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

NCT Number: NCT03748979

Statistical analysis plan Approve Date: 28-OCT-2019

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

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-925-1003

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

Version: 2nd

Date: 28 October 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 3

Protocol Date: 12 June 2019

1.1 CCI [redacted]

CCI [redacted] C
C

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
BP	blood pressure
Ceoi	plasma concentration at the end of infusion
CL	total clearance after intravenous administration
Cmax	maximum observed concentration
CV	coefficient of variation
ECG	electrocardiogram
EEG	electroencephalography
ESS	epworth sleepiness scale
GGT	gamma-glutamyl transferase
GCP	Good Clinical Practice
HV	healthy volunteer
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
KSS	karolinska sleepiness scale
LDH	lactate dehydrogenase
LS	least square
MAV	markedly abnormal value
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
MedDRA	medical dictionary for regulatory activities
MR	metabolic ratio
MRD	multiple rising dose
MWT	maintenance of wakefulness test
CCI [redacted]	CCI [redacted]
NT1	narcolepsy type 1
NT2	narcolepsy type 2
PD	pharmacodynamics
PGI-C	patient global impression of change

PK	pharmacokinetics
CCI	CCI
CCI	CCI
PT	preferred term
PTE	pretreatment event
PTR	peak trough ratio during a dosing interval, at steady state
PVT	psychomotor vigilance task
QTcB	QT interval corrected for heart rate by the Bazett method
QTcF	QT interval corrected for heart rate by the Fridericia method
RBC	red blood cell
Rac AUC	accumulation ratio based on AUC during a dosing interval
Rac Cmax	accumulation ratio based on Cmax
REM	rapid eye movement
RT	reaction time
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
tmax	time of first occurrence of Cmax
t1/2z	half-life period
Vss	volume of distribution at state after intravenous administration
Vz	volume of distribution
WBC	white blood cell
WHO Drug	World Health Organization Drug Dictionary

4.0 TRIAL OBJECTIVES

4.1 Trial Primary Objectives

<All Parts>

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

4.2 Trial Secondary Objectives

<All parts>

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

<Part B and C>

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

4.3 Trial Exploratory Objectives

CCI

CCI

[redacted]

4.4 Trial Design

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

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

Part A – Multiple Rising Dose in Healthy Adults

Part A will have 2 dose cohorts as well as additional 4 optional cohorts. Each cohort of healthy adults will consist of 8 healthy subjects, randomized 6:2 active to placebo to TAK-925 vs. placebo (Table 4.a) in double-blinded fashion. The starting dose is selected based on the available preliminary safety, PK and PD data from the ongoing TAK-925-1001 study. Subsequent doses will be guided by safety, PK and PD data from previous cohorts as well as the TAK-925-1002 study (which is ongoing at the time of this protocol writing). TAK-925 or placebo will be administered as an IV infusion over 9 hours once daily for 7 days. Following review of emerging safety and PK data (when available) in Cohort A1, the dose in Cohort A2 will be determined. Healthy adults may be recruited for up to 3 additional cohorts (A3 to A5) with 8 subjects each (randomized 6:2 active to placebo). The dose may be higher, lower or the same as that of prior cohort dose levels. Shifting the start time of infusion while keeping the dose the same as that previously studied may be considered in these optional cohorts [CCI] [redacted]. The maximum dose and infusion rate in Part A shall not exceed the maximum dose or maximum infusion rate studied in healthy subjects in TAK-925-1001 study. The dose levels in subsequent cohorts will be optimized based on the recommendation of sponsor's unblinded team. The unblinded team will review available unblinded data including [CCI] [redacted]

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

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

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

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

Two additional cohorts (B3 and B4) may be evaluated, with 4-6 subjects in each. With the intention of sequential panel design, NT1 patients in Cohort B1 or B2 may participate in Cohort B3 or B4 if feasible operationally. Patients in cohort B1 and B2 may participate in B3 or B4 after a sufficient washout period if and allowed by regulatory authorities and IRB/IEC. The subject who directly move on to cohort B3 or B4 could skip the Day 8 some assessments and follow up visit and move into Day-2 in B3 or B4. Cohort B3 or B4 will essentially consist of newly enrolled NT1 patients, but patients from B1/B2 who weigh over 50 kg could be also enrolled. There should be sufficient intervals between the last dose in Cohort B1 or B2 and the first dose in Cohort B3 or B4 in order to make dose and dosing duration decisions for Cohorts B3 and B4. If there are fewer than 4 Cohort B1 or B2 subjects enrolled to Cohort B3 or B4, new patients with NT1 will be recruited. In Cohorts B3 and B4, TAK-925 will be administered in a blinded randomized manner (3:1, 4:1 or 5:1). The primary purpose of Cohort B3 is to evaluate the safety and tolerability and PD of longer infusion time, as well as to CCI [redacted] Otherwise, the design and procedures for B3 will be the same as the design of B1. The primary purpose of Cohort B4 is to assess the within-subject exposure-response relationship for PD/efficacy and safety of TAK-925 in NT1 patients. Patients in this cohort will receive different, increasing doses of TAK-925 daily over the 7 day period, the sequence of doses will be identical across patients. All subjects will receive the same dosing schedule. One subject within B3 and B4, respectively, will be randomized to placebo.

