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

NCT Number: NCT03332784

Statistical analysis plan Approve Date: 02-OCT-2018

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-925-1001

A First-in-Human, Two-Part Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-925 in Healthy Adult and Elderly Volunteers and Patients with Narcolepsy

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

Version: 2nd

Date: 2 October 2018

Prepared by:

PPD

[redacted]

Based on:

Protocol Version: Amendment

Protocol Date: 6 March 2018

CCI

[redacted]

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
Ae	amount of drug excreted in urine
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
CL R	renal clearance
Cmax	maximum observed concentration
CRF	case report form
CSF	cerebrospinal fluid
ECG	electrocardiogram
ESS	epworth sleepiness scale
fe	fraction of administered dose of drug excreted in urine
γ-GTP	gamma-glutamyl transferase
KSS	karolinska sleepiness scale
LDH	lactate dehydrogenase
Lambda z	terminal disposition phase rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MWT	maintenance of wakefulness test
PD	pharmacodynamics
PK	pharmacokinetics
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
QTc	corrected QT
RBC	red blood cell
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
tmax	time of first occurrence of Cmax
t1/2z	half-life period
ULN	upper limit of normal
Vz	volume of distribution

WBC	white blood cell
WHO Drug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 Secondary Objectives

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

4.3 Additional Objectives

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[redacted]

4.4 Study Design

This study consists of two parts.

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

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

(1) Part 1

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

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

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

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

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

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

subjects to the placebo group, to evaluate the safety, tolerability and PK. In Healthy Elderly Supplement Cohort, the dose may be higher or lower than or the same to that of prior cohort dose levels, or an intermediate dose between two prior doses.

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

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

(2) Part 2

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

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

See section 3.0 in the Protocol for the schedule of tests/observations /evaluations. Summary of Cohorts is shown in Table 4.a.

Table 4.a Summary of Cohorts

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

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

Dose Level 1	
A	TAK-925 7 mg
B	TAK-925 7 mg

→

Dose Level 2	
E	TAK-925 14 mg
F	TAK-925 14 mg

→

Dose Level 3	
A	TAK-925 28 mg
B	TAK-925 28 mg

C	TAK-925 7 mg
D	Placebo

G	TAK-925 14 mg
H	Placebo

C	Placebo
D	TAK-925 28 mg

→

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

→

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

→

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

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

Figure 4.a Summary of Cohort 1 and Cohort 2

TAK-925 112 mg/TAK-925 TBD
Placebo

TBD: To be dterminied

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

Figure 4.b Summary of Cohort 3 and Cohort R1 (Healthy Elderly Supplement Cohort)

TAK-925 TBD
Placebo

TBD: To be dterminied

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

Figure 4.c Summary of Cohort S1~S4 (Healthy Adult Supplement Cohorts)

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

Cohort transfer →

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

Cohort transfer →

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

TBD: To be dterminied

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

Figure 4.d Summary of Cohort 5~7

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoint

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

5.1.2 Secondary Endpoints

- The average sleep latency in the MWT

5.1.3 Exploratory Endpoints

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[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

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

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

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

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

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after the start of study drug
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV) (%): Standard deviation / mean * 100
- QTcF interval (msec): QT interval (msec) / (RR interval (sec))$^{0.33}$ (rounded to the nearest whole number)
- Period for diagnosis (year): The value of age of onset subtracted from the value of age at date of informed consent
- Change from time-matched baseline: Values of Day -1subtracted from values of Day 1 in the matching column in the table below for each subject

Day	Time postdose（hour）																			
Day -1	-24	-23.75	-23.5	-23.25	-23	-22.5	-22	-21.5	-21	-20.5	-20	-19	-18	-17	-16	-15	-14	-13	-12	0*
Day 1	0*	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	7	8	9	10	11	12	24

* : Just prior to dosing

- Dose level
  - Cohort 1~2
    - ✧ Placebo
    - ✧ TAK-925 7, 14, 28, 56, 112, 134.4 mg
  - Cohort S1~S2
    - ✧ Placebo
    - ✧ TAK-925 180, 240 mg
  - Cohort 3
    - ✧ Placebo
    - ✧ TAK-925 112 mg
  - Cohort 4
    - ✧ Placebo
    - ✧ TAK-925 112 mg
  - Cohort 5~7

- ✧ Placebo
- ✧ TAK-925 44.8, 11.2, 5 mg

- Group
  - Part1 (Healthy Adults or The Healthy Elderly)
    - ✧ Cohort 1 and Cohort 2: See Figure 4.a
    - ✧ Cohort 3: TAK-925, Placebo
    - ✧ Cohort 4: TAK-925
    - ✧ Cohort S1~S2: TAK-925, Placebo
  - Part2 (Patients with Narcolepsy)
    - ✧ Cohort 5~7: See Figure 4.d

7.1.2 Definition of Study Visit Windows

For all variables, evaluable data will be used as entered in the CRF according to the scheduled Study Time.

7.2 Analysis Sets

- Safety analysis set: All subjects who received at least one dose of study drug
- Pharmacokinetic analysis set: All subjects who received at least one dose of study drug and whose plasma or CSF concentration can be measured at least once or whose cumulative urinary excretion can be calculated.
- Pharmacodynamic analysis set: All subjects who received at least one dose of study drug.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s) :	Date First Subject Signed Informed Consent Form Date of Last Subject's Last Visit/Contact MedDRA Version SAS Version Used for Creating the Datasets
Analytical Method(s) :	(1) Study Information Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:	All Subjects Who Did Not Receive Study Drug	
Analysis Variable(s) :	Age (years)	
	Gender	[Male, Female]
Analytical Method(s) :	(1) Screen Failures Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.	

7.3.3 Subject Eligibility

7.3.3.1 Cohort 1~2

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s) :	Study Drug Administration Status	[Treated, Not Treated]
	Primary Reason for Subject Not Being Treated	[Adverse Event, Death, Lost to Follow-up, Pregnancy, Protocol Deviation, Sample Size Sufficient, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical
Method(s) : (1) Study Drug Administration Status
Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being treated, the total number of not treated subjects will be used as the denominator.

7.3.3.2 Cohort S1~S2

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analytical
Method(s) : The same analysis as section 7.3.3.1 will be performed for the Cohort S1~S2

7.3.3.3 Cohort 3

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analytical
Method(s) : The same analysis as section 7.3.3.1 will be performed for the Cohort 3

7.3.3.4 Cohort 4

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analytical
Method(s) : The same analysis as section 7.3.3.1 will be performed for the Cohort 4

7.3.3.5 Cohort 5~7

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analytical
Method(s) : The same analysis as section 7.3.3.1 will be performed for the Cohort 5~7

7.3.4 Disposition of Subjects

7.3.4.1 Cohort 1~2

Analysis Set: All Subjects Who Received Study Drug
Analysis
Variable(s) : Study Completion Status

	[Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]
Reason for Discontinuation of Study Visits	[Adverse Event, Death, Lost to Follow-up, Pregnancy, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s) : (1) Disposition of Subjects

Frequency distributions will be provided by group and overall. When calculating percentages for the reasons for discontinuation, the total number of subjects who did not complete all planned study visits will be used as the denominator.

7.3.4.2 Cohort S1~S2

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.4.1 will be performed for the Cohort S1~S2

7.3.4.3 Cohort 3

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.4.1 will be performed for the Cohort 3

7.3.4.4 Cohort 4

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.4.1 will be performed for the Cohort 4

7.3.4.5 Cohort 5~7

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.4.1 will be performed for the Cohort 5~7

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Cohort 1~2

Analysis Set:	All Subjects Who Received Study Drug	
Analysis Variable(s) :	Significant Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]
Analytical Method(s) :	(1) Protocol Deviations Frequency distribution will be provided by group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.	

