A' will be healthy adults and elderly (only Part A) who do not have any significant diseases, cardiovascular or cerebrovascular health conditions. This will allow evaluation of the safety, tolerability and pharmacokinetic profiles of TAK-925 in a healthy population after repeated IV (Part A) or single oral (Part A') administration. Based on the observations in the single-rising dose study TAK-925-1001, CCI [redacted] The healthy normal subjects in Part A are expected to be recruited quickly, before the NT2 cohorts are completed.

Based on the observations that TAK-925 could also [CCI] determination of the oral bioavailability of TAK-925 after a single dose will determine if oral dosing is a feasible route of administration in humans.

(2) Part B (NT1 patients)

Based on the preliminary findings in the single-rising dose study TAK-925-1001, the subjects included in Part B will be patients with NT1 in order to further evaluate the efficacy and pharmacodynamic effects of TAK-925 after multiple daily dosing, in addition to the safety, tolerability and pharmacokinetics of TAK-925 administered via IV infusion. In non-clinical pharmacology studies, [CCI] This wake-promoting effect was also confirmed during chronic dosing up to 14 days in model mice. Safety/tolerability and efficacy dose range after single dose for NT1 patients in the TAK-925-1001 study will be available before starting this TAK-925-1003 multiple dosing study.

(3) Part C (NT2 patients)

In non-clinical pharmacology study, TAK-925 showed strong wakefulness promoting effects in wild type animals who have normal orexin levels. This observation, and preliminary safety/tolerability data from the ongoing TAK-925-1001 and TAK-925-1002 studies in healthy subjects further support evaluating TAK-925 PD in the NT2 patient population. The NT2 population has orexin levels that may range from 30% to 100% of normal values.

6.3.2 Rationale of Trial Design

(1) Part A

In order to evaluate the safety/tolerability after multiple dosing of TAK-925, part A is a double-blind study consisting of 2 cohorts of 8 subjects each, with each cohort randomized 6:2 (active vs. placebo), for each dose level tested. [CCI] on Day-1, the first day of administration and the last day (Day 1 and Day 7) will be performed to detect any changes and potential tolerance in [CCI] Standard BP measurements at specific times will be checked throughout the study. Unblinded data review will be also performed to make decision for dose levels in subsequent cohorts of Part A. In the TAK-925-1001 study, one subject with NT1 reported feeling high and more talkative. Central nerve system (CNS) effects will be monitored [CCI] Subjects will be in an inpatient facility throughout the conduct of the trial.

(2) Part B

In Part B, a double-blind, placebo-controlled study design will be used. Results on the MWT will be compared between placebo and TAK-925. This part will start from a relatively lower dose level [CCI] compared to the highest tested dose in TAK-925-1001 study (240 mg) as well as tested in NT1 patients in TAK-925-1001 (44 mg) without any safety concerns. Also, the study population in this part is

essentially a medically healthy population other than having narcolepsy. Therefore, available data from TAK-925-1001 study supports starting this cohort in parallel with Part A. While typically healthy normal cohorts are dosed as a group, the NT1 patients would be enrolled individually and not as a cohort. However, if regulatory and IRBs/IEC authorities disagree with conducting the cohorts in parallel, cohorts will be conducting in a sequential or overlapping manner.

The dose escalation process will be based on the safety and tolerability as well as PD effects of TAK-925 on sleep latency on the MWT. As such, it is critical that the data analysis will be done in a timely manner to ensure that this is available to the unblinded team. In order to preserve subject and site blinding and reduce any sponsor bias, a sponsor's unblinded team will be established that is composed of persons who do not have subject contact or involvement with execution of the protocol at the site. This team will review the safety, tolerability, available PK and results of the MWT and any other available data prior to determining the dosage in Cohort B2 and the necessity for any optional cohort, as well as the dose to be used in these cohorts. For cohorts B3, the daily dosing duration may be longer than in cohorts B1 or B2 and the doses may also be different. B3 and B4 will be blinded and the same assessments conducted in B1 and B2 will be done, plus some additional assessments for B4. CCI [redacted]

Patients in cohort B1 and B2 may participate in B3 or B4 after a sufficient washout period. The subject who directly move on to cohort B3 or B4 could skip Day 8 some assessment and follow up visit and move into Day-2 in B3 or B4. The Cohort B3 and B4 will be newly enrolled subjects or subjects from B1 or B2 over 50 kg of weight.

Parallel group design was considered appropriate for narcolepsy patient part. Although cross over design is frequently used in Phase 1b study in order to keep sample size small and to be able to observe drug and placebo responses in the same subject, a cross over design would require patients to be confined for over two weeks and this was not felt to be practical.

Typically, if G-protein coupled receptor (GPCR) desensitization by receptor agonist occurs, this happens within a short time frame of minutes (short reaction) or hours to days (longer reaction). Based on this, seven days dosing should be sufficient to test the hypothesis.

A sample size of 6 subjects (4 active vs. 2 placebo) for B1 and B2 Cohorts was considered to be sufficient based on the fact that 4 subjects in each NT1 cohort in TAK-925-1001 study gave sufficient information to decide the dose level in subsequent cohorts, whereas optional Cohorts B3 and B4 are designed to randomize 4-6 subjects (3:1, 4:1 or 5:1 to TAK-925 vs. placebo). Part B could be started once the appropriate dose level was determined based on TAK-925-1001 study results from the NT1 patient cohorts.

In cohort B4, a better understanding of within-subject exposure-response relationship for MWT and CCI [redacted] will be obtained, along with an understanding of the variability of such relationship across individuals. This will help guide optimal dose selection in future studies. The dose will vary over the 7 days. Doses will be arranged in an increasing order over this period to minimize carry-over effects due to residual drug exposure from prior doses.

(3) Part C

In Part C, a double-blind, placebo-controlled study design will be used. Results on the MWT will be compared between placebo and TAK-925. Whether an optional cohort C2 will be executed or not will be decided based on the safety and tolerability as well as PD effects of TAK-925 on sleep latency on the MWT from cohort C1. Unblinded data review will be conducted to make this decision and to determine dose level in cohort C2. Parallel group design was considered appropriate for narcolepsy patient part with the same reason described above for Part B. Number of subjects as 6 (4 active vs. 2 placebo) was again considered sufficient assuming the same effect size for NT2 with NT1 observed in TAK-925-1001 study. CCI [redacted] Part C may be started once an appropriate dose level is determined based on either of TAK-925-1002 study results from the sleep deprived healthy population and/or results in Part A. In Part C, cohort C2 was not considered to be a mandatory cohort and is optional.

(4) Part A'

Part A' is designed as an open-label single dose study to evaluate the safety, tolerability and CCI of TAK-925 after single oral administration in 6 healthy subjects. This is the first oral dosing in humans. Whether an optional cohort A'2 will be executed or not will be decided based on the emerging safety and CCI data from cohort A'1. CCI [redacted].

6.3.3 Rationale for Dose

6.3.3.1 Starting Dose for This Trial

(1) Part A (healthy subjects)

Single doses from 7 to 240 mg/day of TAK-925 were administered as an 9-hour intravenous (IV) infusion to healthy subjects in the TAK-925-1001 study in 5 cohorts (6 active and 2 placebo). Cohort 1 received 7, 28 and 112 mg single doses and Cohort 2 received 14, 56 and 134.4 mg single doses with a washout period of at least 7 days. Following data review in these 2 initial cohorts, 6 healthy elderly subjects (Cohort 3) received a single 112 mg TAK-925, and 2 supplemental cohorts in healthy adult subjects (Cohorts 4 and 5) received 180 and 240 mg single doses of TAK-925, respectively. It was considered that TAK-925 was generally safe and well-tolerated with no severe or serious adverse events (AEs) based on the blinded information in the dose range of ongoing TAK-925-1001 study. CCI [redacted] Preliminary PK findings showed approximate dose-proportional increases in plasma exposures of TAK-925 over the dose range studied. Mean TAK-925 plasma exposure in elderly subjects was slightly greater (<30%) than that in younger healthy subjects, as a result of the reduced drug clearance. At the end of infusion, TAK-925 concentrations declined rapidly and in a biphasic manner with a mean terminal disposition phase half-life of about 3.8 to 5

hours across all doses. Additionally, single doses of 44 and 112 mg/day of TAK-925 are being evaluated in sleep deprived healthy adults in the TAK-925-1002 study.

