STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-994_1501

A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-994 in Patients with Narcolepsy with or without Cataplexy (Narcolepsy Type 1 or Narcolepsy Type 2)

PHASE 2

Version: 02

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3.0 LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
AUClast	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUCτ	area under the plasma concentration-time curve during a dosing interval
BID	twice daily
BLO	below the lower limit of quantification
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
Cmax	maximum observed plasma concentration
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia - Suicide Severity Rating Scale
ECG	electrocardiogram
[redacted]	[redacted]
ESS	Epworth Sleepiness Scale
eCRF	electronic case report form
FDA	Food and Drug Administration
IA	interim analysis
IRC	internal review committee
IRT	interactive response technology
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAV	markedly abnormal value
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-models for repeated measures
MWT	Maintenance of Wakefulness Test
[redacted]	[redacted]
NT1	narcolepsy type 1
NT2	narcolepsy type 2
PA3	Protocol Amendment 3
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
PK	pharmacokinetic(s)
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
tmax	time of first occurrence of Cmax
ULN	upper limit of normal
WCR	weekly cataplexy rate
WE	weekly episodes
[redacted]	[redacted]

4.0 OBJECTIVES

4.1 Primary Objective--PART A and PART D

- To assess the safety and tolerability of TAK-994 following multiple oral doses in subjects with narcolepsy with or without cataplexy (NT1 or NT2).

4.2 Secondary Objective--PART A and PART D

- To characterize the PK of TAK-994 in subjects with narcolepsy with or without cataplexy (NT1 or NT2).

4.3 Additional/ Exploratory Objectives--PART A and PART D

[redacted]

[redacted]

4.4 Primary Efficacy Objective--PART B and PART C

- To assess the efficacy of TAK-994 on reducing EDS as measured by prolongation of sleep onset in MWT procedure.

4.5 Secondary Objective--PART B and PART C

- To assess the efficacy of TAK-994 on WCR and ESS reduction.
- To assess the safety and tolerability of TAK-994 following chronic administration.

4.6 Additional/ Exploratory Objectives--PART B and PART C

[redacted]

4.7 Study Design

This is a phase 2 randomized, double-blind, placebo-controlled study to assess the safety, tolerability, PK, [redacted] of multiple rising oral doses of TAK-994 administered to subjects with NT1 or NT2. An interactive response technology (IRT) system will be utilized for the randomization of subjects to treatment.

Approximately 202 (male and female) subjects, aged 18 to 65 years (inclusive) who satisfy the inclusion and exclusion criteria will be enrolled in the study in 4 study parts (Table 4.a). The same subjects will not be allowed to be enrolled or randomized into different parts of the study; therefore, these 4 study parts are considered distinct from each other. However, subjects in Part B will have the opportunity to participate in an extension study.

Subjects recruited for the study are expected to be generally healthy, other than having narcolepsy.

For Part B, the randomization will be stratified by baseline WCR (<8 vs ≥8) and regions/countries (ie, North America, Japan, South Korea, and Europe).

For Part C, the randomization will be stratified by baseline WCR (<8 vs ≥8).

For other parts, the randomization will be stratified by regions/countries (North America, Japan, South Korea, and Europe).

Subjects who were in the screening period at the time that coronavirus disease 2019 (COVID-19) related factors resulted in discontinuation may be rescreened with approval (Refer to Section 9.0 in PA3 for additional details). Subjects will receive BID dosing of TAK-994 or matching placebo for 28 days or 56 days, as applicable).

Table 4.a Planned Study Cohorts and Dose Levels

PART/Cohort Number	Daily Dose Level (mg) a	Dosing Regimen b	Randomization and design
PART A-Cohort A1a and A1b	240 mg (A1a), TBD (A1b)	Oral, 120 mg twice daily for 28 days (A1a)	Approximately 18 subjects, 9 subjects each in Cohort A1a and A1b, randomized 2:1 to TAK-994 vs placebo, double-blind
PART A-Cohort A2 (optional)	TBD	Oral, twice daily for 28 days	Approximately 9-18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind
PART B	TBD	Oral, twice daily for 56 days	Approximately 112 subjects in a 4-arm parallel group design: TAK-994 Dose 1, Dose 2, and Dose 3 vs Placebo. 28/group with a randomization of 1:1:1:1
PART C (China-specific)	TBD	Oral, twice daily for 56 days	Approximately 12-18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind
PART D, Cohort D1a and D1b	TBD	Oral, twice daily for 28 days	Approximately 18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind
PART D-Cohort D2 (optional)	TBD	Oral, twice daily for 28 days	Approximately 9-18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind

PK: pharmacokinetic; NT1: narcolepsy type 1 (narcolepsy with cataplexy); NT2: narcolepsy type 2 (narcolepsy without cataplexy).