Cohort S1~S2

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.1 "Cohort 1~2" will be performed for the Cohort S1~S2

Cohort 3

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	

The same analysis as section 7.3.5.1 "Cohort 1~2" will be performed for the Cohort 3

Cohort 4

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.1 "Cohort 1~2" will be performed for the Cohort 4

Cohort 5~7

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.1 "Cohort 1~2" will be performed for the Cohort 5~7

7.3.5.2 Analysis Sets

<u>*Cohort 1~2*</u>

Analysis Set:	All Subjects Who Received Study Drug	
Analysis Variable(s) :	Handling of Subjects	[Categories are based on the specifications in Subject Evaluability List]
	Analysis Sets	
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]
Analytical Method(s) :	(1) Subjects Excluded from Analysis Sets (2) Analysis Sets Frequency distributions will be provided by group and overall. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.	

<u>*Cohort S1~S2*</u>

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort 1~2" will be performed for the Cohort S1~S2

<u>*Cohort 3*</u>

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort 1~2" will be performed for the Cohort 3

Cohort 4

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort 1~2" will be performed for the Cohort 4

Cohort 5~7

Analysis Set:	All Subjects Who Received Study Drug	
Analysis Variable(s) :	Handling of Subjects	[Categories are based on the specifications in Subject Evaluability List]
	Analysis Sets	
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]
	Pharmacodynamic Analysis Set	[Included]
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort 1~2" will be performed for the Cohort 5~7	

7.4 Demographic and Other Baseline Characteristics

7.4.1 Cohort 1~2

Analysis Set:	Safety Analysis Set Pharmacokinetic Analysis Set	
Analysis Variable(s) :	Age (years)	
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg)	
	BMI (kg/m^2)	
	Smoking Classification	[Never, Current, Former]

	Alcohol Classification	[Daily, A Few Times Per Week, A Few Times Per Month, No]
	Caffeine Classification	[Yes, No]

Analytical Method(s) : (1) Summary of Demographics and Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by group and overall.

7.4.2 Cohort S1~S2

Analysis Set: Safety Analysis Set
Pharmacokinetic Analysis Set

Analytical Method(s) : The same analysis as section 7.4.1 will be performed for the Cohort S1~S2

7.4.3 Cohort 3

Analysis Set: Safety Analysis Set
Pharmacokinetic Analysis Set

Analytical Method(s) : The same analysis as section 7.4.1 will be performed for the Cohort 3

7.4.4 Cohort 4

Analysis Set: Safety Analysis Set
Pharmacokinetic Analysis Set

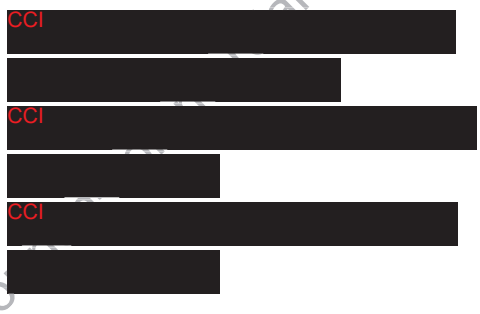
Analytical Method(s) : The same analysis as section 7.4.1 will be performed for the Cohort 4

7.4.5 Cohort 5~7

Analysis Set:	Safety Analysis Set	
	Pharmacokinetic Analysis Set	
	Pharmacodynamic Analysis Set	
Analysis Variable(s) :	Age (years)	[Min<= - <65, 65<= - <=Max]
	Gender	[Male, Female]

Height (cm)	
Weight (kg)	
BMI (kg/m^2)	
Smoking Classification	[Never, Current, Former]
Alcohol Classification	[Daily, A Few Times Per Week, A Few Times Per Month, No]
Caffeine Classification	[Yes, No]
MWT (sleep latency)	
ESS	

Age of onset (year)	
Period for diagnosis (year)	



Analytical Method(s) : (1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by group and overall.

7.5 Medical History and Concurrent Medical Conditions

7.5.1 Cohort 5~7

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medical History

Concurrent Medical Conditions

Analytical Method(s) :
(1) Medical History by System Organ Class and Preferred Term
(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided by group and overall. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

7.6.1 Cohort 5~7

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medication History
Concomitant Medications

Analytical Method(s) :
(1) Medication History by Preferred Medication Name
(2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name
(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline by Preferred Medication Name
(4) Concomitant Medications That Started After Baseline by Preferred Medication Name
(5) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided by group and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several

medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

7.7.1 Cohort 1~2

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Number of Times the Study Drug was Taken	[1, 2, 3]
Analytical Method(s) :	(1) Study Drug Exposure Frequency distributions will be provided by group.	

7.7.2 Cohort 5~7

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Number of Times the Study Drug was Taken	[1, 2]
Analytical Method(s) :	(1) Study Drug Exposure Frequency distributions will be provided by group.	

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results will not be used for hypothesis testing and estimations.

For plasma and CSF concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma/CSF Concentrations

<u>*Cohort 1~2*</u>

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II)

Visit: Predose; 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 9 Hours Postdose;
0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 10 and 15 Hours after End of Infusion
(10 Hours after End of Infusion is excluded for dose level 1 and 2 in Cohort 1~2)

Analytical Method(s): The following summaries will be provided. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit by Dose Level
Descriptive statistics will be provided by visit by dose level.

(2) Case Plot of Plasma Concentrations
Plots over time for each subject will be presented by dose level. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each analysis variable by dose level. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations
Mean will be plotted for each analysis variable by dose level. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

<u>*Cohort S1~S2*</u>

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II)

Analytical Method(s) : The following summaries will be provided. Subjects administered placebo will be excluded from the analysis. The definition of the visit is the same as section 7.9.1.1 "Cohort 1~2".

(1) Summary of Plasma Concentrations by Visit by Dose Level
Descriptive statistics will be provided by visit by dose level.

(2) Case Plot of Plasma Concentrations
Plots over time for each subject will be presented by dose level. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each analysis variable by dose level. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations
Mean will be plotted for each analysis variable by dose level. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

(5) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each dose level by each analysis variable, including the data of Cohort 1~2. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(6) Mean Plot of Plasma Concentrations
Mean will be plotted for each dose level by each analysis variable, including the data of Cohort 1~2. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

Cohort 3

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s) : Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II)

Analytical Method(s) : The following summaries will be provided. Subjects administered placebo will be excluded from the analysis. The definition of the visit is the same as section 7.9.1.1 "Cohort 1~2".

(1) Summary of Plasma Concentrations by Visit
Descriptive statistics will be provided by visit.

(2) Case Plot of Plasma Concentrations
Plots over time for each subject will be presented. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations
Mean will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

(5) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each dose level by each analysis variable, including the data of Cohort 1~2. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(6) Mean Plot of Plasma Concentrations
Mean will be plotted for each dose level by each analysis variable, including the data of Cohort 1~2. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

Cohort 4

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II)
CSF Concentrations of TAK-925 and Its Metabolites (M-I and M-II)

Visit: Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II)

Predose; 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 9 Hours Postdose;
0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 10 and 15 Hours after End of Infusion

CSF Concentrations of TAK-925 and Its Metabolites (M-I and M-II)
6 Hours Postdose

Analytical Method(s):

The following (1) ~ (6) summaries will be provided for the plasma concentrations of TAK-925 and its metabolites (M-I and M-II).
The following (1) summary will be provided for the CSF concentrations of TAK-925 and its metabolites (M-I and M-II).

(1) Summary of Plasma Concentrations by Visit
Descriptive statistics will be provided by visit.

(2) Case Plot of Plasma Concentrations
Plots over time for each subject will be presented. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations
Mean will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

(5) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each dose level by each analysis variable, including the data of Cohort 1~2. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(6) Mean Plot of Plasma Concentrations
Mean will be plotted for each dose level by each analysis variable, including the data of Cohort 1~2. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

Cohort 5~7

Analysis Set:	Pharmacokinetic Analysis Set
Analysis Variable(s) :	Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II)
Visit:	Predose; 1, 2, 4, 6 and 9 Hours Postdose; 0.17, 0.5, and 2 Hours after End of Infusion; Bedtime; Wake up time; 15 Hours after End of Infusion
Analytical Method(s) :	The following summaries will be provided. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit by Dose Level
Descriptive statistics will be provided by visit by dose level.