For Part A, 44 mg over a 9-hour IV infusion is considered to be safe as a starting dose in healthy subjects in order to support further characterization of the safety and tolerability profile of TAK-925 dosed daily for 7 days, specifically any potential tolerance effects in BP after repeat dose administration. Considering the short elimination $t_{1/2}$ of TAK-925, little to no drug accumulation is expected following once daily dosing. Based on the preliminary PK results, mean AUC_{∞} and C_{max} at 44.8 mg were 972 h*ng/mL and 98.3 ng/mL, respectively. In comparison to the exposures in CCI [redacted]

(2) Part B (NT1 patients)

To date, single doses of 11.2 and 44.8 mg/day of TAK-925 were administered as a 9-hour IV infusion to NT1 patients in the TAK-925-1001 study. A third cohort is currently ongoing where patients will receive a single 5 mg IV dose of TAK-925 over 9 hours. Both doses were safe and well-tolerated with no severe or serious adverse events. CCI [redacted] Preliminary PK findings showed approximate dose-proportional increases in plasma exposures of TAK-925 and similarity in the TAK-925 PK profile between NT1 patients and healthy subjects. At 11.2 mg dose level tested in NT1 patients, mean C_{eoi} was 22.1 ng/mL which was close to the estimated minimum effective exposure level from nonclinical studies (21.3 ng/mL).

Therefore, 11 mg is considered to be appropriate as a starting dose to examine safety, pharmacokinetics and pharmacodynamics profiles of TAK-925 dosed daily for 7 days, though 5 mg which will be tested in TAK-925-1001 study as the 3rd NT1 cohort might be selected as an alternative starting dose depending on the result of the 3rd cohort of TAK-925-1001 study.

For Cohort B4, subjects will receive an increasing dose of TAK-925 over Days 1 to 7, although the dose on any one day may be the same as a prior day. The set of dose levels as well as the sequence of dose levels will be identical across subjects. The dose levels selected will target different parts of the anticipated dose-response curve: two dose levels in the plateau region, one in the bottom part and the remaining on the ascending part of the curve. Existing data from TAK-925-1001 study suggests CCI [redacted] There is limited data to identify the lower end of the dose-response curve, an educated guess is that CCI [redacted] Selection of final set of dose levels will be made once data from TAK-925-1001 all NT1 cohorts and TAK-925-1003 B1 and B2 cohorts become available.

(3) Part C (NT2 patients)

The starting dose in this part will be determined once results from the TAK-925-1002 study is available. Since levels of CSF orexin in NT2 patient may be mildly decreased or at normal levels, it is considered that the effective dose level may be similar to the healthy population as compared to orexin deficient NT1 population. In light of this, preliminary PD results from study TAK-925-1002 will guide dose selection for Part C. In addition, CCI [redacted] Therefore, the

efficacious doses used in NT2 patients are expected to be higher than those used in NT1 patients, while the safety/tolerability profile of TAK-925 is expected to closely resemble that in healthy subjects as NT2 patients do not have orexin deficiency.

(4) Part A' (healthy subjects)

Activation of the OX2R by TAK-925 at doses ≤3 mg/kg significantly increased wakefulness in CCI [redacted] of narcolepsy. Results from these nonclinical pharmacological studies were obtained using the CCI [redacted] of administration, which was selected due to CCI [redacted].

In the FIH clinical study (TAK-925-1001), single doses up to 240 mg of TAK-925 given via a 9-hour IV infusion were safe and tolerable in healthy adult subjects. Dose-proportional increases in mean systemic exposure of TAK-925 (C_{max}, C_{eoi} and AUC_{∞}) were observed over the dose range studied. At the end of infusion, TAK-925 plasma concentrations declined in a biphasic manner with a mean $t_{1/2z}$ ranging from 3.4 to 5.1 hours across doses. Mean estimates of TAK-925 plasma clearance ranged from 42.7 to 59.6 L/h in healthy subjects. It is then possible from these human IV data to estimate the CCI [redacted]

1-

A single oral dose of 112 mg is selected as potential starting dose for Part A' based on the following considerations: a) the safety and tolerability data from the FIH study whereby single IV doses of TAK-925 were safe and well tolerated with no severe AEs or serious adverse events, and CCI [redacted] b) CCI [redacted] CCI [redacted] and c) CCI [redacted]

In addition, TAK-925 will be provided as a solution of TAK-925 CCI [redacted] According to the FDA Guidance "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics

in Adult Healthy Volunteers" [14], the calculated human CCI which is considered to be safe for oral administration.

6.3.3.2 Maximum Dose/Exposure for This Trial

For Parts A, B and C, the maximum dose cap in this study will be 240 mg/9h or dose levels which could be administered within equivalent infusion rate with 240 mg/9h when infusion time is longer.

CCI

i. Maximum dose/exposure based on NOAEL

Single doses up to 240 mg/day of TAK-925 were administered as a 9-hour IV infusion to healthy subjects in TAK-925-1001 study. TAK-925 was generally safe and well-tolerated with no severe AEs or serious adverse events. CCI

CCI

ii. Part A (healthy volunteers) and Part C (NT2 patients)

The doses to be evaluated in healthy volunteers (Part A) and NT2 patients (Part C) in this MRD study are guided by the safety/tolerability profile obtained in study TAK-925-1001 and PD results from the TAK-925-1002 study in which 2 doses of TAK-925 are currently studied in healthy subjects for effect on wakefulness during sleep deprivation. If these doses are ineffective in maintaining wakefulness under these conditions, doses greater than 112 mg/day and up to 240 mg/day may be studied in TAK-925-1003 which is in the range of exposure (C_{max}) tested in TAK-925-1001 single dose study.

iii. Part B (NT1 patients)

In part B, NT1 patients will be administered doses up to and including approximately 44 mg in cohort B1 and B2, which is the highest dose tested in the single-rising dose study TAK-925 and considered to be safe in NT1 patients. Considering the short elimination $t_{1/2}$ of TAK-925, little to no drug accumulation is expected following once daily dosing. If attenuation in PD effect is observed after chronic dosing, the higher dose levels evaluated in Part A that did not have significant safety concerns or dose levels which could be administered by equivalent infusion speed may be also administered in Part B.

iv. Part A' (healthy volunteers)

The dose levels will be adjusted as expected levels of exposure post oral dosing will be in the range of maximum exposure level obtained by simulation results described in Section 6.3.3.1 (4). Up to 336 mg per dose may be administered if the expected exposure remained to be in this range.

6.3.4 Rationale for Endpoints

6.3.4.1 Efficacy Endpoints

Not applicable.

6.3.4.2 Safety Endpoints

Since this is the first human multiple dosing study, the standard safety endpoints for early clinical will be included. CCI [redacted]

6.3.4.3 Pharmacokinetic Endpoints

In order to characterize the pharmacokinetics of TAK-925 and its metabolites CCI [redacted] after repeated (Parts A-C via IV infusion) and CCI [redacted], pharmacokinetic parameters will be estimated as data permit. In cohort B3 and B4, PK parameters of the patients who rolled over from cohort B1 or B2 may not be calculated due to limited PK sampling points availability. See Section 9.3.2 for more details.

6.3.4.4 Pharmacodynamic Endpoints

In order to evaluate efficacy of TAK-925 on symptoms of narcolepsy after multiple dosing, PD endpoints will be assessed in Parts B and C in this study. Major narcolepsy symptoms include daytime sleepiness, CCI [redacted] and the assessments will be included to evaluate above symptoms. Change from baseline in these PD/efficacy measures/parameters will be used to evaluate the drug effect. See Section 9.3.3 for more details.

6.3.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this study, the MWT and blood samplings for pharmacokinetic evaluation are the critical procedures.

- At any postdose time point, the MWT and the blood sampling for pharmacokinetic evaluation need to be performed as close to the exact nominal time point/scheduled time as possible.
- All other procedures should be performed as close as possible either before or after the scheduled times.

- CCI [redacted]
- The order of priority can be changed during the study with joint agreement of the investigator and the sponsor.
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.
- In Part B and C, if the MWT and the blood sampling for pharmacokinetic evaluation are scheduled at the same time, MWT should be prioritized and blood sampling for PK will be done within an acceptable time frame (Annex 3).
- Safety evaluation will be performed within the specified time frame as close as possible.
- As BP measurement may interfere the MWT, In Part B and C 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 [redacted] and MWT for further details.
- Blood sampling for PK evaluation should occur before the nominal time of standard meal, if scheduled together.
- If the times for meals and the study procedures are conflicted, meals should be taken basically after all of the study procedures are completed.

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

This is a phase 1 assessment of TAK-925 in humans, and the pharmacokinetic, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures, as outlined below, may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study subjects.

As such, the following alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose/exposure, may not exceed that currently outlined in Section 6.3.3:

- The dose of study drug administered may be repeated or decreased in any given period/cohort.
- Doses between cohorts/periods may be interchanged.
- Entire period(s) or cohort(s) may be omitted.
- A pharmacokinetic data review may be added.
- Instructions to take food or drink may be modified based on newly available data.