TBD: to be determined.

a: Doses will be determined based on the available and emerging safety/tolerability, PK, [redacted] data from prior study TAK-994-1001 and/or previous cohorts in the current study.

b: Doses will be administered approximately 5 hours apart.

c: Parts A to C include subjects with NT1 and part D will include subjects with NT2.

Table 4.b Relative Timing for Initiation of Study Parts

Study Part/ Description	Relative Timing of Cohort Initiation and Rationale	
Part A, Cohort A1a (sentinel)	This will start first	The dosing regimen, 120 mg BID, used in Cohort A1a, is supported by the predicted range of pharmacologically active plasma exposure from animal studies, and available clinical safety and PK data from the completed TAK-994-1001 FIH study. See Section 6.2.1 in PA3 for details.
Part A, Cohort A1b	This will start after 9 sentinel subjects in Cohort A1a are dosed for at least 2 weeks	The dose level for Cohort A1b will be determined based on the available safety, tolerability, PK, [redacted] data from Cohort A1a. See Section 6.2.1 in PA3 for details.
PART A, Cohort A2 (optional)	This will start after Cohort A1b, if deemed necessary based on A1 data	The totality of Cohort A1 data will be used to determine whether Cohort A2 is needed to further evaluate safety, efficacy, PK, [redacted] in NT1 before initiating Part B. The dose level for Cohort A2 will be determined based on the available Cohort A1 data. See Section 6.2.1 in PA3 for details.
PART B	After the last cohort in Part A	Doses in Part B will be determined using all available data from Part A. See Section 6.2.1 in PA3 for details.
PART C	This will start after Part A	The dose for Part C will be selected based on all available data. See Section 6.2.1 in PA3 for details.
PART D, Cohort D1	This will begin after Cohort A1	The dose for Cohort D1a will be determined based on the available clinical safety and PK data from the completed TAK-994-1001 FIH study and available safety, tolerability, PK, [redacted] data from Cohort A1. See Section 6.2.1 in PA3 for details.
PART D-Cohort D2 (optional)	Based on the Cohort D1 data, if additional data are needed	The dose level for Cohort D2 will be determined based on the available safety, tolerability, PK [redacted] from Cohort D1, if the sponsor decides that D2 is needed to further evaluate safety, PK, [redacted] in NT2. See Section 6.2.1 in PA3 for details.

a: Doses will be determined based on the available and emerging safety/tolerability, PK, [redacted] data from prior study TAK-994-1001 and/or previous cohorts in the current study.

b: Doses will be administered approximately 5 hours apart.

PK: pharmacokinetic; NT1: narcolepsy type 1 (narcolepsy with cataplexy); NT2: narcolepsy type 2 (narcolepsy without cataplexy).

TBD: to be determined.

c: Parts A to C include subjects with NT1 and part D will include subjects with NT2.

PART A (Cohorts A1 and A2):

Cohort A1: Cohort A1 will enroll 18 subjects with the sentinel 9 subjects to be randomized 2:1 to receive treatment with oral TAK-994 120 mg BID versus placebo in a double-blinded fashion. The starting dose level in the first cohort of subjects, Cohort A1a, is 120 mg BID, which was based on the preliminary safety, tolerability, and PK data from the FIH Study TAK-994-1001 (Section 6.3.2.1 in PA3), as well as nonclinical data. Sentinel dosing on the first 9 subjects (Cohort A1a) (with randomization ratio of 2:1) will be performed. The second cohort of 9 subjects (Cohort A1b) will be randomized 2:1 to receive treatment with oral TAK- 994 versus placebo in a double-blinded fashion.

Optional Cohort A2: Based on the Cohort A1 data, if an additional dosing cohort is needed, Cohort A2 will be enrolled and started with 9 subjects. They will be randomized in a 2:1 ratio to receive TAK-994 or placebo in a double-blinded fashion. Based on the emerging data from these first 9 subjects, 9 additional subjects may be enrolled in this cohort in a 2:1 ratio.

PART B:

Part B will start after Part A is completed. In order to initiate Part B, 3 dose levels of TAK-994 will be selected based on unblinded safety [redacted] data from the previous Part A cohort(s). A total of 112 subjects will be randomized to either placebo or 1 of the 3 selected TAK-994 dose levels in a 1:1:1:1 ratio administered for 56 days. Subjects completing Part B study treatment will be invited to participate in an extension study, if they are eligible. Details of that extension study design will be communicated via a separate protocol.

PART C (Cohort C1):

PART C, Cohort C1 is a China-specific cohort and is planned to consist of 12 to 18 subjects who will be randomized 2:1 to receive treatment with oral TAK-994 versus placebo in a double-blinded fashion.