(2) Case Plot of Plasma Concentrations
Plots over time for each subject will be presented by dose level. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each analysis variable by dose level. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations
Mean will be plotted for each analysis variable by dose level. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

(5) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each dose level by each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(6) Mean Plot of Plasma Concentrations
Mean will be plotted for each dose level by each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

7.9.1.2 Pharmacokinetic Parameters

Cohort 1~2

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic Parameters of TAK-925 and Its Metabolites (M-I and M-II)

AUClast	AUCinf	Cmax
Ceoi	tmax	t1/2z
Vss (for TAK-925)	Vz (for TAK-925)	CL (for TAK-925)
AUCinf D (for TAK-925)	Cmax D (for TAK-925)	AUC24
MR (for M-I and M-II)		

Analytical Method(s): The following (1) summary will be provided for each analysis variables by dose level. The following (2) summary will be provided for AUCinf D and Cmax D. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters
For AUClast, AUCinf, AUC24, Cmax and Ceoi, descriptive statistics, geometric mean, and CV will be provided. For tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Scatter Plot for each Analysis Variables and Dose Level, including the data of Cohort S1 and S2
Scatter plot for each analysis variables and dose Level, including the data of Cohort S1 and S2 will be provided.

Cohort S1~S2

Analysis Set: Pharmacokinetic Analysis Set

Analytical Method(s): The same analysis as section 7.9.1.2 "Cohort 1~2" (1) will be conducted for the Cohort S1~S2.

Cohort 3

Analysis Set: Pharmacokinetic Analysis Set

Analytical Method(s): The same analysis as section 7.9.1.2 "Cohort 1~2" (1) will be conducted for the Cohort 3.

Cohort 4

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s) : Pharmacokinetic and CSF Parameters of TAK-925 and Its Metabolites (M-I and M-II)

AUClast	AUCinf	Cmax
Ceoi	tmax	t1/2z
Vss (for TAK-925)	Vz (for TAK-925)	CL (for TAK-925)
R CSF/Plasma,SS	AUCinf D (for TAK-925)	Cmax D (for TAK-925)
AUC24	MR (for M-I and M-II)	

Analytical Method(s) : The following summary will be provided by dose level.

(1) Summary of Pharmacokinetic Parameters
For AUClast, AUCinf, AUC24, Cmax and Ceoi, descriptive statistics, geometric mean, and CV will be provided. For tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

Cohort 5~7

Analysis Set: Pharmacokinetic Analysis Set

Analytical Method(s): The same analysis as section 7.9.1.2 "Cohort 1~2" (1) will be conducted for the Cohort 5~7.

7.9.1.3 Urine Pharmacokinetic Parameter

Cohort 1~2

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s) :	Urine Pharmacokinetic Parameters of TAK-925 and its metabolites (M-I and M-II) Ae24 fe24 CL R
Analytical Method(s) :	The following summary will be provided by dose level. Subjects administered placebo will be excluded from the analysis. (2) Summary of Urine Pharmacokinetic Parameter Descriptive statistics and CV will be provided.

Cohort S1~S2

Analysis Set:	Pharmacokinetic Analysis Set
Analytical Method(s):	The same analysis as section 7.9.1.3 "Cohort 1~2" will be conducted for the Cohort S1~S2.

Cohort 3

Analysis Set:	Pharmacokinetic Analysis Set
Analytical Method(s):	The same analysis as section 7.9.1.3 "Cohort 1~2" will be conducted for the Cohort 3.

Cohort 4

Analysis Set:	Pharmacokinetic Analysis Set
Analytical Method(s):	The same analysis as section 7.9.1.3 "Cohort 1~2" will be conducted for the Cohort 4.

7.9.2 Pharmacodynamic Analysis

7.9.2.1 Average Sleep Latency in MWT/Sleep Related Parameters in MWT

<u>*Cohort 5~7*</u>

Analysis Set:	Pharmacodynamic Analysis Set
Analysis Variable(s):	Average Sleep Latency in MWT, CCI [redacted]
Visit:	CCI [redacted]: 10 : 00, 12 : 00, 14 : 00, 16 : 00
Analytical Method(s):	The following summaries will be provided. (1) For the average sleep latency in MWT, descriptive statistics for the observed values will be provided by dose level. An analysis of variance (ANOVA) for crossover design with the observed value as a response, the dose level, the group and the period as factors, the subject as a random effect will be conducted. Least square (LS) means, the standard errors, and the two-sided 90% and 95% confidence intervals will be provided for each dose level. The difference in the LS means between each dose level of TAK-925 and the placebo (each dose level of TAK-925 - the placebo), the standard error of the difference, and the two-sided confidence intervals and p-value will be provided. Bayesian posterior probabilities that the mean differences are greater than the values (3, 4, 5 and 6 minutes) will be provided based on the Bayesian posterior distributions for the mean differences between each dose level of TAK-925 and the placebo (each dose level of TAK-925 - the placebo). (2) For analysis variables other than the average sleep latency in MWT, descriptive statistics of the observed values will be provided for each dose level by visit. An ANOVA for crossover design with the observed value as a response, the dose level, the group and the period as factors, the subject as a random effect will be conducted by visit. LS means, the standard errors, and the two-sided 90% and 95% confidence intervals will be provided for each dose level by visit. The difference in the LS means between each dose level of TAK-925 and the placebo (each dose

level of TAK-925 - the placebo), the standard error of the difference, and the two-sided confidence intervals and p-value will be provided for each dose level by visit.

7.9.2.2 CCI

CCI

[redacted]

7.9.2.3 CCI

CCI

[redacted]

CCI [redacted]

7.9.2.4 CCI [redacted]

CCI [redacted]

7.10 Other Outcomes

7.10.1 Scatter Plot for PK Concentration and Change from Time-matched Baseline in Vital Signs Parameters

7.10.1.1 Cohort1~2, S1~S2

Analysis Set:	Pharmacokinetic Analysis Set
Analysis Variable(s):	Plasma Concentrations of TAK-925 Change from time-matched baseline in Pulse Rate, Systolic Blood Pressure in Sitting, and Diastolic Blood Pressure in Sitting
Visit:	Predose; 0.5, 1, 1.5, 2, 3, 4, 6, 8, 9, 10, 11, 12 and 24 Hours Postdose
Analytical Method(s):	The following summary will be provided. (1) Scatter Plot for PK Concentration and Change from Time-matched Baseline in Vital Signs Parameters

Scatter plot for PK concentrations of TAK-925 and changes from time-matched baseline in vital signs parameters listed above will be provided with a fitted loess curve and 90% confidence interval.

Change from time-matched baseline in each analysis variable is defined as below.

Cohort 1~2

The observed value of the each analysis variable at above visit in Placebo administration period subtracted from the observed value of the each analysis variable at the same visit in TAK-925 administration period. If a subject has no observed value at a Placebo administration period or all TAK-925 administration period, the change from time-matched baseline at the visit will be treated as missing. If a subject has three observed values at the same visit (i.e., two TAK-925 administration periods and one Placebo administration period), two changes from time-matched baseline will be calculated at the visit for the subject.

Cohort S1~ S2

Refer to section 7.1.1.

7.10.1.2 Cohort 5~7

Analysis Set:	Pharmacokinetic Analysis Set
Visit:	Predose; 1, 2, 4, 6, 9, 11 and 24 Hours Postdose
Analytical Method(s):	The same analysis as section 7.10.1.1 will be conducted for the cohort 5~7. Time-matched baseline in each analysis variable is defined same as cohort 1~2 in section 7.10.1.1.