- The pharmacokinetic/pharmacodynamic sampling scheme may be modified during the study based on newly available pharmacokinetic or pharmacodynamic data (eg, to obtain data closer to the time of first occurrence of C_{max}). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.
- Up to an additional 50 mL of blood may be drawn for pharmacokinetic and/or pharmacodynamic analyses. This blood volume may include repeat samples or modified pharmacokinetic/pharmacodynamic time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire study.
- CCI [redacted]
- Additional laboratory tests may be added to blood samples previously drawn to obtain additional safety information.

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

In Part A, not all Cohorts may be run and the doses may be higher, lower or the same to that of prior cohort in those additional healthy adult cohorts. Healthy adult additional cohort and healthy elderly cohort may start with sponsors discretion whenever possible, considering the status of cohort B1, B2, C1 and C2. CCI [redacted] may be executed on selected days in this Part if any major effects of study drug was suggested by actigraphy.

In Part B, cohort B2 could be partly run consecutively with cohort B1 once the first three subjects in cohort B1 completed the study and safety review is done, if sponsor and the investigator should agree. Execution of cohort B3 and B4 may be decided based on the safety, PK and other available information in previous cohorts as well as other relevant information for the program. Cohorts B3 may enroll new NT1 patients if there are no sufficient patients from Cohorts B1 or B2 who weigh over 50 kg to start in this cohort. Cohort B4 will enroll new patients who were not in prior cohorts in Part B and patients who weigh over 50 kg and was enrolled in Cohorts B1 or B2 may be able to be included. Optional MWTs may be performed on Day 4 in all of these cohorts with the exception of B4, where it will be scheduled.

In Part C, an additional optional cohort including 6 narcolepsy patients may be recruited, if investigation of safety, tolerability PK and PD in these cohorts is required. Again, the doses may be higher, lower or the same to that of prior cohorts. Cohort C2 may be started once first three subjects have been evaluated with available safety/tolerability/PK/PD data.

In Part A', an additional optional cohort including 6 healthy subjects may be recruited, if further investigation of safety, tolerability and PK is deemed necessary. Again, the dose may be higher or the same to that of the prior cohort.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

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

6.5.2 Definition of End of the Trial

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

6.5.3 Definition of Trial Completion

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

6.5.4 Definition of Trial Discontinuation

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

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

Study discontinuation because of safety reasons:

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

6.5.5 Criteria for Premature Termination or Suspension of the Trial

6.5.5.1 Criteria for Premature Termination or Suspension of Trial Sites

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

6.5.5.2 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Sites

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

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

<u>All subjects</u>

1. The subject must understand the study procedures and agree to participate by providing written informed consent.
2. The subject must be willing and able to comply with all study procedures and restrictions.
3. The subject must be judged to be in good health by the investigator to participate in the study, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead electrocardiogram, and vital sign measurements performed at the Screening Visit and prior to the first dose of study drug or first invasive procedure.
4. For a male subject who is nonsterilized and sexually active with a female partner of childbearing potential, the subject must meet the following birth control requirements:
    - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from the first dose of study drug until 92 days after the last dose of study drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1 year post bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
    - Is a male subject who agrees to not donate sperm from the first dose of study drug until 92 days after the last dose of study drug.

<u>Healthy adults (Parts A and A') and elderly (Part A)</u>

5. The subject must be male or female.
6. The subject must have a body mass index (BMI) $\geq$18.5 to $\leq$30.0 kg/m^2 at the Screening Visit.
7. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months prior to the first dose of study drug or first invasive procedure.
8. The subject who is normotensive, with no history of hypertension or use of antihypertensive medication. BP <140 systolic and <90 diastolic. BP measures should be obtained after the patient has been resting a minimum of 10 minutes, and may be repeated 3 times in the event that the BP is slightly elevated above these parameters. The average BP may be used based on the investigator's or the subinvestigator's judgement.

9. A female subject must meet one of the following birth control requirements:

   Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or 6 months of spontaneous amenorrhea in females aged >45 years with serum follicle-stimulating hormone levels >40 mIU/mL). Appropriate documentation of follicle-stimulating hormone levels is required.

   Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

   Had a tubal ligation with appropriate documentation of surgical procedure.

   Has a congenital condition resulting in no uterus.

Healthy adults (Parts A and A')

10. The subject must be aged 20 to 55 years, inclusive, at the Screening Visit.
11. The subject must have a body weight ≥50 kg inclusive at the Screening Visit.

Healthy elderly (Part A)

12. The subject must be aged 65 to 80 years, inclusive, at the time of informed consent.
13. The subject must have a body weight ≥40 kg inclusive at Screening.

NT1 and NT2 patients (Parts B and C)

14. The patient must be aged 18 to 80 years inclusive, at the time of informed consent.
15. The patient weighs at least 40 kg inclusive at the Screening Visit (≥50 kg is required for Cohort B4).
16. The patient must have a diagnosis of narcolepsy of type 1 (Part B) or type 2 (Part C), as defined by ICSD-3.
17. The patient's ESS is ≥10 at baseline.
18. The patient must have blood pressure <140 systolic and <90 diastolic. The patient may have a history of hypertension and be on antihypertensive medication treatment as long as the BP meets these criteria. BP measures should be obtained after the patient has been resting a minimum of 10 minutes, and may be repeated 3 times in the event that the BP is slightly elevated above these parameters. The average BP may be used based on the investigator's or the subinvestigator's judgement.
19. The patient must be willing to discontinue all medications used for the treatment of NT1 or NT2 during the screening period (see Section 7.3).

20. A female subject of childbearing potential who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception from signing of informed consent throughout the duration of the study.

* Definitions and procedures for adequate contraception and pregnancy avoidance, and reporting responsibilities are defined in Appendix D of full protocol.

NT1 patients only (Part B)

21. HLA narcolepsy test positivity (HLA-DQB1*06:02)
22. Have ≥3 episodes of cataplexy/week reported during the Screening Period.

NT1 and NT2 patients (Parts B and C)

23. Average (of 4 sessions) Baseline MWT sleep latency is less than or equal to 20 minutes and no single session has a sleep latency of greater than 30 minutes as determined by the site EEG readers and investigators.

7.2 Exclusion Criteria

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

All subjects

1. The subject has participated in another investigational study within 4 weeks (or based on local regulations) prior to the Screening Visit. The 4-week window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the Screening Visit of the current study. This criterion is not applicable to patients who will participate in B3 or B4 after they completed B1 or B2.
2. The subject is an employee of the sponsor or study site or immediate family member (eg, spouse, parent, child, sibling) of the sponsor or study site.
3. The subject has a history of cancer (malignancy).
4. The subject has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-925 or related compounds.
6. The subject has a positive pregnancy test.
7. The subject is a lactating/nursing female.
8. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody/antigen, or serologic reactions for syphilis at the Screening Visit. Note: Subjects with positive hepatitis B virus or hepatitis C virus serology

may be enrolled if quantitative polymerase chain reaction for hepatitis B virus or hepatitis C virus ribonucleic acid is negative.

9. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the Screening Visit.
10. The subject is unable to refrain from or anticipates using excluded medications (see Section 7.3) beginning approximately 7 days prior to administration of the first dose of study drug, throughout the study including washout intervals between treatment periods, until the Follow-up Visit.
11. The subject consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
12. The subject has a moderate to severe substance use disorder.
13. The subject's renal creatinine clearance (CCR) ≤50 mL/min at the time of Screening and Baseline.
14. The subject has poor peripheral venous access.
15. The subject has undergone whole blood draw prior to the start of study drug administration as any of below:

    For both male and female subjects,

    - ≥200 mL within 4 weeks (28 days)

    For male subjects,

    - ≥400 mL within 12 weeks (84 days)
    - ≥800 mL in total within 52 weeks (364 days)

    For female subjects,

    - ≥400 mL within 16 weeks (112 days)
    - ≥400 mL in total within 52 weeks (364 days)
16. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of study drug administration.
17. The subject has a risk of suicide according to endorsement of item 4 or 5 with screening/baseline visit Columbia Suicide Severity Rating Scale (C-SSRS) or has made a suicide attempt in the previous 6 months.
18. The subject has past or current epilepsy, seizure, tremor or the disorders of related symptoms.
19. The subject has a lifetime history of major psychiatric disorder, such as bipolar disorder or schizophrenia. Subject who has history of major depressive disorder (MDD) may be include but a subject who has current active major depressive disorder or who has had active major depressive disorder in the past 6 months is excluded.