PART D (Cohorts D1 and D2):

Cohort D1 will start with sentinel dosing in a cohort of 9 subjects with NT2 (Cohort D1a) who will receive TAK-994 BID or placebo in a randomization ratio of 2:1. Dosing for the next 9 subjects (Cohort D1b) may be adjusted based on the safety and/or efficacy data from the first 9 subjects. Overall randomization ratio for the 18 subjects in Cohort D1 will remain at 2:1.

Based on the Cohort D1 data, if an additional dosing cohort is needed, optional Cohort D2 will start. Cohort D2 will enroll 9 subjects randomized in a ratio of 2:1 to receive TAK-994 or placebo in a double-blinded fashion. Based on the emerging data from these first 9 subjects, 9 additional subjects may be enrolled in this cohort in a 2:1 ratio.

Subjects who are active in screening in Parts A or B and found to not meet the criteria for NT1, may be considered for Part D, if they are eligible. These subjects will not be assigned a new subject number (in these cases when they have not screen-failed), must sign the Part D ICF and will not be required to undergo another screening visit (in these cases where they are still active in screening within the 45-day screening window).

ALL PARTS:

After the screening visit, eligible subjects will participate in study activities as shown in the overview of the study schedule (Table 6.c and Section 2.0 in PA3). The full Schedules of Study Procedures are shown in Table 3.a, Table 3.b, Table 3.c, Table 3.d, Table 3.e, Table 3.f, Table 3.g, Table 3.h, Table 3.i, Table 3.j, Table 3.k, Table 3.l, Table 3.m, Table 3.n in PA3.

Table 4.c Overview of the Study Schedule

Screening, Check-In and Baseline		Treatment Period		Follow-Up Visit
		Dose	Sample Collection	
Days -45 to -3	Day -2 and Day -1	PART A and PART D: Day 1 to Day 28 Study drug administration twice daily	Day 1 to Day 30	Day 35 ±2 days
		PART B and PART C: Day 1 to (See Section 3.2) Day 56 Study drug administration twice daily	Day 1 to Day 56	PART B and PART C: Day 63 ±2 days
←---------- In- and outpatient setting ----------→				

After screening, eligible subjects must discontinue their medication used for treatment of NT1/NT2, including medications used for EDS and cataplexy (valid for NT1 only). Medications that must be discontinued before Day -2 are listed in PA3 Section 7.3. Subjects in Parts A, B and C may undergo optional CSF sampling (single time point) for OX assessment during screening. (NOTE: optional CSF testing at a country-level is dependent upon local regulations [either health authority or other government's] and guidelines and site capacity.)

During confinement, study drug will be administered orally twice every day per the schedule of study procedures. For detailed dosing instructions see PA3 Section 7.4.1. Study assessments will be obtained per the schedules of study procedures in accordance with the priority specified in PA3 Section 6.3.4. Subjects will remain as inpatient from check-in at Day -2 until Day 2; after completion of the scheduled test procedures on Day 2, they will be discharged.

While at home, subjects will take TAK-994 orally BID at approximately the same times each day, with the first dose given in the morning and the second dose approximately 5 hours later and will continue to complete the daily electronic patient-reported outcome (ePRO) diary. See PA3 Section 7.4.1 for complete dosing instructions. Subjects will return to the clinic for safety, PK, [redacted] assessments on in-clinic visit days. Subjects will return home on the discharge day after each in-clinic period. A final follow-up is also required approximately a week after the discharge days. See PA3 Section 3.0 for details.

After the treatment period, a follow-up visit will be done, after which subjects may resume the use of their prior medication for the treatment of narcolepsy.

Sites should see subjects at the study site to conduct the in-clinic study procedures. In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Procedures, contingency measures may be implemented. Restrictions of human activities or institution activities placed by hospitals, local, state and national governments may prevent conduct of study procedures according to the Schedule of Procedures. Alternative approaches to study procedures and data collection for the current study are described in PA3 Section 9.1.1.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints- PART A and PART D

The primary endpoints assessing safety and tolerability are:

- Number of subjects with at least 1 TEAE during the study.
- Number of subjects with at least 1 markedly abnormal value (MAV) for postdose laboratory values during the study.
- Number of subjects with at least 1 MAV for vital signs during the study.
- Number of subjects with at least 1 MAV for ECGs during the study.

5.2 Secondary Endpoints- PART A and PART D

- Day 1: maximum observed concentration [C_{max}], time to reach C_{max} [t_{max}], area under the concentration-time curve [AUC] from time 0 to time of the last quantifiable concentration [AUC_{last}].
- Day 28: C_{max}, t_{max}, AUC_{τ}

5.3 Additional/Exploratory Endpoints- PART A and PART D

[redacted]

[redacted]

5.4 Primary Endpoints- PART B and PART C

- The primary endpoint assessing efficacy is:
- Change from baseline in average sleep latency from MWT to Week 8.