7.11 Safety Analysis

In this study, safety will be evaluated as the primary endpoint.

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Cohort 1~2

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Relationship to Study Drug	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]
Analytical Method(s) :	The following summaries will be provided by dose level.	

(1) Overview of Treatment-Emergent Adverse Events
   1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
   3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
   5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
   7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
   8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below. Percentages for each dose level will be based on the number of subjects who were treated by that dose level in the safety analysis set.

Number of subjects

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2) , 3) , and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

Cohort S1~S2

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.1.1 "Cohort 1~2" will be performed for the Cohort S1~S2.

Cohort 3

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.1.1 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.1.1 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set: Safety Analysis Set

Analytical Method(s) :

The same analysis as section 7.11.1.1 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.1.2 Displays of Treatment-Emergent Adverse events

Cohort 1~2

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
Analytical Method(s) :	The following summaries will be provided using frequency distribution by dose level. TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only. (1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (2) Treatment-Emergent Adverse Events by System Organ Class (3) Treatment-Emergent Adverse Events by Preferred Term (4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term (7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	

The frequency distribution will be provided according to the rules below. Percentages for each dose level will be based on the number of subjects who were treated by that dose level in the safety analysis set.

Number of subjects

- Summary tables other than (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.
- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity.

Cohort S1~S2

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort 1~2" will be performed for the Cohort S1~S2.

Cohort 3

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis Variable(s) : PTE
Analytical Method(s) : The following summaries will be provided using frequency distribution. PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term
(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Cohort 1~2

Analysis Set: Safety Analysis Set
Analysis Variable(s) : Hematology

CCI

Serum Chemistry

CCI

Visit: Predose, Day 2, Day7
(Data obtained at Day -1 will be used as the "Predose" visit)

Analytical Method(s) : The following summaries will be provided by dose level.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Laboratory Test Results
Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

Cohort S1~S2

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.2.1 "Cohort 1~2" will be performed for the Cohort S1~S2.

Cohort 3

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.2.1 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.2.1 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set:	Safety Analysis Set
Visit:	Predose, 1 day Postdose (For the period 1, data obtained at Day -1 will be used as the "Predose" visit and data obtained at Day 2 will be used as the "1 day Postdose" visit. For the period 2, data obtained at Day 3 will be used as the "Predose" visit and data obtained at Day 4 will be used as the "1 day Postdose" visit.)
Analytical Method(s) :	The same analysis as section 7.11.2.1 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.2.2 Urinalysis

Cohort 1~2

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Specific Gravity

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[redacted]

Visit: Predose, Day 2, Day 7
(Data obtained at Day -1 will be used as the "Predose" visit)

Analytical Method(s) : For specific gravity, summaries (1) , (2) and (4) will be provided by dose level.
For Microscopy (RBC, WBC, Squamous Epithelial Cell), summary (3) will be provided by dose level.
For each variable other than specific gravity and Microscopy, summaries (3) and (4) will be provided by dose level.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Urine Laboratory Test Results
Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.

(4) Summary of Shifts of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided. The laboratory value for specific gravity will be classified as "Low", "Normal" or "High" relative to the normal reference range. If applicable, the laboratory value for each urine laboratory test other than specific gravity will be classified as "Normal" or "Abnormal" relative to the normal reference range. The shift tables will be based on these classifications.

Cohort S1~S2

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort 1~2" will be performed for the Cohort S1~S2

Cohort 3

Analysis Set: Safety Analysis Set
Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort 1~2" will be performed for the Cohort 3

Cohort 4

Analysis Set: Safety Analysis Set
Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort 1~2" will be performed for the Cohort 4

Cohort 5~7

Analysis Set: Safety Analysis Set
Visit: Predose, 1 day Postdose
(For the period 1, data obtained at Day -1 will be used as the "Predose" visit and data obtained at Day 2 will be used as the "1 day Postdose" visit. For the period 2, data obtained at Day 3 will be used as the "Predose" visit and data obtained at Day 4 will be used as the "1 day Postdose" visit.)
Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort 1~2" will be performed for the Cohort 5~7

7.11.3 Vital Signs and Weight

7.11.3.1 Body Temperature, Respiratory Rate, Systolic and Diastolic Blood Pressure in Sitting Position, Pulse Rate and Weight

Cohort 1~2

Analysis Set: Safety Analysis Set

Analysis Variable(s) :	Temperature Systolic Blood Pressure in Sitting Diastolic Blood Pressure in Sitting Respiration Rate Pulse Rate Weight
Visit:	Pulse Rate, Systolic Blood Pressure in Sitting, Diastolic Blood Pressure in Sitting: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 Hours Postdose, Day 7 Respiration Rate, Temperature : Predose, 5 Hours Postdose, Day 2 Weight: Predose, Day 2, Day 7 (Data obtained at Day -1 will be used as the "Predose" visit)
Analytical Method(s) :	The following summaries will be provided by dose level. (1) Summary of Vital Signs Parameters and Change from Baseline by Visit Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit. (2) Case Plots of Vital Signs Parameters and Weight Plots over time for each subject will be presented.

Cohort S1~S2

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Temperature Systolic Blood Pressure in Sitting Diastolic Blood Pressure in Sitting Respiration Rate Pulse Rate Weight
Visit:	Pulse Rate, Systolic Blood Pressure in Sitting, Diastolic Blood Pressure in Sitting : -24, -23.75, -23.5, -23.25, -23, -22.5, -22, -21.5, -21, -20.5, -20, -19, -18, -17, -16, -15, -14, -13, and -12 Hours Predose, Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 Hours Postdose, Day 7

Respiration Rate, Temperature : Predose, 5 Hours Postdose, Day 2
Weight: Predose, Day 2, Day 7
(Data obtained at Day -1 will be used as the "Predose" visit)

Analytical Method(s) :

The following (1) ~ (3) summaries will be provided for Pulse Rate, Systolic Blood Pressure in Sitting, and Diastolic Blood Pressure in Sitting by dose level.

The following (4) summary will be provided for Pulse Rate, Systolic Blood Pressure in Sitting, and Diastolic Blood Pressure in Sitting.

The following (1), and (3) summaries will be provided for Respiration Rate, Temperature, and Weight by dose level.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Summary of Change from time-matched baseline by Visit
Descriptive statistics for Change from time-matched Baseline will be provided.

(3) Case Plots of Vital Signs Parameters and Weight
Plots over time for each subject will be presented.

(4) For each post-treatment time point, change from time-matched baseline in each analysis variable will be analyzed using a Mixed Effect Model for longitudinal data with change from time-matched baseline in each analysis variable as dependent variable, and dose level, visit, and dose level-by-visit interaction as independent variables. LS means, the standard errors and the two-sided 90% and 95% confidence intervals will be provided for each dose level. The differences in the LS means between each TAK-925 group and the placebo group (each TAK-925 group – the placebo group) and the two-sided confidence intervals will be provided.

Cohort 3

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.3.1 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.3.1 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Temperature Systolic Blood Pressure in Sitting Diastolic Blood Pressure in Sitting Respiration Rate Pulse Rate
Visit:	Pulse Rate, Systolic Blood Pressure in Sitting, Diastolic Blood Pressure in Sitting: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 Hours Postdose Respiration Rate, Temperature : Predose, 5 hours Postdose, 1 day Postdose (For the period 1, data obtained at Day 2 will be used as the "1 day Postdose" visit. For the period 2, data obtained at Day 4 will be used as the "1 day Postdose" visit.)
Analytical Method(s) :	The same analysis as section 7.11.3.1 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.3.2 Systolic and Diastolic Blood Pressure in Standing Position

Cohort 1~2

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Systolic Blood Pressure (1 Minute after Standing) Diastolic Blood Pressure (1 Minute after Standing)

Systolic Blood Pressure (5 Minutes after Standing)
Diastolic Blood Pressure (5 Minutes after Standing)

Visit: 1, 2 and 4 Hours Postdose

Analytical Method(s) : The following summary will be provided by dose level.