20. The subject has a clinically significant history of head injury and trauma.
21. The subject has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
22. The subject has known coronary artery disease, a history of myocardial infarction (MI), angina, cardiac rhythm abnormality, or heart failure.
23. The subject's screening ECG reveals a QT interval with Frederica correction method (QTcF) >450 milliseconds (men) or >470 milliseconds (women).
24. The subject has a resting PR outside of the range of 45 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes, at the Screening Visit or Day -1.
25. The subject has medical condition (in case of Part B and C, narcolepsy is exceptional.) that would preclude enrollment in the view of the investigators, such as medically significant unstable cardiovascular, pulmonary, hepatic, renal, or Gastro-intestinal (GI) disease.
26. The subject has abnormal laboratory test values that suggest a clinically significant underlying disease at the Screening Visit or baseline or any subject with transaminase (Alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) >1.5 (Part A and A') or >2.0 (Part B and C)×upper limit of normal (ULN) at the Screening Visit (or baseline in Part A and A').
27. Subjects experienced sleep wake cycle disturbance with external factors such as irregular work hours; routine night-shift work or travel with significant jet lag within 7 days before randomization.
28. The subject who, in the opinion of the investigator or sub-investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

Healthy adults (Parts A and A') and elderly (Part A)

29. The subject administered TAK-925 in the past clinical trial.
30. The subject has a positive alcohol or drug screen.
31. The subject has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to the following: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz] per day).
32. The subject is unwilling to discontinue smoking while confined on the inpatient unit
33. If female, the subject is of childbearing potential (premenopausal and not sterilized).
34. The subject has clinically relevant sleep related disorders (including sleep apnea syndrome and prior diagnosis of insomnia).

NT1 and NT2 patients (Part B and C)

35. The subject is unwilling to discontinue smoking no later than 40 minutes prior to the scheduled MWT and 1 hour before sleep for Day 1 to Day 7.

36. The subject is an excessive caffeine (>400 mg/day) user one week prior to study drug administration.
37. The subject used any product with stimulating or sedating properties or anticonvulsant agents within 7 days or 5 times the elimination half-lives prior to dosing, whichever is greater. Selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressants will be tapered off before the wash out period which is 7 days or 5 times the elimination half-lives prior to dosing. See Section 7.3.
38. The subject has medical disorder (including sleep apnea syndrome), other than narcolepsy, associated with excessive daytime sleepiness. The subject has clinically significant obstructive sleep apnea (OSA) or restless legs syndrome (RLS) which has significant impact on daytime sleepiness confirmed by past PSG data (such as Apnea Hypopnea Index>20, Periodic limb movements of sleep arousals index (PLMSAI)>15) or interviews at the Screening Visit. The patient who has no PSG data within past three years needs to have investigator's interview and appropriate questionnaires for disease screening (Berline questionnaires or pulse oximeter screening for OSA, Cambridge-Hopkins screening questionnaire or International Restless Legs Syndrome study group severity scale for RLS) at the Screening Visit. Significant OSA or RLS found at Day-2 CCI is also excluded.
39. The subject has any other medical condition that requires subject to take excluded medications, such as anxiety, depression or epilepsy, heart disease, significant hepatic, pulmonary or renal disease.

Healthy adults (Part A')

40. Subjects with current or recent (within 6 months) gastrointestinal disease that is expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn), or any history of surgical intervention (ie, gastrectomy or cholecystectomy)

7.3 Excluded/Allowed Concomitant Medications, Supplements, Dietary Products

Use of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

<Part B and C>

Prohibited drugs (a)	**From 7 days or 5-half-lives period (longer one of either periods) before administration to completion of all tests planned on Day 8**
(1) Psychostimulant	Methylphenidate hydrochloride, modafinil, pemoline, methanphetamine hydrochloride. Discontinue at least 5 half-lives before baseline visit.
(2) Antipsychotic drugs	As for depot preparation of antipsychotic drugs, they are appropriately setup with consideration of disappearance period.
(3) Antianxiety drugs (Tranquilizers)	Including benzodiazepine
(4) Anti-depressants	The drugs that are used in principle for the purpose of cataplexy inhibition such as tricyclic anti-depressants, SSRI and SNRI are gradually reduced

	carefully and a washout period which is 5-folds or more of the disappearance half-life period of each drug is set up before baseline visit.
(5) Mood stabilizers	-
(6) Anticonvulsants	-
(7) Sleeping pills	The Chinese medicine (*Yokukansan, Yokukansankachinpihange*) used for insomnia is included.
(8) Anti-Parkinson's disease drugs	-
(9) Adrenocorticosteroid	Only systemic administration.
(10) Interferon, interleukin-formulation	-

Footnotes are on last table page.

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

Prohibited drugs (a)	From 7 days or 5-half-lives period (longer one of either periods) before administration to completion of all tests planned on Day 8
(11) Muscle-relaxant drug	-
(12) Antihistamines	Only oral administration. A combination drug is also included.
(13) β-blockers which has a central-nerves action	-
(14) Antitussive which has a central-nerves action	-
(15) Antiemetic which has a central-nerves action	-
(16) Narcotic analgesic and non-narcotic analgesics (Opioid system and Pregabalin only)	-
(17) St. John's Wort, Health foods containing melatonin	-
(18) Moderate to strong CYP3A inhibitors or inducers 1) Strong CYP3A4 inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir, ritonavir, elevitegravir, indinavir, saquinavir, idelalisib, itraconazole, ketoconazole, Lopinavir, netazodone, Nelfinavir, Paritaprevir, Ombitasvir, Dasabuvir, posaconazole, Telaprevir, tipranavir, troleandomycin, voriconazole 2) Moderate CYP3A4 inhibitors: Amprenavir, Aprepitant, Atazanavir, casopitant, cimetidine, ciprofloxacin, clotrimazole, Crizatinib, cyclosporin, diltiazem, dronadarone, erythromycin, fluconazole, Fosamprenavir, fluvozamin, Miconazole, imatinib, istradefylline, tofisopam, verapamil 3) Strong CYP3A4 inducers: Carbamazepine, Enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin 4) Moderate CYP3A4 inducers: Bosentan, Efavirenz, etravirine, Modafinil	-

(a) If medications are required to treat an AE, certain medications, including supplements, may be allowed after discussion and agreement between the Sponsor and principal investigator, unless the investigator or designee considers immediate administration is necessitated.

7.3.1 Concomitant Medications

In Part A and A', the use of concomitant medications (Prescribed drugs, OTC drugs, Supplements [St. John's wort, ginseng, kava kava, Ginkao biloba and melatonin], Kampo medicines, Vaccination/vaccine) is not permitted throughout all study participation period. Subjects must be instructed not to take any medications without first consulting with the investigator. Any concomitant medication use must first be discussed with the sponsor, unless the investigator or designee considers immediate administration is necessitated. The occasional use of acetaminophen (approximately <1 g/day) is allowed.

In Part B or C, it is allowed for subjects to take any medication which is not banned in Section 7.3. The investigator or the subinvestigator will review the concomitant medication use at screening,

and determine the time of discontinuation for certain drugs that should not be used anymore, and also remember the drugs whose doses need to be reduced. Subjects will also be instructed not to take any medications including OTC drugs without prior consultation with the investigator or subinvestigator. The use of sleepiness-related supplements may be allowed with the discussion of the investigators or subinvestigators.

In Part A, B, C and A', the use of any investigational drug other than TAK-925 is not permitted throughout all study participation period.

7.3.2 Fruit Juice

In Part A, subjects will refrain from consuming grapefruit juice, grapefruits, and products containing grapefruit beginning approximately 1 week prior to administration of the first dose of study drug, throughout the study, and until the Follow-up Visit.

In Part B and C, juices restrictions are not applicable.

In Part A', subjects will refrain from any foods or beverages containing grapefruit or grapefruit juice, Seville-type (sour) oranges and marmalade, apple juice beginning approximately 1 week prior to administration of the dose of study drug, throughout the study, and until the Follow-up Phone call.

7.3.3 Alcohol

In Part A and A', subjects will refrain from consuming alcohol 7 days prior to the Screening Visit and Follow-up Visit (Part A)/discharge (Part A') and from 7 days prior to dosing and until the last PK blood sample has been collected. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 alcoholic beverage is approximately equivalent to: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz]) per day.

In Part B and C, subjects will follow the PSG/MWT manual.

7.3.4 Caffeine

In Part A and A', subjects will refrain from consuming caffeinated beverages 24 hours prior to the Screening Visit and Follow-up Visit and from 24 hours prior to dosing and until the last PK blood sample has been collected. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit=120 mg of caffeine).

In Part B and C, on the day of MWT, caffeine will not be allowed, and subjects will follow the PSG/MWT manual. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit=120 mg of caffeine).

7.3.5 Smoking

In Part A and A', smoking and nicotine containing foods are not permitted during the study.

In Part B and C, subjects will follow the [redacted]/MWT manual.