5.5 Secondary Endpoints- PART B and PART C

The secondary endpoints assessing efficacy are:

- Change from baseline in total ESS scores to Week 8.
- WCR at Week 8.

The secondary endpoints assessing safety are:

- Number of subjects with at least 1 treatment-emergent AE (TEAE) during the study.
- Number of subjects with at least 1 MAV for post dose laboratory values during the study.
- Number of subjects with at least 1 MAV for vital signs (clinical VS only) during the study.
- Number of subjects with at least 1 MAV for ECGs during the study.

5.6 Additional/Exploratory Endpoints- PART B and PART C

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

PARTs A, C and D:

In PART A (Cohorts A1 and A2), PART C and PART D (Cohorts D1 and D2), the number of subjects planned are not based on statistical hypothesis testing consideration. They are considered sufficient for dose selection under a typical multiple dose rising design.

PART B:

In Part B, change from baseline in the mean sleep latency, change from baseline in the total ESS score and post dose WCR will be used to evaluate the TAK-994 effect on delaying the sleep onset, reducing ESS and reducing WCR.

A sample size of 21 in each group will have 98% power to detect a 14-min difference in means of change from baseline between a TAK-994 dose group and placebo in sleep latency using a two-sample t-test with a 5% two-sided significance level. The power to detect an 8-point reduction in means of change from baseline between a TAK-994 dose group and placebo in the total ESS score is estimated to be approximately 95% using a two-sample t-test with a 5% two-sided significance level. The power to detect a 50% reduction in WCR from that of placebo group is estimated to be approximately 93% using a two-incidence-rate ratio test using Poisson model with a 5% two-sided significance level.

A fixed sequence of tests with MWT at high and low doses first followed by ESS at high and low doses and WCR at high and low doses will be applied. The overall power for the entire testing procedure is approximately 75% (the square of the product of the power of each individual test at a dose level, 98%, 95% and 93% respectively) under the assumption that these three endpoints are independent. The overall power for the above 6 tests combined may be higher or lower than 75% depending on the correlation structure of these three endpoints. There is no known reliable data to support any particular assumption on the correlation structure.

To allow for a 25% dropout rate, 28 subjects per group will be enrolled for Part B. The enrollment can be stopped once the number of evaluable 21 subjects is reached. A blinded sample size re-estimation will be performed before Part B starts. The change in the sample size of Part B after the re-evaluation, along with justification, will be documented in the clinical study report.

The SD for the change from baseline in the sleep latency is assumed to be 11 min. The SD for the change from baseline in the ESS score is assumed to be 7. The WCR at baseline is assumed to be 3.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Unless otherwise described, general principles, definitions, and summaries described in Section 7.1 to 7.7 will be applied to each part of the study as well as the subgroups defined in Section 7.1.1.

Randomized subjects are the subjects who are enrolled and received a randomization number.

For Parts A and D, placebo subjects from different cohorts will be grouped into the “placebo” group in the summaries and inferential analyses for each part, respectively.

For integrated group analysis that include subjects from different parts with NT1 subjects, subject receiving the same treatment (same TAK-994 dose levels or placebo) will be pooled together.

Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the coefficient of variation (%CV) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the

number and percent of subjects for each category, where appropriate. When presenting summary statistics by treatment groups, the treatment groups include placebo, each of TAK-994 dose groups, and TAK-994 overall. The "overall" group will also be presented for specific summaries.

All p-values will be rounded to 3 decimal points (eg, 0.123) before comparing to the specific α level (for example, 0.05). Posterior probabilities will be presented in % and rounded to one decimal points (eg, 12.3%).

Unless otherwise stated, baseline value is defined as the last observed value before the first dose of study drug.

All data analyses and figures will be generated using SAS System® Version 9.4 or higher.

7.1.1 Study Definitions

In addition to each part described in Section 4, the following groups for NT1 subjects in this study are defined:

- Group 1 (NT1): All NT1 subjects.
- Group 2 (NT1- Japan): All NT1 subjects from the sites in Japan.
- Group 3 (NT1-Asia): NT1 subjects from China, Japan and other Asian countries/places.
- Group 4 (NT1- HLA positive) and Group 5 (NT1- HLA negative): Baseline HLA test positive and HLA test negative subjects, respectively. Subjects may come from Parts A, B and Part C.
- Group 6 (NT1- low baseline WCR): Subjects with baseline WCR≤8.
- Group 7 (NT1- high baseline WCR): Subjects with baseline WCR>8.