(1) Summary of Systolic and Diastolic Blood Pressure in Standing Position

Descriptive statistics for observed values and changes from baseline (observed values of each analysis variable – observed values in sitting for each analysis variable) will be provided.

Cohort S1~S2

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.3.2 "Cohort 1~2" will be performed for the Cohort S1~S2.

Cohort 3

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.3.2 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.3.2 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set: Safety Analysis Set

Visit: 1 Hour Postdose

Analytical Method(s) : The same analysis as section 7.11.3.2 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.4 12-Lead ECGs

Cohort 1~2

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Heart Rate
RR Interval
PR Interval
QRS Interval
QT Interval
QTcF Interval
Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit: Predose, 2~9 Hours Postdose, Day 2
(Data obtained at Day -1 will be used as the "Predose" visit)

Analytical Method(s) : For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by dose level.
For 12-lead ECG interpretation, summary (3) will be provided by dose level.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of ECG Parameters
Plots over time for each subject will be presented.

(3) Summary of Shift of 12-lead ECG Interpretation
Shift table showing the number of subjects in each category at "Predose" visit and each postdose visit will be provided.

Cohort S1~S2

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.4 "Cohort 1~2" will be performed for the Cohort S1~S2.

Cohort 3

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.4 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.4 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set:	Safety Analysis Set
Visit:	Predose, 2~9 Hours Postdose, 1 day Postdose (For the period 1, data obtained at Day -1 will be used as the "Predose" visit and data obtained at Day 2 will be used as the "1 day Postdose" visit. For the period 2, data obtained at Day 2 will be used as the "Predose" visit and data obtained at Day 4 will be used as the "1 day Postdose" visit.)
Analytical Method(s) :	The same analysis as section 7.11.4 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

In this study, a sponsor's unblinded team will be organized. The sponsor's unblinded team must not directly be involved in the execution of the study at a study site or directly contact the site. After cohort 5, this team will review unblinded data on the safety, tolerability and pharmacodynamic effects (MWT) and available PK of TAK-925 obtained from cohort 5, and recommend a dose level for cohort 6 based on such data. After cohort 6, the dose and the number of subjects to be used in Cohort 7 will be recommended by the sponsor's unblinded team on the basis of safety, tolerability, pharmacodynamic effects (MWT) and available PK data of TAK-925 obtained from Cohorts 5 and 6.

7.13 Changes in the Statistical Analysis Plan

The changes from 1st version of the SAP were described in the Annex "Summary of Changes of TAK-925-1001 SAP".

8.0 REFERENCES

No reference.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-925-1001

A First-in-Human, Two-Part Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-925 in Healthy Adult and Elderly Volunteers and Patients with Narcolepsy

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

Version: 1st

Date: 14 February 2018

Prepared by:

PPD

[redacted]

Based on:

Protocol Version: Amendment1

Protocol Date: 22 January 2018

CCI

[redacted]

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

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LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
Ae	amount of drug excreted in urine
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
CL R	renal clearance
Cmax	maximum observed concentration
CRF	case report form
CSF	cerebrospinal fluid
ECG	electrocardiogram
ESS	epworth sleepiness scale
fe	fraction of administered dose of drug excreted in urine
γ-GTP	gamma-glutamyl transferase
KSS	karolinska sleepiness scale
LDH	lactate dehydrogenase
Lambda z	terminal disposition phase rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MWT	maintenance of wakefulness test
PD	pharmacodynamics
PK	pharmacokinetics
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
QTc	corrected QT
RBC	red blood cell
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
tmax	time of first occurrence of Cmax
t1/2z	half-life period
ULN	upper limit of normal
Vz	volume of distribution

WBC	white blood cell
WHO Drug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 Secondary Objectives

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

4.3 Additional Objectives

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[redacted]

4.4 Study Design

This study consists of two parts.

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

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

(1) Part 1

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

assess the safety, tolerability, and PK of TAK-925 including CSF-PK of TAK-925, 4 healthy adults will be enrolled as Cohort 4.

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

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

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

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

In Cohort 3, 8 healthy elderly subjects will be enrolled. Of these 8 subjects, six will be randomly assigned to the TAK-925 group and 2 to the placebo group. This cohort will be initiated after started with the dose of which the safety and tolerability has been established in healthy adults.

In Cohort 4, 4 healthy adults will be enrolled to evaluate the safety, tolerability and the CSF concentration of TAK-925 measured at one time point and the plasma concentration of TAK-

925. In Cohort 4, subjects, study sites and the sponsor will not be blinded. This cohort will be initiated after the safety and tolerability of the dose to be evaluated in Cohort 4 has been established in healthy adults.

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

(2) Part 2

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

In Cohorts 5 and 6, 4 subjects each will be enrolled, and TAK-925 or placebo will be intravenously infused for 9 hours on Day 1 and Day 3. Of 4 subjects in each cohort, 2 subjects each will be randomly assigned to one of the defined sequences (Groups I to L, TAK-925 may be given at one dose level in each cohort). A maximum of 12 patients with type 1narcolepsy will be enrolled in Cohort 7. Of a maximum of 12 patients, 6 each will be randomly assigned to Group M or Group N. The dose level to be used in Cohort 5 will be determined based on the safety, tolerability and PK data obtained from Part 1. After the safety, tolerability, PD effects (MWT) in Cohort 5 and available PK have been investigated, dosing in Cohort 6 will be started using another 4 new subjects. The same trial design as Cohort 5 will be used in Cohort 6. The dose level to be used in Cohort 6 will be discussed by the sponsor's unblinded team. The sponsor's unblinded team must not directly be involved in the execution of the study at a study site or directly contact the site. This team will review unblinded data on the safety, tolerability, PD effects (MWT) and available PK of TAK-925, and recommend a dose based on those data. The dose level to be used in Cohort 6 may be higher or lower than the one used in Cohort 5. Cohort 7 will be composed of up to 12 subjects. The dose and the number of subjects to be used in Cohort 7 will be recommended by the sponsor’s unblinded team on the basis of safety, tolerability, PD effects (MWT) obtained from Cohorts 5 and 6 and available PK data of TAK-925. The dose may be higher or lower than the doses used in Cohorts 5 and 6, or intermediate dose between these cohorts. See section 3.0 of protocol for the schedule of tests/observations /evaluations. Summary of Cohorts is shown in Table 4.a.

Table 4.a Summary of Cohorts

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

1) In Part 1, the same subjects are used for Dose Levels 1, 3 and 5, and similaly, the same subjects are used for Dose Levels 2, 4 and 6. In Part 2, different subjects are used in each Cohort. The target plasma level totake into consideration as a standard is as follows. Dose Level 1: 20 ng/mL, Dose Level 2: 40 ng/mL, Dose Level 3: 80 ng/mL, Dose Level 4: 150 ng/mL, Dose Level 5: 300 ng/mL, Dose Level 6: 600 ng/mL. The steady-state concentration (Css) of TAK-925 is estimated to be 21.3 ng/mL when 7 mg is administered as Dose level 1.

2) In Cohort 1 Dose Level 1, 2 subjects are enrolled and each subject is assigned randomly to either the TAK-925 or placebo group to evaluate the safety, tolerability and pharmacokineticsof TAK-925. Additional 6 subjects are enrolled, and 5 subjects and 1 subject are assigned randomly to the TAK-925 and placebo groups, respectively, to evaluate the safety and tolerability of TAK-925.
3) In the event that further investigation of the safety, tolerability and pharmacokinetics of TAK-025 is needed after completion of Cohorts 1 and 2, up to 4 additional cohorts that include 32 healthy adults can be commenced without amendment of the protocol.
4) In Part 2, the dose to be used in Cohort 5 should be equal or less than one-third of the maximum dose of TAK-925 whose safety and tolerability were already confirmed.