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

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

Part A' – Single Oral Doses in Healthy Adults

Part A' will investigate the pharmacokinetics of TAK-925 after oral administration in healthy subjects. Cohort A'1 will consist of 6 healthy subjects who will be administered a single dose of TAK-925 as an oral solution in an open-label fashion (Table 4.a). An oral dose of 112 mg is selected based on the safety and tolerability profiles in TAK-925-1001 study and available nonclinical data as a potential starting dose. CCI [redacted] 925-[redacted] An optional Cohort A'2 is allowed based on the emerging information.

The study parts and planned dosing cohorts are outlined in Table 4.a.

Table 4.a Outline of the Study Parts and Planned Dosing Cohorts

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

Doses in subsequent cohorts in all parts will be determined based on the emerging safety/tolerability and PK (when available) and PD information and available safety/tolerability, and PK/PD data from previous cohorts as well as the ongoing TAK-925-1001 and TAK-925-1002 studies. Planned number of subjects in each cohort is shown.

All doses given by IV infusion over 9 hours daily for 7 days except B3

* Optional cohorts

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoint

<All Parts>

- Safety and tolerability: number of subjects with AEs

5.1.2 Secondary Endpoints

< Parts A, B and C>

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

<Part B and C>

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

5.1.3 CCI

CCI [redacted]

5.1.4 CCI

CCI [redacted]

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

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

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 that occurs on or after the start of study drug administration.
- 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
- Average Sleep Latency in MWT: Average of four MWTs measured on the same day
- 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 -1 subtracted from values of Day 1 and 7 in the matching column in the table below for each subject
  - MWT

Day	Time (Time postdose （hour）)			
Day -1	10:00	12:00	14:00	16:00
Day 1,7	10:00 (2 hr)	12:00 (4 hr)	14:00 (6 hr)	16:00 (8 hr)

  - CCI [redacted]
  - CCI [redacted]

- CCI [redacted]
- CCI [redacted]

- Time-matched baseline: observed value of Day -1 obtained time-matched with Day1 and 7 in the table above for each subject
- Change from Time-matched Day 1 to Day 7: For MWT and vital sign parameters, values of Day 1 subtracted from values of Day 7 in the matching column in the table above for each subject
- Treatment Group
  - Cohort A1~A3
    - ✧ Placebo (pooled Cohort A1, A2 and A3)
    - ✧ TAK-925 44mg, 112mg, 180mg
  - Cohort B1~B2
    - ✧ Placebo (pooled Cohort B1 and B2)
    - ✧ TAK-925 11mg, 44mg
  - Cohort C1~C2
    - ✧ Placebo
    - ✧ TAK-925 44mg, 112mg
  - Cohort A'1
    - ✧ TAK-925 112mg

7.2 Analysis Sets

- Safety set: All subjects who received at least one dose of study drug
- PK set: All subjects who received at least one dose of study drug and provided sufficient PK measurements available to estimate PK parameters, at least 1 estimable PK parameter.
- PD 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 Were Not Randomized	
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 A1~A3

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s) :	Study Drug Administration Status	[Rnadomized, Not Randomized]
	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 B1~B2

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 B1~B2

7.3.3.3 Cohort C1~C2

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 C1~C2

7.3.3.4 Cohort A'1

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 A'1

7.3.4 Disposition of Subjects

7.3.4.1 Cohort A1~A3

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 treatment 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 B1~B2

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 B1~B2

7.3.4.3 Cohort C1~C2

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 C1~C2

7.3.4.4 Cohort A'1

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 A'1

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Cohort A1~A3

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 treatment 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 B1~B2

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.5.1 "Cohort A1~A3" will be performed for the Cohort B1~B2

Cohort C1~C2

Analysis Set: All Subjects Who Received Study Drug

Analytical Method(s) : The same analysis as section 7.3.5.1 "Cohort A1~A3" will be performed for the Cohort C1~C2

Cohort A'1

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.1 "Cohort A1~A3" will be performed for the Cohort A'1

7.3.5.2 Analysis Sets

Cohort A1~A3

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 Set	[Included]
	PK Set	[Included]
Analytical Method(s) :	(1) Subjects Excluded from Analysis Sets (2) Analysis Sets Frequency distributions will be provided by treatment 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.	

Cohort B1~B2

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 Set	[Included]

	PK Set	[Included]
	PD Set	[Included]
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort A1~A3" will be performed for the Cohort B1~B2	

Cohort C1~C2

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 Set	[Included]
	PK Set	[Included]
	PD Set	[Included]
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort A1~A3" will be performed for the Cohort C1~C2	

Cohort A'1

Analysis Set:	All Subjects Who Received Study Drug
Analytical Method(s) :	The same analysis as section 7.3.5.2 "Cohort A1~A3" will be performed for the Cohort A'1

7.4 Demographic and Other Baseline Characteristics

7.4.1 Cohort A1~A3

Analysis Set:	Safety Set	
Analysis Variable(s) :	Age (years)	
	Gender	[Male, Female]
	Height (cm)	

Weight (kg)
BMI (kg/m^2)
CCI [redacted]

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 treatment group and overall.

7.4.2 Cohort B1~B2

Analysis Set: Safety 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]
average MWT (sleep latency)	
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
[redacted]	
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
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 treatment group and overall.

7.4.3 Cohort C1~C2

Analysis Set: Safety Set

Analytical Method(s) : The same analysis as section 7.4.2 will be performed for the Cohort C1~C2

7.4.4 Cohort A'1

Analysis Set: Safety Set

Analytical Method(s) : The same analysis as section 7.4.1 will be performed for the Cohort A'1

7.5 Medical History and Concurrent Medical Conditions

7.5.1 Cohort B1~B2

Analysis Set: Safety 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 for each treatment 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.