Analyses using above groups will be described in Sections 7.11.9 and 7.12.7.

7.1.2 Definition of Study Days

Study day will be calculated relative to the date of the first dose of the study drug for each subject. Study days prior to the first dose of study drug will be calculated as: (date of assessment/event – date of first dose of study drug of the subject). Study days on or after the first dose of study drug will be calculated as: (date of assessment/event – date of first dose of study drug of the subject + 1).

7.1.3 Definition of Study Visit Windows

For each visit, a window is defined; this window establishes a time interval around which data will be considered for the analysis of the scheduled visit pertaining to that window. The lower and upper bounds of each window are the approximate midpoints between the scheduled days for the current visit and its adjacent scheduled visits. The value used in analysis for by-visit summaries is the value within the specified window that is the closest to the scheduled study day. If two observations are equidistant from the scheduled visit date, the observation with a later date

will be used. The visit windows and applicable study day ranges are presented in Table 7.a and Table 7.b for Part A and D, Table 7.c and Table 7.d for Part B and C. Cut-off days for inclusion in the window (number of days following the date of the last dose of double-blind study drug) are provided. If the last dosing day is before the upper bound of a particular visit window except for the last week, the subject will be included in that visit and will not be included in the ET visit.

If the date of first dose of double-blind study drug is missing, then for summary purposes the day after the first dispense date will be used as an estimate for the date of first dose. However, if all dispensed study drug is returned, then the subject is assumed to have not taken any study drug, and the first dose date will not be imputed.

If the date of last double-blind study drug dose is missing, then the earliest of the following dates will be used for the last dose date for analysis and summary purposes: date of death, date of last visit (recorded in the eCRF), last double-blind study drug return date, and the last double-blind study drug dispense date (if the last drug return date is missing) + 7 days for Part A and D; +14 days for Part B and C (ie, the longest double-blind study drug dispensing interval).

Table 7.a Visit Windows (Days) for Scheduled Visits During the Treatment Period—Part A and D

Visit	Scheduled Day	Lab, VS, ECG	PK
Baseline[a]	-1	≤1	
Day 1 Post Dose / Day 2[b]	1	1	1
Week 1	7	4 – 10	4– 10
Week 2	14	11 – 17	11 – 17
Week 3	21	18 – 24	18 – 24
Week 4/ET	28	ET: the Last Dosing Day + 7 Week 4: 25- 28	(the Last Dosing Day -3) (the Last Dose + 3)

a. last non-missing value prior to the first dose is defined as Baseline.

b. Labs and ECG are scheduled on Day 2, others are scheduled on Day 1 post dose.

ET: early termination.

Table 7.b Visit Windows (Days) for ABPM for Scheduled Visits During the Treatment Period---Part A

1

Visit	Scheduled Day	Part A ABPM
Baseline[a]	-45 to -3	<1[b]
Week 1	5	3-7
Week 3	19	12 – the Last Dosing Day

a. ABPM readings will be obtained over 24 hours at home before Day -2 check-in.
b. last non-missing value prior to the first dose is defined as Baseline.

Table 7.b Visit Windows (Days) for ABPM for Scheduled Visits During the Treatment Period---Part D

2

	Scheduled Day	Part D ABPM
Baseline[a]	-45 to -3	<1[b]
Week 1	3-6	3-6
Week 3	15-20	15-20

a. ABPM readings will be obtained over 24 hours at home before Day -2 check-in.
b. last non-missing value prior to the first dose is defined as Baseline.

Table 7.c Visit Windows (Days) for Scheduled Visits During the Treatment Period—Part B and C

Visit	Scheduled Day	MWT	ESS	Lab, VS, ECG	[redacted]
Baseline[a]	-1	≤1	≤1	≤1	
Day 1 Post Dose/Day 2	1	1	1	1	
Week 1	7	[redacted]	[redacted]	4 – 10	
Week 2	14			11 – 17	
Week 3	21			NA	
Week 4	28			25 – 31	
Week 5	35			NA	
Week 6	42			39 - 45	
Week 7	49			NA	
Week 8/ET	56	the Last Dosing Day+-3	the Last Dosing Day	ET: the Last Dosing Day + 7 Week 8: 53- 56	[redacted]

a. last non-missing value prior to the first dose is defined as Baseline.
ET. early termination.

Table 7.d Visit Windows (Days) for ABPM for Scheduled Visits During the Treatment Period---Part B and C

Visit	Scheduled Day	ABPM
Screen/Baseline[a]	-45 to -3	<1[b]
Week 2	3-12	3-13
Week 3	15-25	15 – 25
Week 6	43-54	43-54

a. ABPM readings will be obtained over 24 hours at home before Day -2 check-in.
b. last non-missing value prior to the first dose is defined as Baseline.