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

→

Dose Level 2	
E	TAK-925 TBD
F	TAK-925 TBD
G	TAK-925 TBD
H	Placebo

→

Dose Level 3	
A	TAK-925 TBD
B	TAK-925 TBD
C	Placebo
D	TAK-925 TBD

→

Dose Level 4	
E	TAK-925 TBD
F	TAK-925 TBD
G	Placebo
H	TAK-925 TBD

→

Dose Level 5	
A	TAK-925 TBD
B	Placebo
C	TAK-925 TBD
D	TAK-925 TBD

→

Dose Level 6	
E	TAK-925 TBD
F	Placebo
G	TAK-925 TBD
H	TAK-925 TBD

TBD: To be determined

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

Figure 4.a Summary of Cohort 1 and Cohort 2

TAK-925 TBD
Placebo

1) Double-blind study. Cohort 3 consists of 8 subjects: 6 subjects in the TAK-925 group and 2 subjects in the placebo group.

Figure 4.b Summary of Cohort 3

TAK-925 TBD
Placebo

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

Figure 4.c Summary of Cohort S1~S4 (Healthy Adult Supplement Cohorts)

1. Cohort 5-7 (Patients with narcolepsy)[1]

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

Cohort transfer →

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

Cohort transfer →

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

1) Double-blind (the sponsor is unblinded), 2x2 crossover study.

2) Cohorts 5 and 6 consist of 4 subjects. Two subjects are assigned to each group (Groups I-L). Cohort 7 consists of a maximum of 12 subjects, and each group (Groups M and N) consists of a maximum 6 subjects.

3) Each Cohort will be investigated in different subjects.

Figure 4.d Summary of Cohort 5~7

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoint

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

5.1.2 Secondary Endpoints

- The average sleep latency in the MWT

5.1.3 Exploratory Endpoints

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[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

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

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

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

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

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after the start of study drug
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV) (%): Standard deviation / mean * 100
- QTcF interval (msec): QT interval (msec) / (RR interval (sec))$^{0.33}$ (rounded to the nearest whole number)
- Dose level
  - Cohort 1~2
    - ✧ Placebo
    - ✧ TAK-925 xx mg
  - Cohort 3
    - ✧ Placebo
    - ✧ TAK-925 xx mg
  - Cohort 4
    - ✧ TAK-925 xx mg
  - Cohort 5~7
    - ✧ Placebo
    - ✧ TAK-925 xx mg
- Group
  - Part1 (Healthy Adults or The Healthy Elderly)
    - ✧ Cohort 1 and Cohort 2: See Figure 4.a
    - ✧ Cohort 3: See Figure 4.b
    - ✧ Cohort 4: TAK-925
    - ✧ Cohort S1~S4: See Figure 4.c
  - Part2 (Patients with Narcolepsy)
    - ✧ Cohort 5~7: See Figure 4.d

7.2 Analysis Sets

- Safety analysis set: All subjects who received at least one dose of study drug
- Pharmacokinetic analysis set: All subjects who received at least one dose of study drug and whose plasma or CSF concentration can be measured at least once or whose cumulative urinary excretion can be calculated.
- Pharmacodynamic analysis set: All subjects who received at least one dose of study drug.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s) :	Date First Subject Signed Informed Consent Form Date of Last Subject's Last Visit/Contact MedDRA Version SAS Version Used for Creating the Datasets
Analytical Method(s) :	(1) Study Information Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:	All Subjects Who Did Not Receive Study Drug	
Analysis Variable(s) :	Age (years)	
	Gender	[Male, Female]
Analytical Method(s) :	(1) Screen Failures Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.	

7.3.3 Subject Eligibility

7.3.3.1 Cohort 1~2

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s) :	Study Drug Administration Status	[Treated, Not Treated]
	Primary Reason for Subject Not Being Treated	[Adverse Event, Death, Lost to Follow-up, Pregnancy, Protocol Deviation, Sample Size Sufficient, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical
Method(s) : (1) Study Drug Administration Status
Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being treated, the total number of not treated subjects will be used as the denominator.

7.3.3.2 Cohort 3

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analytical
Method(s) : The same analysis as section 7.3.3.1 will be performed for the Cohort 3

7.3.3.3 Cohort 4

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analytical
Method(s) : The same analysis as section 7.3.3.1 will be performed for the Cohort 4

7.3.3.4 Cohort 5~7

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analytical
Method(s) : The same analysis as section 7.3.3.1 will be performed for the Cohort 5~7

7.3.4 Disposition of Subjects

7.3.4.1 Cohort 1~2

Analysis Set: All Subjects Who Received Study Drug
Analysis
Variable(s) : Study Completion Status [Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]
Reason for Discontinuation of Study Visits [Adverse Event, Death, Lost to Follow-up, Pregnancy, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s) : (1) Disposition of Subjects

Frequency distributions will be provided by group and overall. When calculating percentages for the reasons for discontinuation, the total number of subjects who did not complete all planned study visits will be used as the denominator.

7.3.4.2 Cohort 3

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.4.1 will be performed for the Cohort 3

7.3.4.3 Cohort 4

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.4.1 will be performed for the Cohort 4

7.3.4.4 Cohort 5~7

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.4.1 will be performed for the Cohort 5~7

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Cohort 1~2

Analysis Set: All Subjects Who Received Study Drug

Analysis Variable(s) : Significant Protocol Deviation [Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s) :	(1) Protocol Deviations Frequency distribution will be provided by group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

Cohort 3

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.1 "Cohort 1~2" will be performed for the Cohort 3

Cohort 4

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.1 "Cohort 1~2" will be performed for the Cohort 4

Cohort 5~7

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.1 "Cohort 1~2" will be performed for the Cohort 5~7

7.3.5.2 Analysis Sets

<u>*Cohort 1~2*</u>

Analysis Set:	All Subjects Who Received Study Drug	
Analysis Variable(s) :	Handling of Subjects	[Categories are based on the specifications in Subject Evaluability List]
	Analysis Sets	
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]
Analytical Method(s) :	(1) Subjects Excluded from Analysis Sets (2) Analysis Sets Frequency distributions will be provided by group and overall. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.	

<u>*Cohort 3*</u>

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort 1~2" will be performed for the Cohort 3

<u>*Cohort 4*</u>

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort 1~2" will be performed for the Cohort 4

Cohort 5~7

Analysis Set:	All Subjects Who Received Study Drug	
Analysis Variable(s) :	Handling of Subjects	[Categories are based on the specifications in Subject Evaluability List]
	Analysis Sets	
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]
	Pharmacodynamic Analysis Set	[Included]
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort 1~2" will be performed for the Cohort 5~7	

7.4 Demographic and Other Baseline Characteristics

7.4.1 Cohort 1~2

Analysis Set:	Safety Analysis Set Pharmacokinetic Analysis Set	
Analysis Variable(s) :	Age (years)	
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg)	
	BMI (kg/m^2)	
	Smoking Classification	[Never, Current, Former]
	Alcohol Classification	[Daily, A Few Times Per Week, A Few Times Per Month, No]
	Caffeine Classification	[Yes, No]
Analytical Method(s) :	(1) Summary of Demographics and Baseline Characteristics Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by group and overall.	

7.4.2 Cohort 3

Analysis Set:	Safety Analysis Set Pharmacokinetic Analysis Set
Analytical Method(s) :	The same analysis as section 7.4.1 will be performed for the Cohort 3

7.4.3 Cohort 4

Analysis Set:	Safety Analysis Set Pharmacokinetic Analysis Set
Analytical Method(s) :	The same analysis as section 7.4.1 will be performed for the Cohort 4

7.4.4 Cohort 5~7

Analysis Set:	Safety Analysis Set Pharmacokinetic Analysis Set Pharmacodynamic Analysis Set	
Analysis Variable(s) :	Age (years)	[Min<= - <65, 65<= - <=Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg)	
	BMI (kg/m^2)	
	Smoking Classification	[Never, Current, Former]
	Alcohol Classification	[Daily, A Few Times Per Week, A Few Times Per Month, No]
	Caffeine Classification	[Yes, No]
	MWT (sleep latency)	
	ESS	
	CCI [redacted]	
	CCI [redacted]	
	[redacted]	
	CCI [redacted]	
	CCI [redacted]	
	CCI [redacted]	

CCI
CCI
Age of onset
Period for diagnosis
CCI
CCI
CCI

Analytical Method(s) :
(1) Summary of Demographics and Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by group and overall.