7.5.2 Cohort C1~C2

Analysis Set: Safety Set
Analytical Method(s) : The same analysis as section 7.5.1 will be performed for the Cohort C1~C2

7.6 Medication History and Concomitant Medications

7.6.1 Cohort B1~B2

Analysis Set: Safety 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 for each treatment group and overall. A summary of (2) ~ (5) will also be provided for concomitant medications whose primary purpose was "primary diagnosis". 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.

7.6.2 Cohort C1~C2

Analysis Set: Safety Set
Analytical
Method(s) : The same analysis as section 7.6.1 will be performed for the Cohort C1~C2

7.7 Study Drug Exposure and Compliance

7.7.1 Cohort A1~A3

Analysis Set: Safety Set
Analysis
Variable(s) : Number of Times the Study Drug was Taken [1, 2, 3, 4, 5, 6, 7]
Analytical
Method(s) : (1) Study Drug Exposure
Frequency distributions will be provided by treatment group.

7.7.2 Cohort B1~B2

Analysis Set: Safety Set
Analytical
Method(s) : The same analysis as section 7.7.1 will be performed for the Cohort B1~B2

7.7.3 Cohort C1~C2

Analysis Set: Safety Set
Analytical
Method(s) : The same analysis as section 7.7.1 will be performed for the Cohort C1~C2

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

No imputations will be performed for missing PD (exclude CCI) and safety measures. CCI [redacted]

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. CCI [redacted]

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

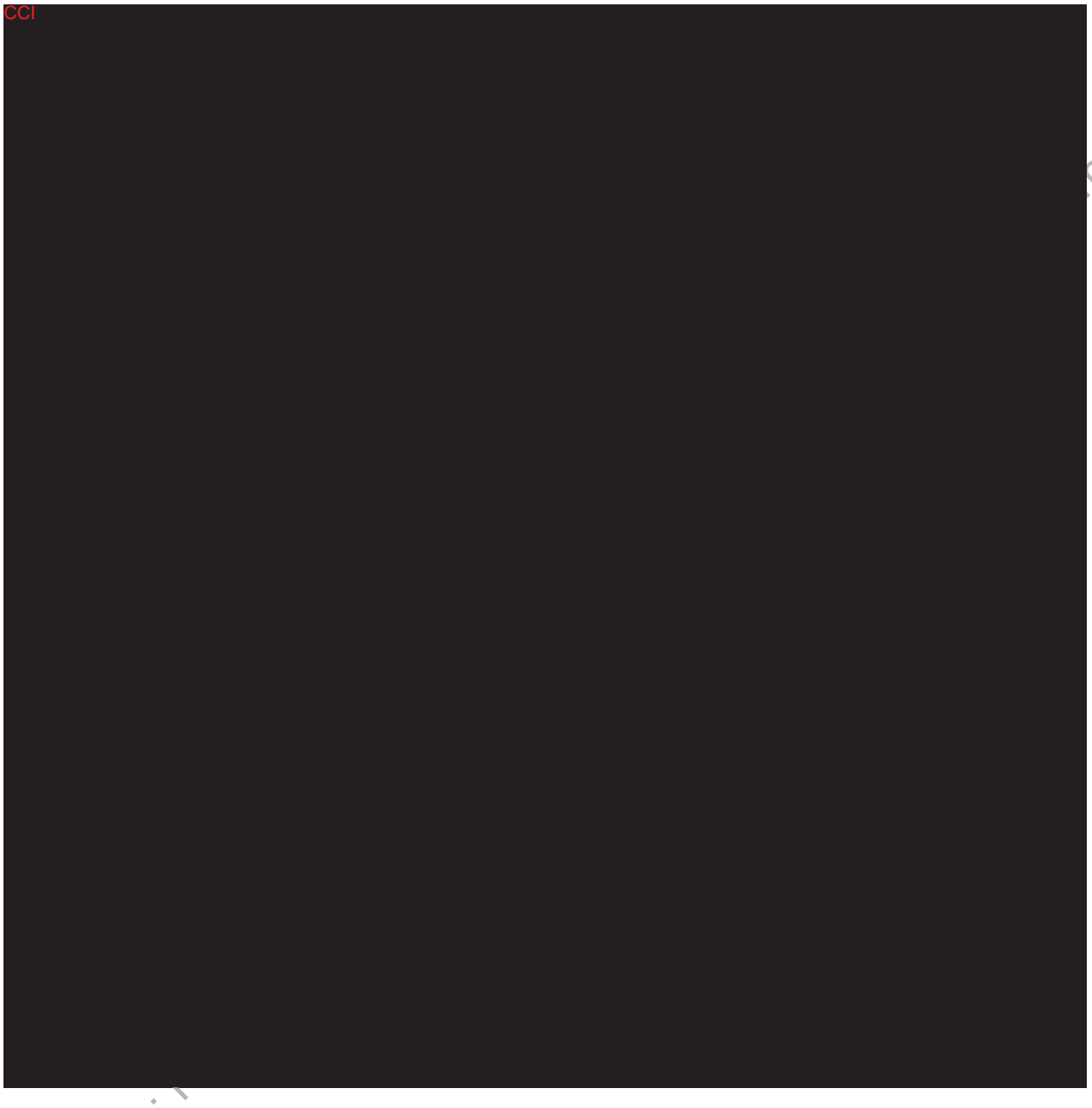
7.9.1 Pharmacokinetic Analysis

7.9.1.1 CCI [redacted]

CCI [redacted]