For other efficacy and safety data, data that are obtained more than 3 days after the last dose of study medication (start date – last dose date +1 >3) will be listed but excluded from summaries and analyses. Adverse events that start more than 30 days after the last dose of study medication (start date – last dose date +1>30) will be listed but excluded from the summaries and analyses.

7.1.4 Conventions for Missing Adverse Event Dates

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If month and year are known but day is missing.
  - If month and year are the same as month and year of first dose date, then impute to first dose date.
  - If month and year are different than month and year of first dose date, then impute to first date of the month
- If year is known but day and month are missing.
  - If year is same as year of 1st dose date, then 1st dose date will be used instead.
  - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.
- If start date is completely missing, using first dosing date to impute it.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.

- If year is known, but day and month are missing.
  - If YYYY ≤year of last dose, then 31st of December will be imputed.
  - If YYYY >year of last dose, then 1st of January will be imputed.
- If all are missing, no imputation is necessary. The event will be considered "ongoing."

If an AE is ongoing, AE stop date could be missing. Otherwise, AE stop date could be imputed per above rules. If a subject dies during the study and AE stop date is missing, then the death date will be used for AE stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

The imputed dates will not be populated on the data listing, they are used for derivation purpose only. The actual and incomplete date will be on the data listing.

7.1.5 Conventions for Missing Concomitant Medication Dates

Concomitant medications with start date that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month.
- If year is known, but day and month are missing, then 1st of January of the year will be imputed.

Concomitant medications with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing.
  - If YYYY ≤year of last dose, then 31st of December will be imputed.
  - If YYYY >year of last dose, then 1st of January will be imputed.
- If all are missing, no imputation is necessary. Concomitant medication will be considered as "ongoing".

If a concomitant medication is ongoing, the stop date could be missing. Otherwise, concomitant medications stop date could be imputed per above rules. If a subject dies during the study and the concomitant medication stop date is missing, then the death date will be used for the stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

The imputed dates will not be populated on the data listing, they are used for derivation purpose only. The actual and incomplete date will be on the data listing.

7.1.6 Conventions for Missing PK Data

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarization of concentration values. The treatment of BLQs for the calculation of PK parameters, and exclusions/flagging of PK concentration and parameter data will follow the processes detailed in the Clinical Pharmacology Analysis Plan (CPAP).

7.1.7 Conventions for Missing Efficacy Data

If not specified, the primary analysis on the change from baseline in mean sleep latency, total ESS scores and WCR will be performed using MMRM. Sensitivity analyses to evaluate the impact of missing data will be performed for Part B only. Following imputation methods will be used for these sensitivity analyses:

- A multiple imputation (MI) procedure to assess the impact of missing data and drop-outs. The analysis based on MI assumes the data to be missing at random stratified within each treatment group while retaining consistency for each subject across various visits.
- ANCOVA method which the response variable will be the change from baseline to Week 8 only, using only the observed case (OC) data.
- Missing data will be imputed by the worst observation among all subjects at Week 8.
- Missing data will be imputed by the average from the placebo arm.
- [redacted]

7.2 Major Protocol Violation

Major Protocol Violations which will be used to identify the Per Protocol Set for Part B include:

1. Subject took study drug of a treatment different from the one randomized.
2. Dosing compliance is outside of the range of 70%-130%.
3. Prohibited medication use that potentially could have an effect on sleep latency from the MWT procedure at Week 8.
4. Subject has been off IP for more than 3 days prior to the last visit.

Additional major protocol violations may be identified prior to unblinding. If so, the additional criteria will be finalized and documented prior to database lock and used to select subjects into the Per Protocol Set. Major Protocol Violations will be summarized in the table by treatment groups including overall, and presented in the listings.

In addition to the major protocol violations defined above, significant protocol deviations collected in eCRF will be summarized by the categories and treatment groups, as well as listed in the listings.

7.3 Analysis Sets

All subjects who are randomized more than once will be excluded from all analysis sets. A summary of all analysis sets will be presented by treatment groups and overall.

Safety Set

The safety set will consist of all subjects who are randomized and receive at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries. In summaries and analysis using the Safety Set, subjects will be analyzed by the treatment to which they received.

PK Set

The PK analysis set will consist of all subjects who receive at least 1 dose of TAK-994 and have at least 1 measurable plasma concentration. In summaries and analysis using the Safety Set, subjects will be analyzed by the treatment to which they received.