7.4 Diet, Fluid, and Activity

7.4.1 Diet and Fluids

A standard breakfast, lunch, dinner, and snacks will be provided at the times specified in the schedule of study procedures. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

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

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

Meals and drinks (except water) prior to the laboratory tests must be taken 8 hours prior to the tests. See below for fasting period before dosing specifically for Part A'.

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

In Part A, the caloric content and composition of meals will be basically the same for all subjects.

Light lunch will be served on the following days.

- Part A: Day 1 and Day 7.
- Part B and C: The specified days when MWT will be conducted.

Light lunch is defined as a meal eaten in the middle of the day, typically one that is lighter or less formal than an usual lunch meal.

The meals on Day 1 and Day 7 should be the same.

In Part A', TAK-925 (as an oral solution) will be administered in the morning on Day 1 after a fast of at least 10 hours and subjects will be instructed to fast for an additional 4 hours postdose. Subjects will refrain from any drink including water from 1 hour prior to dosing and until 2 hour after dosing except for water that will be taken with dosing.

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc.) from the Screening Visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), and until the Follow-up Visit.

Blood donation within at least 12 weeks (84 days) after the last laboratory test is prohibited.

In Part A, subjects will record their sleep status from Day -1 to the night of discharge including information about wake up time, time of sleep onset and approximate time and duration of nocturnal awakenings at the minimum. In Part B and C, a patient will [redacted]

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

The investigator or subinvestigator 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 investigator or subinvestigator 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>.
- Study termination 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 discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form 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. Adverse event

   The subject has experienced a pretreatment event or adverse event that requires early termination because continued participation imposes an unacceptable risk to the subject's

health or the subject is unwilling to continue because of the pretreatment event or adverse event.

- Liver Function Test Abnormalities

  Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.2.14), if the following circumstances occur at any time during study drug treatment:

  – ALT or AST >8 × ULN, or

  – ALT or AST >5 × ULN and persists for more than 2 weeks, or

  – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or

  – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

- CCI [redacted]

3. Protocol deviation.

   The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up.

   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.

5. Withdrawal by subject.

   The subject or subject's legally acceptable representative wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the electronic case report form.

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

6. Study terminated by sponsor.

   The sponsor, institutional review board, or regulatory agency terminates the study.

7. Pregnancy.

   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately.

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the electronic case report form.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or subinvestigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or subinvestigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

7.8 Subject Replacement

Due to the risk of screen failures and subject withdrawals, more subjects may be enrolled than planned/cohort. If a subject discontinues from the study, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The study site should contact the sponsor for the replacement of subject's treatment assignment and allocation number.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation, of the active drug and placebo can be found in the pharmacy manual or in the referenced compounding manual when applicable. Study drug will be packaged to support enrollment and replacement of subjects as required.

[Compound]

Code name: TAK-925

Dosage form and strength:

<Parts A, B and C>

TAK-925 injection consists of CCI [redacted]. TAK-925 injection is diluted in saline for administration via IV infusion.

The Sponsor will not supply placebo in the form of saline for infusion. TAK-925 placebo injection used in the study is a commercially available sterile 0.9% sodium chloride solution (0.9% normal saline).

<Part A'>

TAK-925 for oral administration will be prepared with TAK-925 injection solution. TAK-925 injection solution will be diluted with saline for oral administration route and adjusted to appropriate volume for oral dosing. More details of the procedure for preparation of oral solution could be found in Section 9.2.7 and pharmacy manual.

Manufacturing

The drug substance of TAK-925 is manufactured by CCI [redacted] Osaka, Japan.

TAK-925 injection is manufactured by the CCI [redacted]

8.1.1 Clinical Study Drug Labeling

A clinical label will be affixed to study drug containers in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

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

8.1.3 Clinical Study Drug Blinding

This is a double-blind study except Part A'; the investigator or subinvestigator and subjects are blinded to treatment assignment accordingly. The study drug will be provided as TAK-925 injection to the investigational site and for double-blind parts, randomization personnel designated by the investigational site with its assistant will retain the blind according to the randomization schedule and procedure, by affixing a label with a medication identification number on each dispensing carton containing one vial of TAK-925 injection or an empty carton for placebo; this should be done and then diluted in saline for administration of IV infusion in the room where the other site personnel or the sponsor employees are kept out.

8.1.4 Randomization Code Creation and Storage

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

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

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

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

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

8.2 Ancillary Supplies

All ancillary supplies will be provided by either the study site or the sponsor or designee, depending upon availability. The list of ancillary supplies and source information can be found in the pharmacy manual or in the referenced compounding manual when applicable. If provided by

the sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the sponsor or designee.

9.0 STUDY PROCEDURES

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

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.1.1 Assignment of Screening and Randomization Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur before randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be reused for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening event.

For Parts A, B and C, all eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be reassigned to another subject.

For Part A', all eligible subjects will be assigned a subject identification number, which identifies the subject for all procedures after dosing. Once a subject identification number is assigned to a subject, it can never be reassigned to another subject.

9.1.1.2 Study Drug Assignment

In Parts A, B and C, on Day 1 of Treatment Period, subjects will be assigned a randomization number in ascending numerical order at each clinical site. The randomization number encodes the subject assignment to either TAK-925 or placebo, according to the randomization schedule generated before the study. Each subject will be dispensed blinded study drug, labeled with his/her unique randomization number, throughout the study.

In Part A', on Day 1 of Treatment Period, subjects will be assigned a subject identification number in ascending numerical order at clincal site.

9.1.2 Inclusion and Exclusion

Each subject will be assessed through randomization (Part A, B and C), or dosing (Part A') according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History, Demographics, and Prior and Concomitant Medications

Qualified site personnel will collect subject significant medical history (past and concurrent medical conditions), per the clinical site's standard of care and appropriate clinical judgment, and subject demographics (date of birth, sex, race [reported by the subject], height, weight, caffeine consumption, alcohol consumption, and smoking status of the subject).

In the part B and C, the following information will be collected: information for primary disease (narcolepsy): the age of onset, a diagnostic period, whether CSF orexin concentration and CCI [redacted] (part B only to assure satisfaction of inclusion criteria). If test results are available, orexin concentration data, and CCI [redacted] will be also recorded in the eCRF.

Qualified site personnel will review subject prior and concomitant medication use. Medications are defined as prescription and over-the-counter drugs, vaccines, supplements, nutraceuticals, and oral herbal preparations.

Subjects will be asked whether they have taken any medications other than the study drug (during a period from the signing of informed consent through the end of the study), and all medications including vitamins, OTC drugs and Chinese herbal medicines used by a subject must be recorded in each subject's eCRF. The nonproprietary name, route of administration, dates of initial and final administrations and reasons for use must also be recorded in the eCRF.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Examination

Qualified site personnel will conduct full physical examinations. When a physical examination is performed in Part B and C, the items described in Section 9.3.3.7 will be completed by subjects and their assessment will be recorded.

9.2.2 Height and Weight

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

9.2.3 Body Mass Index

Body mass index equals a subject's weight in kilograms divided by height in meters squared (body mass index=kg/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 CCI

CCI [redacted]

9.2.5 CCI

CCI [redacted]

CCI

[redacted]

9.2.6 CCI

CCI

[redacted]

9.2.7 Study Drug Administration

On Day 1 of each treatment period, study drug (TAK-925 or placebo) will be administered. The study drug is intravenously administered to subjects over 9 hours up to 7 days in Part A, B and C, while the administration duration in Cohort B3 in Part B may be longer [TBD]. The times of the beginning and the end of study drug administrations will be recorded.

In Part A'1, a single oral dose of TAK-925 can be administered as approximately 50 mL oral solution diluted in a bottle, followed by 2x water rinse of a bottle, each with approximately 50 mL of water, in the morning of Day 1. The total administration volume will be approximately 150 mL. In case of administration of higher dose of TAK-925 up to 336 mg, basically the same procedures will be used for drug administration and the total administration volume is expected not to exceed approximately 250 mL. More details of administration procedure of oral solution and volumes to be taken can be also found in the pharmacy manual.

In Part A, B and C, in case that interruption or discontinuation of study drug administration might occur, 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 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures (Section 3.0). Two versions of the C-SSRS will be used in this trial: the screening/baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS. Any suicidal ideation or suicidal behavior during the trial periods detected by C-SSRS will be recorded as AEs. The investigator or subinvestigator will ensure that any suicidal ideation or behavior is medically addressed, including assessment and treatment by qualified medical personnel.

9.2.9 CCI

CCI [redacted]

9.2.10 CCI

CCI [redacted]

9.2.11 CCI

CCI [redacted]

9.2.12 AE Monitoring

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

9.2.13 Other Safety Monitoring

CCI [redacted]

CCI [redacted], as well as in the TAK-925-1001 clinical study, the following safety risks will be closely monitored CCI [redacted].