CCI

CCI



7.9.1.2 Pharmacokinetic Parameters

Cohort A1~A3

Analysis Set: PK Set

Analysis Variable(s): Pharmacokinetic Parameters of TAK-925 and CCI

CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI
AUCtau
Ceoi
Rac AUC(only Day 7)

Visit: Day 1, Day 7

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

(1) Summary of Pharmacokinetic Parameters
For CCI, CCI, AUCtau, CCI, CCI Ceoi, descriptive statistics, geometric mean, and CV will be provided. CCI
CCI
CCI

(2) CCI
CCI
CCI

Cohort B1~B2

Analysis Set: PK Set

Analytical Method(s): The same analysis as section 7.9.1.2 "Cohort A1~A3" will be conducted for the Cohort B1~B2.

Cohort C1~C2

Analysis Set: PK Set

Analytical Method(s): The same analysis as section 7.9.1.2 "Cohort A1~A3" will be conducted for the Cohort C1~C2.

CCI [redacted]

CCI [redacted]

7.9.2 Pharmacodynamic Analysis

7.9.2.1 Average Sleep Latency in MWT/Sleep Latency in Each Session in MWT

Cohort B1~B2

Analysis Set: PD Set

Analysis Variable(s): Average Sleep Latency in MWT, Sleep Latency in Each Session in MWT

Visit: Average Sleep Latency in MWT: Day -1, Day 1, Day 7
Sleep Latency in Each Session in MWT:
Day -1: 10：00, 12：00, 14：00, 16：00
Day 1 and Day 7: 10:00 (2hr), 12：00 (4hr), 14：00 (6hr), 16：00 (8hr)

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

(1) For the average sleep latency in MWT, descriptive statistics for the CCI [redacted], changes from baseline and CCI [redacted]

CCI will be provided by visit by treatment group. The effect of TAK-925 will be evaluated with a linear mixed effects model. The response variable in the model will be the change from baseline in the average sleep latency in the MWT. The model will include treatment (each treatment of TAK-925 and placebo), day (as a categorical variable), the treatment-by-day as fixed effects, baseline average sleep latency in the MWT as a covariate, and subjects as a random effect. Least square (LS) means, the standard errors, and the two-sided 95% confidence intervals will be provided for each treatment group. For each day, the difference in the LS means between each treatment of TAK-925 and the placebo (each treatment of TAK-925 - the placebo), the standard error of the difference and the two-sided confidence intervals will be provided. CCI [redacted] The differences in the LS means between each treatment of TAK-925 group and the placebo group (each treatment of TAK-925 group - placebo group), the standard error and the two-sided 95% confidence intervals will be provided.

CCI [redacted]

CCI [redacted]

If there is a missing value of sleep latency in MWT at Day -1, it will be imputed by the predicted value of the same subject and the same session based on a model with sleep latency in MWT at Day -1 as a response, session as a fixed effect, and a subject as a random effect. After conducting imputation, the average sleep latency in MWT will be recalculated and the model analysis as above will be conducted as reference.

(2) CCI [redacted]

Cohort C1~C2

Analysis Set: PD Set

Analytical Method(s): The same analysis as section 7.9.2.1 "Cohort B1~B2" will be conducted.

7.9.2.2 CCI [redacted]

CCI [redacted]

CCI

[redacted]

7.9.2.3 CCI [redacted]

CCI

[redacted]

CCI

[redacted]

7.9.2.4 CCI

CCI

[redacted]