7.5 Medical History and Concurrent Medical Conditions

7.5.1 Cohort 5~7

Analysis Set: Safety Analysis Set

Analysis Variable(s) :
Medical History
Concurrent Medical Conditions

Analytical Method(s) :
(1) Medical History by System Organ Class and Preferred Term
(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided by group and overall. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.
A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

7.6.1 Cohort 5~7

Analysis Set: Safety Analysis Set

Analysis Variable(s): Medication History
Concomitant Medications

Analytical Method(s):
(1) Medication History by Preferred Medication Name
(2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name
(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline by Preferred Medication Name
(4) Concomitant Medications That Started After Baseline by Preferred Medication Name
(5) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided by group and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

7.7.1 Cohort 1~2

Analysis Set: Safety Analysis Set

Analysis Variable(s): Number of Times the Study Drug was Taken [1, 2, 3]

Analytical Method(s):
(1) Study Drug Exposure

Frequency distributions will be provided by group.

7.7.2 Cohort 5~7

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Number of Times the Study Drug was Taken [1, 2]
Analytical Method(s) :	(1) Study Drug Exposure Frequency distributions will be provided by group.

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results will not be used for hypothesis testing and estimations.

For plasma and CSF concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma/CSF Concentrations

<u>*Cohort 1~2*</u>

Analysis Set:	Pharmacokinetic Analysis Set
Analysis Variable(s) :	Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II)
Visit:	Predose; 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 9 Hours Postdose; 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 10 and 15 Hours after End of Infusion (10 Hours after End of Infusion is excluded for dose level 1 and 2 in Cohort 1~2)
Analytical Method(s) :	The following summaries will be provided by dose level. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit
Descriptive statistics will be provided by visit.

(2) Case Plot of Plasma Concentrations
Plots over time for each subject will be presented. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations
Mean will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

(5) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for dose level. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(6) Mean Plot of Plasma Concentrations
Mean will be plotted for dose level. Visit will be plotted on the

horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

Cohort 3

Analysis Set:	Pharmacokinetic Analysis Set
Analytical Method(s):	The same analysis as section 7.9.1.1 "Cohort 1~2" will be conducted for the Cohort 3. For the results of (3) ~ (6) will be presented with the results of the cohort 1~2.

Cohort 4

Analysis Set:	Pharmacokinetic Analysis Set
Analysis Variable(s):	Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II) CSF Concentrations of TAK-925 and Its Metabolites (M-I and M-II)
Visit:	Plasma Concentrations of TAK-925 and Its Metabolites (M-I and M-II) Predose; 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 9 Hours Postdose; 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 10 and 15 Hours after End of Infusion CSF Concentrations of TAK-925 and Its Metabolites (M-I and M-II) 6 Hours Postdose
Analytical Method(s):	(1) For the plasma concentrations of TAK-925 and its metabolites (M-I and M-II), the same analysis as section 7.9.1.1 "Cohort 1~2" will be conducted. (2) For the CSF concentrations of TAK-925 and its metabolites (M-I and M-II), the same analysis as section 7.9.1.1 "Cohort 1~2" (1) will be conducted.

Cohort 5~7

Analysis Set:	Pharmacokinetic Analysis Set
Visit:	Predose; 1, 2, 4, 6 and 9 Hours Postdose; 0.17, 0.5, and 2 Hours after End of Infusion; Bedtime; Wake up time; 15 Hours after End of Infusion

Analytical Method(s): The same analysis as section 7.9.1.1 "Cohort 1~2" will be conducted for the Cohort 5~7.

7.9.1.2 Pharmacokinetic Parameters

<u>*Cohort 1~2*</u>

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic Parameters of TAK-925 and Its Metabolites (M-I and M-II)

AUClast	AUCinf	Cmax
Ceoi	tmax	t1/2z
Lambda z	Vss (for TAK-925)	Vz (for TAK-925)
CL (for TAK-925)	AUCinf D	Cmax D

Analytical Method(s): The following summary will be provided by dose level. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters
For AUClast, AUCinf, Cmax and Ceoi, descriptive statistics, geometric mean, and CV will be provided. For tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

<u>*Cohort 3*</u>

Analysis Set: Pharmacokinetic Analysis Set

Analytical Method(s): The same analysis as section 7.9.1.2 "Cohort 1~2" will be conducted for the Cohort 3.

<u>*Cohort 4*</u>

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic and CSF Parameters of TAK-925 and Its Metabolites (M-I and M-II)

AUClast	AUCinf	Cmax
Ceoi	tmax	t1/2z
Lambda z	Vss (for TAK-925)	Vz (for TAK-925)
CL (for TAK-925)	R CSF/Plasma,SS	AUCinf D

Cmax D

Analytical Method(s) : The following summaries will be provided by dose level. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters
For AUClast, AUCinf, Cmax and Ceoi, descriptive statistics, geometric mean, and CV will be provided. For tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

Cohort 5~7

Analysis Set: Pharmacokinetic Analysis Set

Analytical Method(s): The same analysis as section 7.9.1.2 "Cohort 1~2" will be conducted for the Cohort 5~7.

7.9.1.3 Urine Pharmacokinetic Parameter

Cohort 1~2

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s) : Urine Pharmacokinetic Parameters of TAK-925 and its metabolites (M-I and M-II)

Ae24 fe24 CL R

Analytical Method(s) : The following summary will be provided by dose level. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Urine Pharmacokinetic Parameter
Descriptive statistics and CV will be provided.

Cohort 3

Analysis Set:	Pharmacokinetic Analysis Set
Analytical Method(s):	The same analysis as section 7.9.1.3 "Cohort 1~2" will be conducted for the Cohort 3.

Cohort 4

Analysis Set:	Pharmacokinetic Analysis Set
Analytical Method(s):	The same analysis as section 7.9.1.3 "Cohort 1~2" will be conducted for the Cohort 4.

7.9.2 Pharmacodynamic Analysis

7.9.2.1 Average Sleep Latency in MWT/Sleep Related Parameters in MWT

<u>Cohort 5~7</u>

Analysis Set:	Pharmacodynamic Analysis Set
Analysis Variable(s):	Average Sleep Latency in MWT, CCI [redacted]
Visit:	CCI [redacted]: 10 : 00, 12 : 00, 14 : 00, 16 : 00
Analytical Method(s):	The following summaries will be provided.

(1) For the average sleep latency in MWT, descriptive statistics for the observed values will be provided by dose level. An analysis of variance (ANOVA) for crossover design with the observed value as a response, the dose level, the group and the period as factors, the subject as a random effect will be conducted. Least square (LS) means, the standard errors, and the two-sided 90% and 95% confidence intervals will be provided for each dose level. The difference in the LS means between each dose level of TAK-925 and the placebo (each dose level of TAK-925 - the placebo), the standard error of the difference, and the two-sided confidence intervals and p-value will be provided. CCI [redacted]

(2) CCI [redacted]

CCI [redacted]

7.9.2.2 CCI [redacted]

CCI [redacted]

7.9.2.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

7.9.2.4 CCI [redacted]

CCI [redacted]

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

In this study, safety will be evaluated as the primary endpoint.

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Cohort 1~2

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Relationship to Study Drug	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]
Analytical Method(s) :	The following summaries will be provided by dose level.	