CCI [redacted]

9.2.14 CCI

CCI [redacted]

9.2.14.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

9.2.15 Diagnostic Screening

The investigator will report the results of immunology and urine drug, urine, Alcohol screen, and if applicable Serum hCG and Serum follicle stimulating hormone (FSH) (Serum hCG is for childbearing potential only and Serum FSH is for nonchildbearing potential only), directly to subjects. The sponsor will confirm the overall test results ("Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug. Regarding the result of a drug test in the part B and C, in the event that the medicine of "positive" is detected, the details are identified and eligibility is judged.

Serum

The serum diagnostic screening assessment will include the following tests:

HIV	Hepatitis screen (hepatitis B surface antigen, hepatitis C virus antibody)
Syphilis serum reaction test	

Alcohol Screen

In Part A and A', subjects will undergo an alcohol breath test. A urine alcohol test may be performed at the discretion of the investigator or subinvestigator.

Urine

The urine drug screening assessment will include the following tests:

Barbiturates	Morphines
Benzodiazepines	Phencyclidine
Cannabinoids	Stimulants
Cocaines	Tricyclic antidepressants
Cotinine (a)	

(a) Part A and A' only.

*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 B and Part C. In almost all narcolepsy 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. The test will be skipped for patients who participated in B1 or B2 and rolled over to B3 or B4.

9.3 Pharmacokinetic, Biomarker, Pharmacodynamic, and Pharmacogenomic Samples

9.3.1 Pharmacokinetic, Biomarker, Pharmacodynamic, and Pharmacogenomic Evaluations

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

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

It is anticipated that the total blood volume drawn for each subject in Part A will be approximately 193/202 mL (male/female). For each subject in Part B (B1 and B2) and C, the volume will be approximately 147-174 mL, whereas it will be approximately 141-168 mL for subjects in Cohort B3. For Cohort B4, it is 255-282 mL. The volume for subject who participates in Cohorts B3 just after completing Cohorts B1 and B2 will be approximately 200-227 mL. The volume for subject who participates in Part A' will be approximately 77-86 mL (male/female).

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

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-925 and its metabolites CCI [redacted] PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory
Blood sample for DNA PGx	Blood	DNA	Blood sample for PGx analysis	Optional

Abbreviations: PGx, pharmacogenomic(s); PK, pharmacokinetic(s).

9.3.2 Pharmacokinetic Evaluation

The pharmacokinetic parameters of TAK-925 and its metabolites CCI [redacted] will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following pharmacokinetic parameters will be calculated from plasma concentrations of TAK-925 and its metabolites CCI [redacted], as data permit:

(1) Part A, B and C

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
$AUC_{last, ss}$	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration, at steady state
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
$AUC_{\tau, ss}$	Area under the plasma concentration-time curve during a dosing interval, at steady state
C_{max}	Maximum observed concentration
$C_{max\ ss}$	Maximum observed concentration, at steady state
C_{min}	Minimum observed concentration during a dosing interval
$C_{min, ss}$	Minimum observed concentration during a dosing interval, at steady state
C_{eoi}	Concentration at the end of infusion
$C_{eoi, ss}$	Concentration at the end of infusion, at steady state
PTR	Peak trough ratio during a dosing interval, at steady state
$R_{ac(AUC)}$	Accumulation ratio based on AUC_{τ}
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}
t_{max}	Time of first occurrence of C_{max}
$t_{max, ss}$	Time of first occurrence of C_{max}, at steady state
$t_{1/2z}$	Terminal disposition phase half-life
$t_{1/2z, ss}$	Terminal disposition phase half-life, at steady state
C Cl	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)
$V_{z, ss}$	Apparent volume of distribution during the terminal phase, at steady state (only for TAK-925)
CL	Total clearance after intravenous administration (only for TAK-925)
CL_{ss}	Total clearance after intravenous administration, at steady state (only for TAK-925)

(2) Part A'

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 plasma concentration-time curve from time 0 to infinity
C_{max}	Maximum observed concentration
t_{max}	Time of first occurrence of C_{max}
$t_{1/2z}$	Terminal disposition phase half-life
CCI	CCI [redacted]
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration (only for TAK-925)
CL/F	Apparent clearance after extravascular administration (only for TAK-925)

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

9.3.2.1 Plasma for Pharmacokinetic Measurements

Blood samples for pharmacokinetic analysis of TAK-925 and its metabolites CCI [redacted] will be collected into blood collection tubes (vacutainer) containing the anticoagulant K_2EDTA. The collected blood samples may be archived for additional analysis of potential metabolites.

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

To reflect the plasma exposure more precisely in Parts A, B and C, 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.

Table 9.b Sampling of blood samples for pharmacokinetic analysis (Part A)

Analyzed substances	Samples	Study date	Blood sampling time
TAK-925 and its metabolites CCI [redacted]	Plasma	Day 1-8	Day 1 and 7: Predose, 0.5, 1, 1.5, 2, 4, 6, 8, 9 hours after start of infusion, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 6, 10 and 15 hours after end of infusion. Day 5 and 6: Predose, 9 hours after start of infusion

Table 9.c Sampling of blood samples for pharmacokinetic analysis (Part B and C)

Analyzed substances	Samples	Study date	Blood sampling time
TAK-925 and its metabolites CCI [redacted]	Plasma	Day 1-8	B1, B2, B4, C1 and C2 • Day 1 and 7: Predose, 1, 2, 4, 6, 9 hours after start of infusion, 0.17, 0.5, 2, 6, 10 and 15 hours after end of infusion. B1, B2, C1 and C2 • Day 5 and 6: Predose, 9 hours after start of infusion B3 • Day 1 and 7: Predose, 1, 2, 4, 6 after start of infusion, end of infusion , 0.17 and 0.5 hour after end of infusion, bed time, just after wake up and 24 hours after start of infusion. • Day 5 and 6: Predose, end of infusion B4 • Day 4: Predose, 1, 2, 4, 6, 9 hours after start of infusion, 0.17, 0.5, 2, 6, 10 and 15 hours after end of infusion • Days 2, 3, 5 and 6: 2, 6 and 9 hour after start of infusion, 0.17, 0.5, 2 hours after end of infusion, bed time

In Cohort B3, samples will be taken at following time points in patients who participated in B1 or B2 as well.
Day 1: Predose, end of infusion
Day 2: Predose
Day 7: Predose, 2 hours after start of infusion, end of infusion, 0.17 and 0.5 hour after end of infusion, bed time, just after wake up and 24 hours after start of infusion.

Table 9.d Sampling of blood samples for pharmacokinetic analysis (Part A')

Analyzed substances	Samples	Study date	Blood sampling time
TAK-925 and its metabolites CCI [redacted]	Plasma	Day 1	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours postdose

In the case when the subject prematurely discontinues the study between the first and the last scheduled PK sample blood draw, final blood samples to be used for pharmacokinetic analysis are sampled from subjects during hospitalization. If the IV infusion is interrupted in Parts A, B and C, 2 additional PK samples (1 sample drawn when the infusion is stopped and 1 sample drawn when the infusion is restarted) would be collected so that the subject may be considered evaluable. The exact date and time of each sample should be recorded.

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

9.3.2.2 Pharmacokinetic Sample Analysis

Plasma concentrations of TAK-925 and its metabolites [redacted] will be measured by a [redacted]

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

Moreover, the retained material of a measurement sample may be used for exploratory use and measured if needed an unidentified metabolite and for the purpose of exploratory biomarker.

9.3.3 Pharmacodynamic Measurements

The pharmacodynamic assessments described below will be performed at the time points stipulated in the schedule of procedures (Section 3.0). Additional details regarding these pharmacodynamic assessments are provided in the study manual including PSG and MWT manual.

Table 9.e Primary PD Parameters Collections

Endpoint	Subitems	Collection in eCRF	Notes
Objective sleepiness			
MWT	Sleep latency	Yes	Each session
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	[redacted]
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
		[redacted]	
Subjective sleepiness			
[redacted]			
Other PD			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]

Footnotes are on last table page.

Table 9.e Primary PD Parameters Collections (continued)

Endpoint	Subitems	Collection in eCRF	Notes
CCI	CCI	CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
CCI	CCI	CCI	CCI
		CCI	
		CCI	
		CCI	
		CCI	
		CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
		CCI	CCI
CCI		CCI	CCI
CCI	CCI	CCI	CCI
			CCI
		CCI	CCI
			CCI
		CCI	CCI
			CCI

CCI parameters wih asterisk (*) can be calculated automatically on eCRF following AASM scoring manual (ver. 2.3) based on parameters read and collected from raw EEG data.
All raw EEG data will be collected and stored at the sponsor.