CCI

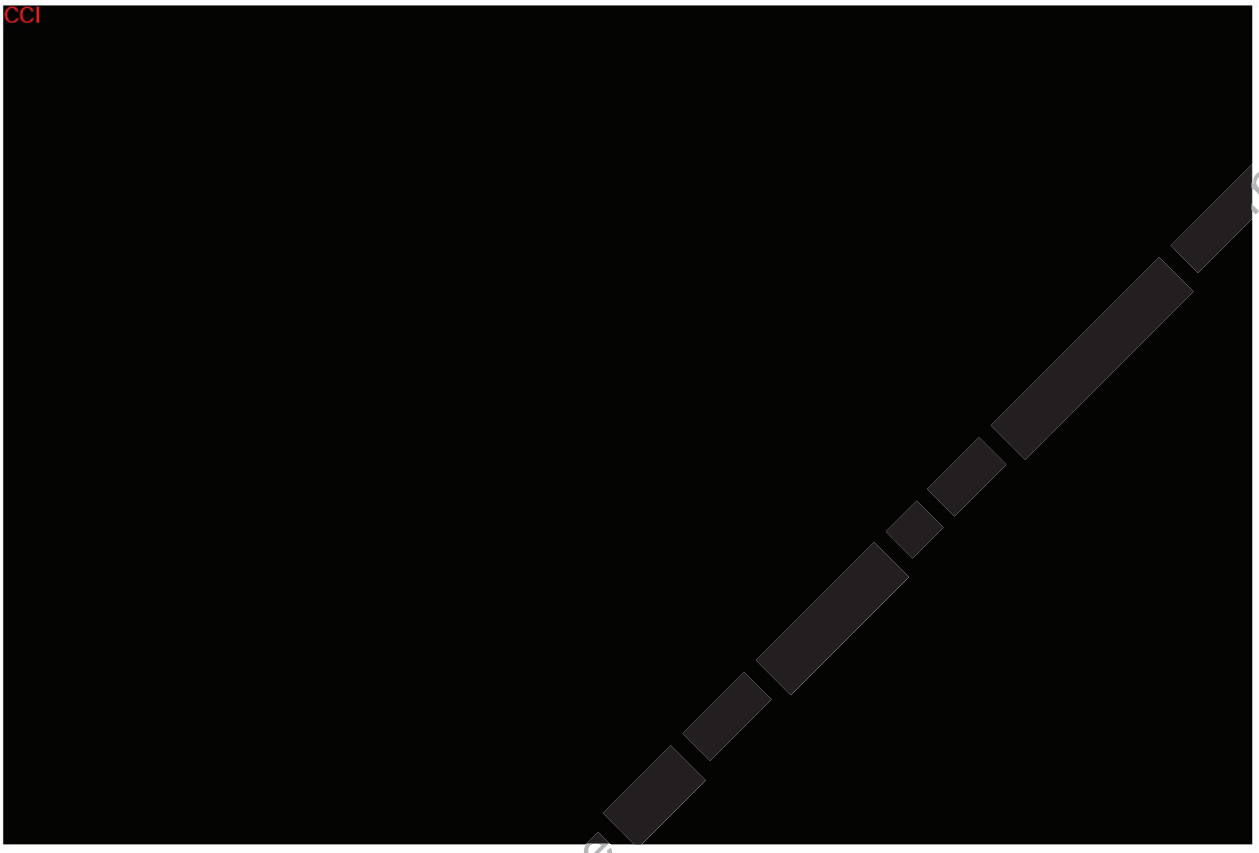
7.9.2.5 CCI

CCI

7.9.2.6 CCI

CCI

CCI



7.9.2.7 CCI

CCI

CCI

7.9.2.8 CCI

CCI

CCI

[redacted]

7.10 CCI

7.10.1 CCI

7.10.1.1 CCI

CCI

[redacted]

CCI

7.10.1.2 CCI

CCI

7.10.1.3 CCI

CCI

CCI

[redacted]

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 A1~A3

Analysis Set:	Safety 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 for each treatment group.	

(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 treatment group will be based on the number of subjects in the safety 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 B1~B2

Analysis Set: Safety Set

Analytical Method(s) : The same analysis as section 7.11.1.1 "Cohort A1~A3" will be performed for the Cohort B1~B2.

Cohort C1~C2

Analysis Set: Safety Set

Analytical Method(s) : The same analysis as section 7.11.1.1 "Cohort A1~A3" will be performed for the Cohort C1~C2.

Cohort A'1

Analysis Set: Safety Set

Analytical Method(s) : The same analysis as section 7.11.1.1 "Cohort A1~A3" will be performed for the Cohort A'1

7.11.1.2 Displays of Treatment-Emergent Adverse events

Cohort A1~A3

Analysis Set: Safety Set

Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of Onset (day)	[Day 1, Day 2, Day 3, Day 4, Day5, Day 6, Day 7, Day8 - Max]

Analytical Method(s) : The following summaries will be provided using frequency distribution for each treatment group.

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
(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time
(10) Treatment-Emergent Adverse Events Occurred during Infusion by System Organ Class and Preferred Term
(11) Treatment-Emergent Adverse Events Occurred after Infusion by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below. Percentages for each treatment group will be based on the number of subjects 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.
- Summary table for (9)
  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.
  When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

Cohort B1~B2

Analysis Set: Safety Set

Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort A1~A3" will be performed for the Cohort B1~B2.

Cohort C1~C2

Analysis Set: Safety Set

Analytical Method(s) : The same analysis as section 7.11.1.2 "Cohort A1~A3" will be performed for the Cohort C1~C2.

Cohort A'1

Analysis Set:	Safety Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
Analytical Method(s) :	The following summaries will be provided using frequency distribution. 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	

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 A1~A3

Analysis Set:	Safety Set		
Analysis Variable(s) :	Hematology		
	RBC	Hemoglobin	Hematocrit
	Platelet	WBC	
	WBC Differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes)		
	MCH	MCHC	MCV
	Serum Chemistry		
	Albumin	Alkaline Phosphatase	ALT
	AST	Total Bilirubin	Blood Urea Nitrogen
	Calcium	Chloride	Creatinine
	GGT	Glucose	Potassium
	Total Protein	Sodium	C-reactive Protein
	Total Cholesterol	LDH	Magnesium
	Phosphorus	Triglycerides	Uric acid
Visit:	Predose, Day 4, Day 8, Day 15		
	(Data obtained at Day 1 will be used as the "Predose" visit)		

Analytical
Method(s) : The following summaries will be provided by treatment group.

CCI

Cohort B1~B2

Analysis Set: Safety Set
Analytical
Method(s) : The same analysis as section 7.11.2.1 "Cohort A1~A3" will be performed for the Cohort B1~B2.

Cohort C1~C2

Analysis Set: Safety Set
Analytical
Method(s) : The same analysis as section 7.11.2.1 "Cohort A1~A3" will be performed for the Cohort C1~C2.