[redacted]

Full Analysis Set (FAS)

A full analysis set will be used for the analysis of primary efficacy endpoints. It consists of subjects who are randomized to the study and receive at least 1 dose of double-blind study drug after randomization. In the Full Analysis Set efficacy summaries and analysis, subjects will be analyzed by the treatment to which they are randomized. The Full Analysis Set will be used for the efficacy analysis for Part B subjects, as well as the subgroups defined in Section 7.1.1 if efficacy analysis will be performed for the subgroup. In these analysis, subjects with baseline measures and at least one post dose values will be included.

Per Protocol Set (PPS)

All subjects in the FAS excluding any subjects who had major protocol violations. Per Protocol Set analyses will be performed only for Part B.

7.4 Disposition of Subjects

All summaries in this section will be performed for Part A, B, C, and D, as well as subgroups defined in Section 7.1.1, respectively.

Disposition of all screened subjects will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

- All subjects who signed informed consent form.
- All subjects who were randomized.
- All subjects who were not randomized.

The primary reasons for subjects who were not randomized will be summarized.

Disposition of randomized subjects will be tabulated as below by corresponding treatment groups and overall:

- All subjects who randomized but did not receive any study drug.
- All subjects who received at least one dose of study drug.
- Subjects who completed the study drug.
- Subjects who prematurely discontinued study drug.
- Subjects who completed all study visits.
- Subjects who prematurely discontinued study visits.

Primary reasons for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. The primary reasons for premature discontinuation of study drug/study visit will be presented for each subject in listings.

7.5 Demographic and Other Baseline Characteristics

All summaries in this section will be performed for Part A, B, C, and D, as well as subgroups defined in Section 7.1.1, respectively.

Demographics of the screening failures collected on the eCRF will be summarized.

For subjects in the Safety Set, demographics and other baseline characteristics will be summarized by treatment groups and will be listed. Data from subjects receiving the same dose, including placebo, will be pooled across cohorts or parts as appropriate. Descriptive statistics will be used to summarize data for continuous variables like age and weight (number of subjects [N], mean, median, SD, minimum, and maximum) and for categorical variables like sex, ethnicity, race, HLA positive/negative, and baseline WCR (≤8 vs. >8) (number and percentage of subjects within each category).

Individual subject demographic and baseline characteristic data will be listed. Study part and/or cohorts will be included in the listing.

7.6 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases present at signing of informed consent. Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, Version 23 or higher) coding system.

All summaries in this section will be performed for Part A, B, C, and D, as well as subgroups defined in Section 7.1.1, respectively.

Medical history and concurrent medical conditions will be summarized using the Safety Set by treatment group and overall using system organ class (SOC) and preferred term (PT). The table will include number and percentages of subjects. The denominator used for calculating the percentages will be the total number of subjects included in each treatment group. SOC will be sorted in alphabetical order and the PT will be sorted in decreasing frequency based on the total number of subjects. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms.

All medical history and concurrent medical condition data will be listed by subject. The listing will contain study part, cohort, subject identifier, treatment, system organ class (SOC), preferred term (PT), whether there was any medical history or concurrent condition, and, if yes, a detail of the medical history or concurrent condition.

7.7 Medication History and Concomitant Medications

Medication history information obtained includes any medication stopped at or within 28 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

All summaries in this section will be performed for Part A, B, C, and D, as well as subgroups defined in Section 7.1.1, respectively.

Medication history and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO Drug) and summarized by treatment groups and overall by giving the number and percentage of subjects by preferred term within each therapeutic class, with therapeutic class and medications in each class sorted in alphabetical order. If a subject reports taking 2 drugs belonging to the same class, he/she will only be counted once within that class.

The Safety Set will be used for the summaries of medication history and concomitant medication. For concomitant medications, the above summaries will be provided for the concomitant medication that started or continued from informed consent and stopped prior to the first dose of study drug, that started or continued during the screening period and continued into the treatment period, and started after the first dose of the study drug. All medication history and concomitant medications data will be listed by subject including the duration of concomitant condition. Study part and/or cohorts will be included in the listing.

7.8 Study Drug Exposure and Compliance

All summaries in this section will be performed for Part A, B, C, and D, as well as subgroups defined in Section 7.1.1, respectively.

The date and time of each dose for each subject will be reported in the data listing. Listings and summary statistics for TAK-994 plasma concentrations and pharmacokinetic parameters will also be provided.

The summary of study drug exposure and compliance will be based on the Safety Set. Duration of exposure to study medication for each subject is defined as (date of last dose – date of first dose +1). In the event that the date of last dose is missing, the last dose date will be estimated as described in Section 7.1.3.

Treatment duration (days) will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment group and overall.