9.3.3.1 Maintenance of Wakefulness Test (MWT)

The MWT is a validated objective measure that evaluates a person's ability to remain awake under soporific conditions for a defined period of time. As there is no biological measure of wakefulness, this is measured indirectly by the inability or delayed tendency to fall asleep. This tendency to fall asleep is measured via EEG-derived sleep latency in MWT. Four forty minutes (1 session) MWTs will be done on Day -1, Day 1 and Day 7 (and Day 4 in cohort B4). MWT will be conducted 4

times (approximately at 10:00, 12:00, 14:00, 16:00) on each of these days. Sleep latency of each session will be recorded. Subjects will be required to stay awake in between the MWT tests.

9.3.3.2 CCI

CCI [redacted]

9.3.3.3 CCI

CCI [redacted]

9.3.3.4 CCI

CCI [redacted]

9.3.3.5 CCI

CCI [redacted]

9.3.3.6 CCI

CCI

9.3.3.7 Assessment of Cataplexy and other Narcolepsy Symptoms

Cataplexy has been defined as a "sudden and bilateral loss of postural muscle tone in association with intense emotion and is a typical symptom of NT1. CCI

CCI

CCI

CCI

9.3.4 Biomarker Measurements

9.3.4.1 Exploratory Biomarker Research

CCI

However, as the study is to be conducted in healthy subjects and narcolepsy patients who undergo limited dosing period as seven days, the likelihood of finding significant changes, as well as changes related to the study drug, will be low. Therefore, formal fluid biomarkers will not be collected in this study.

9.3.4.2 Future Biomedical Research (unplanned exploratory biomarker research)

No future biomedical research is currently planned, however the retained material of a measurement sample may be used for exploratory use and measured if needed an unidentified metabolite and for the purpose of exploratory biomarkers. Similarly, CCI [redacted]

9.3.5 Pharmacogenomic Measurements

9.3.5.1 Blood Sample for DNA Pharmacogenomic Measurements

Sampling of whole blood for pharmacogenomic analysis is optional in this study and will only be performed for subjects who provide consent to participate in this assessment. The test will be skipped in B3 and B4 for patients who participated in B1 or B2 and rolled over to B3 or B4.

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

Pharmacogenomic research in this study may be conducted to understand how individual genetic variation in subjects impacts their response to study drug treatment. This information may also be used, for example, to develop a better understanding of the safety and efficacy of TAK-925 and other study drugs, to increase understanding of the disease/condition being studied and other related conditions, to gain a better understanding of the drug pharmacology, and to generate information needed for research, development, and regulatory approval of tests to predict response to TAK-925.

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

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

9.3.5.2 Biological Sample Retention and Destruction

In this study, blood samples for pharmacogenomic analysis will be collected as described in Section 9.3.5.1. Genetic material will be initially stored at a vendor or comparable laboratory, under contract to the sponsor, with validated procedures in place, and then preserved and retained

at a long-term storage vendor, or a comparable laboratory, with validated procedures in place, for up to but not longer than 15 years from the end of the study when the clinical study report is signed, or if less, the maximum period permitted under applicable law or until consent is withdrawn.

The sponsor and vendors working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access, and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

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

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

9.4 Confinement

Part A, B and C

Subjects will be admitted to a hospital during a period from Day -2 to Day 8 and discharged from the hospital if no clinically significant abnormalities were found at the physical examination and tests on Day 8, and confirmed by the investigator or subinvestigator.

In Part B and C

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 investigator or subinvestigator must be careful for frequent occurrence of cataplexy and ensure the subject safety in the most appropriate way.

Part A'

Subjects will be admitted to a hospital during a 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 investigator or subinvestigator.

9.5 Childbearing Status and Methods of Contraception

9.5.1 Women of Childbearing Potential

9.5.1.1 Definition of Women of Childbearing Potential

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile.

9.5.1.2 Acceptable Methods of Contraception for Women of Childbearing Potential

Refer to the Appendix D.

9.5.2 Women of Nonchildbearing Potential

9.5.2.1 Definition of Women of Nonchildbearing Potential

A female subject of nonchildbearing potential is defined as satisfying at least 1 of the following criteria:

1. Postmenopausal: At least 12 months of spontaneous amenorrhea and an FSH concentration >40 mIU/mL.
2. Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
3. Has no uterus as a result of a congenital condition.

9.5.2.2 Contraception for Women of Nonchildbearing Potential

No contraception is required for women of nonchildbearing potential.

9.6 Patient Interview

In order to obtain patients' point of views such as meaningfulness of narcolepsy treatment or its benefits, a post-clinical trial participation interview (questionnaires) may be conducted in the patient who gives consent. This interview will be done separately from the study.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator or subinvestigator 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 or subinvestigator 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 worsening of laboratory values or abnormal 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. The first evaluation (eg, laboratory test, ECG, X-ray, etc.) after obtaining the consent should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a

worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigator or subinvestigators 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 investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg, "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, 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. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the subinvestigator 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 on subjects who signed the informed consent forms as follows:

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

Table 10.a Takeda Medically Significant AE List

Term
CCI [redacted]

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the following manner (see Section 10.2.9.3). Considering the nature of this study that has scheduled confinement period it is noted that possible extension of the confinement period in the study sites in the purpose of follow up AEs may occur by the investigator's or the subinvestigator's discretion and this extension will be considered as a part of scheduled confinement period and basically will not be considered to fullfill above serious criteria No. 3.

10.1.2 Special Interest AEs

Not applicable.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug or control 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 or control drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Assigning Causality of AEs to Study Procedures

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

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

10.2.4 Start Date

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

10.2.5 End Date

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

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.

- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular 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, Adverse Event related to Convulsion and Abnormal liver function tests [LFTs]) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up period.

10.2.9.2 Reporting AEs

At each study visit, the investigator or subinvestigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to study drug must be monitored until the

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

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

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

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator or subinvestigator to the Sponsor (see Protocol Annex 1) within 1 business day of the first onset or notification of the SAE, along with any relevant information. The investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator or subinvestigator's name.

- Name of the study medication(s).
- Causality assessment.

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

Safety Follow-Up

SAE Follow-Up

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

10.2.9.4 Reporting Adverse Event Related to CCI [redacted]

CCI [redacted] 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

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

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator must contact the trial clinician or its delegates or designee (contact information may be found in Annex 1) for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.14.1 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.10).

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/head of the study site and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized 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.

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

11.1.1 Analysis Sets

In this study, 3 analysis sets will be used: the safety set, the PK set, and the PD 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 Set

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

11.1.1.2 PK Set

The PK set will be defined as all subjects who received at least one dose of study drug and provided sufficient PK measurements available to estimate PK parameters, at least 1 estimable PK parameter.

11.1.1.3 PD Set

The PD 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 set by treatment.

11.1.3 PK Analysis

(1) Endpoints and analysis methodologies

[Endpoints]

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

M-[redacted]

[Analysis methodologies]

All data analyses and summaries will be performed using the PK set separately for Part A, B, C and A' by treatment.

Plasma concentrations and pharmacokinetic parameters of TAK-925 and its metabolites [redacted] M-[redacted] will be summarized for each scheduled sampling time using descriptive statistics.

For Parts A, B and C, the relationship between TAK-925 exposure and safety will be explored graphically. For SBP, a scatterplot of TAK-925 plasma concentration (x-axis) versus the change from time-matched baseline in SBP (y-axis) will be produced. Only measurements from time points common to both assessments (SBP and PK) will be used. The plots will be produced separately for Day 1 and Day 7. Similar scatterplots will be produced for changes in DBP and [redacted] parameter(s) (QT).

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, the sleep latency in the MWT in each session [redacted]

[Analysis methodologies]

All data analyses and summaries will be performed using the PD set separately for Part B and C by treatment.

The average sleep latency in the MWT will be summarized (N, mean, median, SD, minimum, and maximum) for baseline, post-dose, change from baseline and change from Day 1 to Day 7 by treatment. Percentage of the patient who recorded the average sleep latency in the MWT equal to or over 40 minutes in Day 1 and Day 7 will be provided by treatment group.

If applicable, the effect of TAK-925 will be evaluated with a linear mixed effects model. The response variable in the model will be the change from baseline in the average sleep latency in the MWT. The model will include treatment (each dose level of TAK-925 and placebo), day (as a categorical variable), the treatment-by-day as fixed effects, baseline average sleep latency in the MWT as a covariate, and subjects as a random effect.

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, CCI [redacted]

All data analyses and summaries will be performed using the safety set separately for Part A, B, C and A' by treatment.