Cohort A'1

Analysis Set: Safety Set
Visit: Predose, Day 2
(Data obtained at Day 1 will be used as the "Predose" visit)
Analytical
Method(s) : The same analysis as section 7.11.2.1 "Cohort A1~A3" will be performed for the Cohort A'1

7.11.2.2 Urinalysis

Cohort A1~A3

Analysis Set:	Safety Set	
Analysis Variable(s) :	Protein	[-, +-, +, 2+, 3+]
	Glucose	[-, +, 2+, 3+, 4+]
	Occult Blood	[-, +-, +, 2+, 3+]
	Nitrite	[-, +]
	Ketone Bodies	[-, +-, +, 2+, 3+]
	pH	[5.0<= - <=7.5, 8.0<= - <=9.0]
	Specific Gravity	
	Urobilinogen	[+-, +, 2+, 3+]
Visit:	Predose, Day 4, Day 8, Day 15 (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 treatment group. For each variable other than Specific Gravity, summaries (3) and (4) will be provided by treatment group.	

CCI

CCI [redacted]

Cohort B1~B2

Analysis Set: Safety Set
Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort A1~A3" will be performed for the Cohort B1~B2.

Cohort C1~C2

Analysis Set: Safety Set
Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort A1~A3" will be performed for the Cohort C1~C2.

Cohort A'1

Analysis Set: Safety Set
Visit: Predose, Day 2
(Data obtained at Day 1 will be used as the "Predose" visit)
Analytical Method(s) : The same analysis as section 7.11.2.2 "Cohort A1~A3" will be performed for the Cohort A'1

7.11.3 CCI [redacted]

7.11.3.1 CCI [redacted]

CCI [redacted]

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

[redacted]

7.11.4 CCI [redacted]

CCI

[redacted]

CCI

CCI

[redacted]

7.11.5 CCI

CCI

[redacted]

CCI

[redacted]

7.11.6 CCI

CCI

[redacted]

CCI

[redacted]

7.11.7 CCI

CCI

[redacted]

7.11.8 Other Observations Related to Safety

Not applicable.

7.12 Interim Data Review

The dose level chosen for Cohorts in Part A, B, C after the first cohort in each group and whether to proceed to next cohort or stop the part may be evaluated by the sponsor's unblinded team composed of persons who do not have subject contact or involvement with execution of the protocol at the site, who will review unblinded data on safety, tolerability, available PK and PD results, and this dose may be higher, lower or the same than that used in the prior cohorts.

7.13 Changes in the Statistical Analysis Plan

From the SAP version 1.0, the following parts were updated. Cohort A3, C2 and A'1 were added in each section. Other main modified parts are as below.

Before the change

Cover

Prepared by:

PPD

[redacted]

Based on:

Protocol Version: Initial Version

Protocol Date: 10 October 2018

After the change

Cover

Prepared by:

PPD

Based on:

Protocol Version: Amendment 3

Protocol Date: 12 June 2019

Reason for the change

Department name changed and protocol was amended.

Before the change

7.1.1 Study Definitions

- Treatment Group
  - Cohort A1~A2
    - ✧ Placebo (pooled Cohort A1 and A2)
    - ✧ TAK-925 44mg, TBD
  - Cohort B1~B2
    - ✧ Placebo (pooled Cohort B1 and B2)
    - ✧ TAK-925 11mg, TBD
  - Cohort C1
    - ✧ Placebo
    - ✧ TAK-925 TBD

After the change

7.1.1 Study Definitions

- Treatment Group
  - Cohort A1~A3
    - ✧ Placebo (pooled Cohort A1, A2 and A3)
    - ✧ TAK-925 44mg, 112mg, 180mg
  - Cohort B1~B2
    - ✧ Placebo (pooled Cohort B1 and B2)

- ✧ TAK-925 11mg, 44mg
- Cohort C1~C2
  - ✧ Placebo
  - ✧ TAK-925 44mg, 112mg
- Cohort A'1
  - ✧ TAK-925 112mg

Reason for the change

The conducting cohorts and each dose level were determined.

Before the change

7.9.1.1 CCI

CCI

[redacted]

After the change

CCI

[redacted]

CCI

CCI

Reason for the change

CCI

Before the change

Cohort A1~A2

Analysis Set: PK Set

Analysis Variable(s): Pharmacokinetic Parameters of TAK-925 and CCI

CCI

Ceoi

RAUC(only Day 7)

Visit: Day 1, Day 7

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

(3) Summary of Pharmacokinetic Parameters

For CCI, CCI, CCI and Ceoi, descriptive statistics, geometric mean, and CV will be provided. CCI

After the change

Cohort A1~A3

Analysis Set: PK Set

Analysis Variable(s): Pharmacokinetic Parameters of TAK-925 and CCI

CCI

AUCtau

Ceoi

CCI

Rac AUC(only Day 7)

CCI

Visit: Day 1, Day 7

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

(1) Summary of Pharmacokinetic Parameters

For CCI, CCI AUCtau, CCI, CCI Ceoi, descriptive statistics, geometric mean, and CV will be provided. CCI

CCI

CCI

(2) CCI

CCI

Reason for the change

Pharmacokinetic parameters were added.