(1) Overview of Treatment-Emergent Adverse Events
   1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
   3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
   5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
   7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
   8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below. Percentages for each dose level will be based on the number of subjects who were treated by that dose level in the safety analysis set.

Number of subjects

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2) , 3) , and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

Cohort 3

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.1.1 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.1.1 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.1.1 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.1.2 Displays of Treatment-Emergent Adverse events

<u>*Cohort 1~2*</u>

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
Analytical Method(s) :	The following summaries will be provided using frequency distribution by dose level. TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only. (1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (2) Treatment-Emergent Adverse Events by System Organ Class (3) Treatment-Emergent Adverse Events by Preferred Term (4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term (7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term The frequency distribution will be provided according to the rules below. Percentages for each dose level will be based on the number of subjects who were treated by that dose level in the safety analysis set. <u>Number of subjects</u> • Summary tables other than (5) and (6)	

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity.

Cohort 3

Analysis Set: Safety Analysis Set
Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set: Safety Analysis Set
Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set: Safety Analysis Set
Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis Variable(s) : PTE
Analytical Method(s) : The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term
(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Cohort 1~2

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Hematology

CCI

[redacted]

Serum Chemistry

CCI

[redacted]

Visit: Predose, Day 2, Day7
(Data obtained at Day -1 will be used as the "Predose" visit)

Analytical Method(s) : The following summaries will be provided by dose level.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Laboratory Test Results
Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

Cohort 3

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.2.1 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.2.1 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set: Safety Analysis Set

Visit: Predose, 1 day Postdose
(For the period 1, data obtained at Day -1 will be used as the "Predose" visit and data obtained at Day 2 will be used as the "1 day Postdose" visit. For

the period 2, data obtained at Day 3 will be used as the "Predose" visit and data obtained at Day 4 will be used as the "1 day Postdose" visit.)

Analytical Method(s) : The same analysis as section 7.11.2.1 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.2.2 Urinalysis

Cohort 1~2

Analysis Set: Safety Analysis Set

Analysis Variable(s) : CCI

Visit: Predose, Day 2, Day 7
(Data obtained at Day -1 will be used as the "Predose" visit)

Analytical Method(s) : For specific gravity, summaries (1) , (2) and (4) will be provided by dose level.
For Microscopy (RBC, WBC, Squamous Epithelial Cell), summary (3) will be provided by dose level.

For each variable other than specific gravity and Microscopy, summaries (3) and (4) will be provided by dose level.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Urine Laboratory Test Results
Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.

(4) Summary of Shifts of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided. The laboratory value for specific gravity will be classified as "Low", "Normal" or "High" relative to the normal reference range. If applicable, the laboratory value for each urine laboratory test other than specific gravity will be classified as "Normal" or "Abnormal" relative to the normal reference range. The shift tables will be based on these classifications.

Cohort 3

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort 1~2" will be performed for the Cohort 3

Cohort 4

Analysis Set: Safety Analysis Set

Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort 1~2" will be performed for the Cohort 4

Cohort 5~7

Analysis Set: Safety Analysis Set

Visit:	Predose, 1 day Postdose (For the period 1, data obtained at Day -1 will be used as the "Predose" visit and data obtained at Day 2 will be used as the "1 day Postdose" visit. For the period 2, data obtained at Day 3 will be used as the "Predose" visit and data obtained at Day 4 will be used as the "1 day Postdose" visit.)
Analytical Method(s) :	The same analysis as section 7.11.2.2 "Cohort 1~2" will be performed for the Cohort 5~7

7.11.3 Vital Signs and Weight

7.11.3.1 Body Temperature, Respiratory Rate, Systolic and Diastolic Blood Pressure in Sitting Position, Pulse Rate and Weight

<u>*Cohort 1~2*</u>

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Temperature Systolic Blood Pressure Diastolic Blood Pressure Respiration Rate Pulse Rate Weight
Visit:	Pulse Rate, Systolic Blood Pressure, Diastolic Blood Pressure: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 Hours Postdose, Day 7 Respiration Rate, Temperature : Predose, 5 Hours Postdose, Day 2 Weight: Predose, Day 2, Day 7 (Data obtained at Day -1 will be used as the "Predose" visit)
Analytical Method(s) :	The following summaries will be provided by dose level. (1) Summary of Vital Signs Parameters and Change from Baseline by Visit Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit. (2) Case Plots of Vital Signs Parameters and Weight Plots over time for each subject will be presented.

Cohort 3

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.3.1 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.3.1 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Temperature Systolic Blood Pressure Diastolic Blood Pressure Respiration Rate Pulse Rate
Visit:	Pulse Rate, Systolic Blood Pressure, Diastolic Blood Pressure: Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 Hours Postdose Respiration Rate, Temperature : Predose, 5 hours Postdose, 1 day Postdose (For the period 1, data obtained at Day 2 will be used as the "1 day Postdose" visit. For the period 2, data obtained at Day 4 will be used as the "1 day Postdose" visit.)
Analytical Method(s) :	The same analysis as section 7.11.3.1 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.3.2 Systolic and Diastolic Blood Pressure in Standing Position

Cohort 1~2

Analysis Set:	Safety Analysis Set

Analysis Variable(s) :	Systolic Blood Pressure (1 minute after standing) Diastolic Blood Pressure (1 minute after standing) Systolic Blood Pressure (5 minutes after standing) Diastolic Blood Pressure (5 minutes after standing)
Visit:	1 Hour Postdose
Analytical Method(s) :	The following summary will be provided by dose level. (1) Summary of Systolic and Diastolic Blood Pressure in Standing Position Descriptive statistics for observed values will be provided.

Cohort 3

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.3.2 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.3.2 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.3.2 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.4 12-Lead ECGs

Cohort 1~2

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Heart Rate	
	RR Interval	
	PR Interval	
	QRS Interval	
	QT Interval	
	QTcF Interval	
	Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit:	Predose, 2~9 Hours Postdose, Day 2 (Data obtained at Day -1 will be used as the "Predose" visit)	
Analytical Method(s) :	For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by dose level. For 12-lead ECG interpretation, summary (3) will be provided by dose level. (1) Summary of ECG Parameters and Change from Baseline by Visit Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit. (2) Case Plots of ECG Parameters Plots over time for each subject will be presented. (3) Summary of Shift of 12-lead ECG Interpretation Shift table showing the number of subjects in each category at "Predose" visit and each postdose visit will be provided.	

Cohort 3

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.4 "Cohort 1~2" will be performed for the Cohort 3.

Cohort 4

Analysis Set:	Safety Analysis Set
Analytical Method(s) :	The same analysis as section 7.11.4 "Cohort 1~2" will be performed for the Cohort 4.

Cohort 5~7

Analysis Set:	Safety Analysis Set
Visit:	Predose, 2~9 Hours Postdose, 1 day Postdose (For the period 1, data obtained at Day -1 will be used as the "Predose" visit and data obtained at Day 2 will be used as the "1 day Postdose" visit. For the period 2, data obtained at Day 2 will be used as the "Predose" visit and data obtained at Day 4 will be used as the "1 day Postdose" visit.)
Analytical Method(s) :	The same analysis as section 7.11.4 "Cohort 1~2" will be performed for the Cohort 5~7.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

In this study, a sponsor's unblinded team will be organized. The sponsor's unblinded team must not directly be involved in the execution of the study at a study site or directly contact the site. After cohort 5, this team will review unblinded data on the safety, tolerability and pharmacodynamic effects (MWT) and available PK of TAK-925 obtained from cohort 5, and recommend a dose level for cohort 6 based on such data. After cohort 6, the dose and the number of subjects to be used in Cohort 7 will be recommended by the sponsor’s unblinded team on the basis of safety, tolerability, pharmacodynamic effects (MWT) and available PK data of TAK-925 obtained from Cohorts 5 and 6.

7.13 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

8.0 REFERENCES

No reference.