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 Medical Dictionary for Regulatory Activities (MedDRA) dictionary and tabulated by the system organ class (SOC) and the Preferred Term (PT).

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

11.1.5.2 CCI [redacted]

CCI [redacted]

11.1.5.3 CCI [redacted]

CCI [redacted]

11.1.5.4 CCI [redacted]

12-CCI [redacted]

11.2 Interim Data Review

The dose level chosen for Cohorts in Part A, B, C after the first cohort in each group and whether to proceed to next cohort or stop the part may be evaluated by the sponsor's unblinded team

composed of persons who do not have subject contact or involvement with execution of the protocol at the site, who will review unblinded data on safety, tolerability, available PK and PD results, and this dose may be higher, lower or the same than that used in the prior cohorts.

11.3 Determination of Sample Size

The sample size in Part A (8 subjects per cohort: 6 active and 2 placebo), Part B and C (6 patients per cohort: 4 active and 2 placebo) and Part A' (open label, 6 subjects per cohort) is assumed to be sufficient for investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of TAK-925 when multiple doses of TAK-925 are administered intravenously in healthy adults, healthy elderly, and narcolepsy patients, or when a single dose of TAK-925 is administered orally in healthy adults. The sample size is not based on considerations of statistical power.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

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

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

12.2 Protocol Deviations

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

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. The investigator should document all 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 designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). 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 access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

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

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

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

13.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

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

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

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

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

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

13.4.2 Clinical Trial Registration

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

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

14.1.2 INVESTIGATOR AGREEMENT

An agreement will be provided to each study site separately.

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
BP	blood pressure
C_{max}	maximum observed concentration
CHO	Chinese hamster ovary
CNS	central nerve system
CCI	CCI
C-SSRS	Columbia Suicide Severity Rating Scale
CCI	CCI
DNA	deoxyribonucleic acid
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
ESS	Epworth Sleepiness Scale
EEG	electroencephalography
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastro-intestinal
γ-GTP	gamma-glutamyl transferase
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Term	Definition
HLA	human leukocyte antigen
ICH	International Council on Harmonisation of Technical Requirements for Human Use
IEC	Independent Ethics Committee
ICSD-3	International Classification of Sleep Disorders, third edition
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
KSS	Karolinska Sleepiness Scale
CCI	CCI
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	The Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
MRD	multiple rising dose
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
NOAEL	no observed adverse effect level
CCI	CCI
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OSA	obstructive sleep apnea
OX	orexin
OX1R	orexin 1 receptor
OX2R	orexin 2 receptor
PD	pharmacodynamics
PGx	pharmacogenomics
CCI	CCI
PK	pharmacokinetics
PT	Preferred Term
PMDA	The Pharmaceuticals and Medical Devices Agency
CCI	CCI
CCI	CCI
CCI	CCI
QOL	quality of life
QTcF	QT interval with Frederica correction method
RBC	red blood cell
REM	rapid eye movement
RLS	restless legs syndrome
SAE	serious adverse event
SAP	statistical analysis plan

Term	Definition
SBP	systolic blood pressure
CCI	CCI
SRD	single rising dose
SSRI	selective serotonin reuptake inhibitor
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 full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic)

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

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

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

The following data will not be recorded in the eCRF:

- PGx results
- Laboratory results
- Drug concentration measurement results
- CCI [redacted] results

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

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

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor.

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

16.0 REFERENCES

[1] 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] Ohno K, Sakurai, T. Orexin neuronal circuitry: role in the regulation of sleep and wakefulness. Front Neuroendocrinol. 2008;29(1):70-87.

[10] Scammell TE, Winrow CJ. (2011) Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol. 2011;51:243-66.

[11] Krahn LE, Pankratz VS, Oliver L, Boeve BF, Silber MH. Hypocretin (orexin) levels in cerebrospinal fluid of patients with narcolepsy: relationship to cataplexy and HLA DQB1*0602 status. Sleep 2002;25(7):733-6.

[12] De la Herran-Arita AK, Garcia-Garcia F. Narcolepsy as an immune-mediated disease. Sleep Disord 2014;2014:792687.

[13] 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.

[14] Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 06 July 2005. Publication No. 5541.

[15] Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol. 2013;12(11):1068-75.

[16] Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med. 2005;15;1(4):391-7.

[17] US Modafinil in Narcolepsy Multicenter Study Group Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998;43(1):88-97.

[18] Gast H, Schindler K, Rummel C, Herrmann US, Roth C, Hess CW, et al. EEG correlation and power during maintenance of wakefulness test after sleep-deprivation. Clin Neurophysiol. 2011;122(10):2025-31.

[19] Blaivas AJ, Patel R, Hom D, Antigua K, Ashtyani H. Quantifying microsleep to help assess subjective sleepiness. Sleep Med. 2007;8(2):156-9.

[20] Tirunahari VL, Zaidi SA, Sharma R, Skurnick J, Ashtyani H. Microsleep and sleepiness: a comparison of multiple sleep latency test and scoring of microsleep as a diagnostic test for excessive daytime sleepiness. Sleep Med. 2003;4(1):63-7.

[21] An H, Cho MH, Kim DH, Chung S, Yoon SY. Orexin Impairs the Phagocytosis and Degradation of Amyloid-beta Fibrils by Microglial Cells. J Alzheimers Dis. 2017;58(1):253-61.

[22] Wei M, Zhao B, Huo K, Deng Y, Shang S, Liu J, et al. Sleep Deprivation Induced Plasma Amyloid-beta Transport Disturbance in Healthy Young Adults. J Alzheimers Dis. 2017;57(3):899-906.

[23] 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

Appendix A [redacted]

[redacted]

Appendix B CCI

CCI

[redacted]

CCI

[redacted]

CCI

Appendix C CCI

CCI

[redacted]

Appendix D [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix E [redacted]

[redacted]

Appendix F Summary of Changes and Detailed Description of Amendments

Summary of Changes

- An addition of new inclusion criterion and the corresponding adjustment
- Easing of an exclusion criterion
- Editorial changes

Detailed Description of Amendments

The details of Amendment 3 are described as follows.

The previous descriptions are shown with italicized underline, and the amended descriptions are represented with bold letter.

Page 7-12, Section 1.0 Study Summary

The descriptions were revised as per the amendments in the corresponding Sections. See below for the details.

Page 19, Section 3.0 Schedule of Study Procedures

Existing Text

a. To confirm eligibility of patients, [redacted] orexin examination could be done as a study procedure(s) during the screening period, if necessary.

Revised Text

a. To confirm eligibility of patients, [redacted] **maintenance of wakefulness test (MWT),** and/or [redacted] orexin examination could be done as a study procedure(s) during the screening period, if necessary.

Rationale for Amendment

The corresponding adjustment to the addition of new inclusion criterion.

Page 35, Section 6.1 Trial Design

Existing Text

(Omitted)

The initiation of cohorts in parallel with each other is contingent on *regulatory and* Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, and if not approved, the cohorts will enroll as required, which may be sequentially or overlapping with each other.

(Omitted)

Revised Text

(Omitted)

The initiation of cohorts in parallel with each other is contingent on Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, and if not approved, the cohorts will enroll as required, which may be sequentially or overlapping with each other.

(Omitted)

Rationale for Amendment

Editorial changes (This regulatory approval is not applicable in Japan)

Page 57, Section 7.1 Inclusion Criteria

Existing Text

No texts.

Revised Text

NT1 and NT2 patients (Parts B and C)

23. Average (of 4 sessions) Baseline MWT sleep latency is less than or equal to 20 minutes and no single session has a sleep latency of greater than 30 minutes as determined by the site EEG readers and investigators.

Rationale for Amendment

To exclude subjects who have too long MWT sleep latency to assess the PD of TAK-925.

Page 59, Section 7.2 Exclusion Criteria

Existing Text

26. The subject has abnormal laboratory test values that suggest a clinically significant underlying disease or any subject with transaminase (Alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) >1.5 *×upper limit of normal (ULN) at the Screening Visit or baseline.*

Revised Text

26. The subject has abnormal laboratory test values that suggest a clinically significant underlying disease **at the Screening Visit or baseline** or any subject with transaminase (Alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) >1.5 **(Part A and A') or >2.0 (Part B and C)×upper limit of normal (ULN) at the Screening Visit (or baseline in Part A and A').**

Rationale for Amendment

After the completion of healthy adults dose escalation part, preliminary blind safety and tolerability were confirmed and no concern was suggested for aggravation of liver function.

Generally, >2.0 × ULN for ALT/AST as an exclusion criterion is acceptable for patient study once clinical safety and tolerability was confirmed in healthy adults.

A 3-Part, Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-925 in Healthy Volunteers and Patients with Narcolepsy

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	PPD	PPD