Before the change

7.9.2.1 Average Sleep Latency in MWT/Sleep Latency in Each Session in MWT Cohort B1~B2

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

(1) For the average sleep latency in MWT, descriptive statistics for the CCI, changes from baseline and CCI will be provided by visit by treatment group. The effect of TAK-925 will be evaluated with a linear mixed effects model. The response variable in the model will be the observed value of the average sleep latency in the MWT. The model will include treatment (each treatment of TAK-925 and placebo), day (as a categorical variable), the treatment-by-day as fixed effects, baseline average sleep latency in the MWT as a covariate, and subjects as a random effect. Least square (LS) means, the standard errors, and the two-sided 95% confidence intervals

will be provided for each treatment group. For each day, the difference in the LS means between each treatment of TAK-925 and the placebo (each treatment of TAK-925 - the placebo), the standard error of the difference and the two-sided confidence intervals will be provided. CCI [redacted] The differences in the LS means between each treatment of TAK-925 group and the placebo group (each treatment of TAK-925 group - placebo group), the standard error and the two-sided 95% confidence intervals will be provided.

CCI [redacted]

CCI [redacted]

(2) CCI [redacted]

CCI [redacted]

After the change

7.9.2.1 Average Sleep Latency in MWT/Sleep Latency in Each Session in MWT

Cohort B1~B2

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

(1) For the average sleep latency in MWT, descriptive statistics for the CCI [redacted], changes from baseline and CCI [redacted] will be provided by visit by treatment group. The effect of TAK-925 will be evaluated with a linear mixed effects model. The response variable in the model will be the change from baseline in the average sleep latency in the MWT. The model will include treatment (each treatment of TAK-925 and placebo), day (as a categorical variable), the treatment-by-day as fixed effects, baseline average sleep latency in the MWT as a covariate, and subjects as a random effect. Least square (LS) means, the standard errors, and the two-sided 95% confidence intervals will be provided for each treatment group. For each day, the difference in the LS means between each treatment of TAK-925 and the placebo (each treatment of TAK-925 - the placebo), the standard error of the difference and the two-sided confidence intervals will be provided. CCI [redacted] The differences in the LS means between each treatment of TAK-925 group and the placebo group (each treatment of TAK-925 group - placebo group), the standard error and the two-sided 95% confidence intervals will be provided.

CCI [redacted]

CCI [redacted]

If there is a missing value of sleep latency in MWT at Day -1, it will be imputed by the predicted value of the same subject and the same session based on a model with sleep latency in MWT at Day -1 as a response, session as a fixed effect, and a subject as a random effect. After conducting imputation, the average sleep latency in MWT will be recalculated and the model analysis as above will be conducted as reference.

(2) CCI [redacted]

Reason for the change

The response variable for model analysis was changed for better assessment. Because missing value was occurred at Day -1 of MWT value, the analysis using imputation method was added for reference.

Before the change

7.9.2.2 CCI

CCI [redacted]

After the change

7.9.2.2 CCI

CCI [redacted]

CCI [redacted]

Reason for the change

CCI [redacted]

Before the change

7.9.2.3 CCI [redacted]

CCI [redacted]

After the change

7.9.2.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

Reason for the change

Error correction.

Before the change

7.9.2.4 CCI [redacted]

CCI [redacted]

After the change

7.9.2.4 CCI [redacted]

CCI [redacted]

Reason for the change

To meet another department request.

Before the change

7.9.2.5 CCI

CCI [redacted]

Reason for the change

Error correction.

Before the change

7.9.2.6 CCI [redacted]

CCI [redacted]

After the change

7.9.2.6 CCI [redacted]

CCI [redacted]

Reason for the change

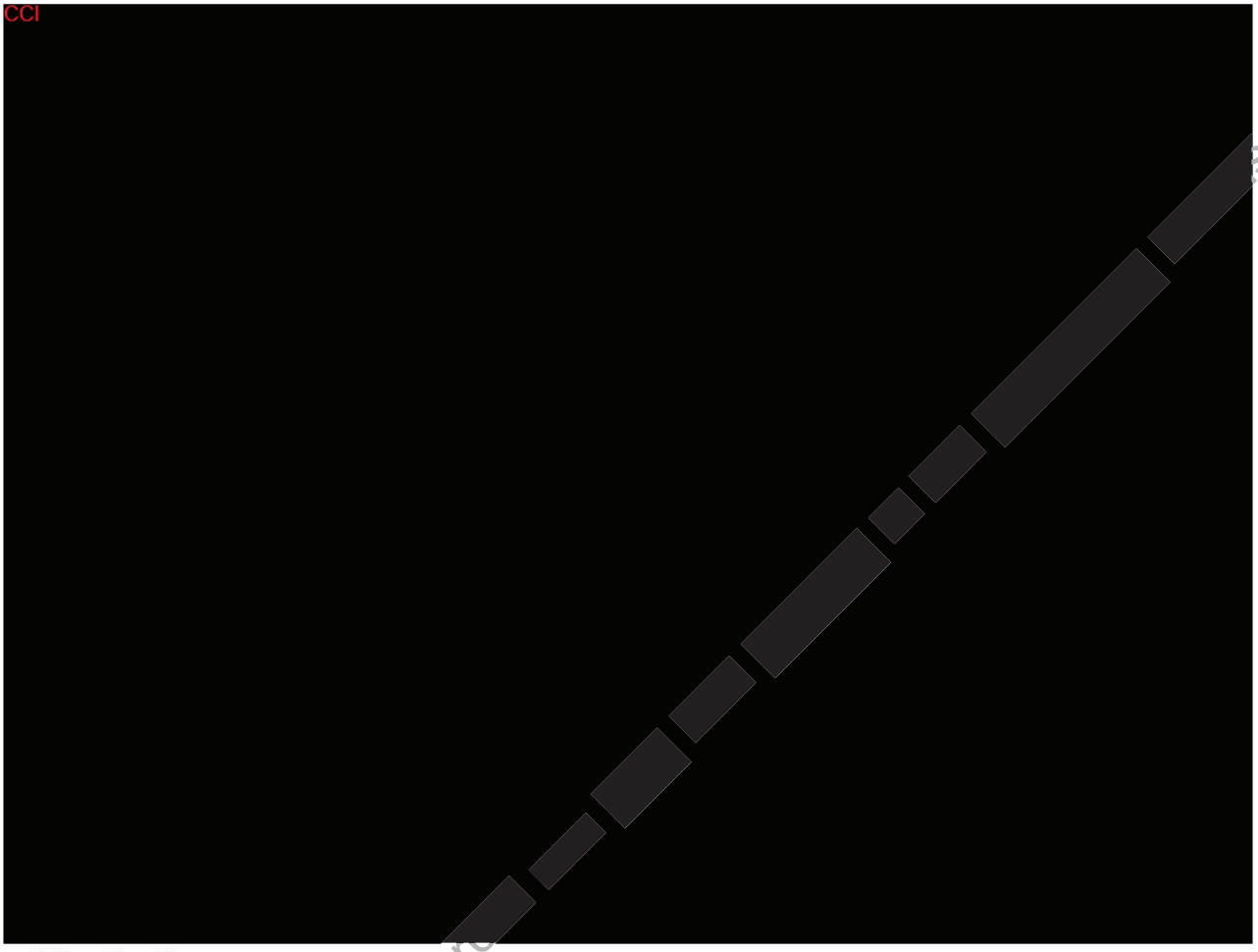
To meet another department request.

Before the change

7.9.2.7 CCI [redacted]

CCI [redacted]

CCI



After the change

7.9.2.7 CCI

CCI

CCI

[redacted]

Reason for the change

To meet another department request.

Before the change

7.9.2.8 CCI

CCI

[redacted]

After the change

CCI

[redacted]

CCI

[redacted]

Reason for the change

Error correction and adding another analysis variable and another analysis due to other department request.

Before the change

7.10.1 CCI [redacted]

7.10.1.1 CCI [redacted]

CCI

[redacted]

CCI [redacted]

After the change

7.10.1 CCI [redacted]

7.10.1.1 CCI [redacted]

CCI [redacted]

Reason for the change

Error correction and to clarify the description.

Before the change

7.10.1 CCI [redacted]

7.10.1.2 CCI [redacted]

CCI

[redacted]

After the change

7.10.1 CCI [redacted]

7.10.1.2 CCI [redacted]

CCI

[redacted]

Reason for the change

Error correction and to clarify the description.

Before the change

7.11.2.2 Urinalysis

Cohort A1~A2

Analysis Variable(s) :	Protein	[-, +-, +, 2+, 3+]
	Glucose	[-, +, 2+, 3+, 4+]
	Occult Blood	[-, +-, +, 2+, 3+]
	Nitrite	[-, +]
	Ketone Bodies	[-, +-, +, 2+, 3+]
	pH	[5.0<= - <=7.5, 8.0<= - <=9.0]
	Specific Gravity	
	Urobilinogen	[+-, +, 2+, 3+]
	Microscopy	
	RBC	[below 1/HPF, 1-4/HPF, 5-9/HPF, 10-19/HPF, 20-29/HPF, 30-49/HPF, 50-99/HPF, above or equal to 100/HPF]
	WBC	[below 1/HPF, 1-4/HPF, 5-9/HPF, 10-19/HPF, 20-29/HPF, 30-49/HPF, 50-99/HPF, above or equal to 100/HPF]
	Casts	[below 1/HPF, 1-4/HPF, 5-9/HPF, 10-19/HPF, 20-29/HPF, 30-49/HPF, 50-99/HPF, above or equal to 100/HPF]
Visit:	Predose, Day 4, Day 8, Day 15 (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 treatment group. For Microscopy (Erythrocytes (RBC), Leukocytes (WBC), Squamous Cells), summaries (3) will be provided by treatment group. For each variable other than Specific Gravity and Microscopy, summaries (3) and (4) will be provided by treatment group.	

After the change

7.11.2.2 Urinalysis

Cohort A1~A3

Analysis		
Variable(s) :	Protein	[-, +-, +, 2+, 3+]
	Glucose	[-, +, 2+, 3+, 4+]
	Occult Blood	[-, +-, +, 2+, 3+]
	Nitrite	[-, +]
	Ketone Bodies	[-, +-, +, 2+, 3+]
	pH	[5.0<= - <=7.5, 8.0<= - <=9.0]
	Specific Gravity	
	Urobilinogen	[+-, +, 2+, 3+]
Visit:	Predose, Day 4, Day 8, Day 15 (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 treatment group. For each variable other than Specific Gravity, summaries (3) and (4) will be provided by treatment group.	

Reason for the change

Error correction.

Before the change

7.11.3.1 [redacted]

CCI

[redacted]

After the change

7.11.3.1 CCI

[redacted]

CCI

[redacted]

Reason for the change

Error correction and to clarify the description.

Before the change

7.11.4 CCI

CCI

After the change

7.11.4 CCI

CCI

Reason for the change

Error correction.

Before the change

7.11.5 CCI

CCI

After the change

7.11.5 CCI

CCI

CCI

Reason for the change

To make the definitions more appropriate and the analysis for change from time-matched day 1 to day 7 was added

7.14 REFERENCES

No reference.

APPENDIX A CCI [redacted]

CCI [redacted]