For each Part, percent of study drug compliance associated with the dose for each bottle (10 mg or 10 mg placebo, 30 mg or 30 mg placebo, 90 mg or 90 mg placebo) is defined as:

$$\frac{(number\ of\ tablets\ of\ a\ dose\ dispensed - number\ of\ tablets\ of\ the\ dose\ returned)}{number\ of\ bottles\ associated\ with\ that\ dose * 2 * (date\ of\ last\ dose - date\ of\ first\ dose + 1)} * 100\%$$

If a value for the number of returned tablets is missing or the return date is missing, then 100% compliance will be assigned for each day up to the number of tablets dispensed or up to the date of return or the date of completion if the date of return is missing, whichever is earlier. The overall compliance for a treatment group will be the average of these percentages.

For each treatment group, study medication compliance will be summarized by the dose associated with the bottles (ie, 10 mg or 10 mg placebo, 30 mg or 30 mg placebo, 90 mg or 90 mg placebo) and overall using the number of subjects and the frequency in each compliance category (<70%, 70 to 130%, and ≥130%). Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment group.

All study drug administration and accountability data will be listed by treatment, study site, and subject number. The following variables will be listed: study part, subject identifier, site number, visit number, first and last dose dates, medication bottle identification number, dose associated with the medication bottle, date dispensed and returned, number of tablets dispensed and returned, and compliance percentage.

7.9 Efficacy Analysis

The analyses described in this section will be performed for Part B and the subgroups defined in Section 7.1.1, respectively. Sensitivity analyses for the primary efficacy endpoint will also be described. All summary statistics described will be performed for both Parts B and C. If there are sufficient number of subjects in Part C, inferential statistical analyses might be performed for Part C.

The planned summaries and analyses for other efficacy endpoints are described in Section 7.11.

The analysis is focused on the following efficacy endpoints:

- Sleep latency from MWT;
- Epworth sleepiness scale total scores;
- Weekly cataplexy rate and [redacted]

A fixed-sequence hypothesis testing procedure will be used for the primary efficacy endpoints and key secondary endpoints. The following testing order in comparison to placebo will be of change from baseline to Week 8 (Day 56) in: sleep latency at TAK-994 high dose, sleep latency at TAK-994 middle dose, ESS at TAK-994 high dose, ESS at TAK-994 middle dose, WCR at TAK-994 high dose, and WCR at TAK-994 middle dose. If the p-value from the last comparison, WCR between TAK-994 middle dose and placebo is <0.05, then the test will continue to sleep latency at TAK-994 low dose, ESS at TAK-994 low dose, and WCR at TAK-994 low dose. If p-value>0.05 at any of these steps, the hypothesis test will be stopped. Superiority of TAK-994 over placebo will be considered established at 0.05 in all comparisons between TAK-994 and placebo conducted before this step. No superiority of TAK-994 over placebo is established for the comparisons at this step and thereafter. Details will be described in the following subsection of 7.9.1, 7.9.2, 7.9.3 and 7.9.4 by Step 1 to Step 9.

7.9.1 Sleep Latency and other MWT Parameters

Sleep latency and other MWT parameters will be derived for each of the 4 MWT sessions on Day -1 and post dose days as described in the protocol. The mean of a parameter from the 4 MWT sessions on a given day will be calculated for each subject. If there are 2 or more missing values, the mean will be assigned as missing for that day. In addition, change from time-matched baseline for each MWT parameter and the change from baseline for the mean of the 4 MWT sessions will be derived for each subject.

All summary statistics (N, mean, median, SD, minimum, and maximum) will be prepared for the each MWT parameters for each MWT session and the mean of the 4 MWT sessions by treatment at baseline and post dose days. Summary statistics will also be prepared for the change from baselines to post dose days by treatment. FAS will be used for these summaries.

7.9.1.1 Analysis of the Primary Efficacy Endpoint – Change from Baseline in Mean Sleep Latency to Week 8

The primary efficacy endpoint, change from baseline in mean sleep latency to Week 8, will be analyzed using the linear mixed-effect models for repeated measures (MMRM). Change from baseline in mean sleep latency will be the response. The models will contain fixed effects for baseline, treatment, visit (Day 1, [redacted] and Week 8), and the treatment-by-visit interaction. Visit will be a repeated factor. The least squares means of change from baseline in mean sleep latency for each treatment and the associated SE and 95% CI will be calculated for each week, along with all pairwise differences from placebo and associated SEs, 95% CIs, and p-values.

FAS will be used as the primary analysis. Following fixed hierarchical testing order will be used with the p-values from the MMRM model above to control the overall type 1 error rate of 0.05 for the primary efficacy endpoint:

Step 1: A test for significant difference between TAK-994 high dose vs. placebo will be performed at 5% level. If the p-value is ≤0.05, then proceed to Step 2. Otherwise, the test will be stopped.

Step 2: A test for significant difference between TAK-994 middle dose vs. placebo will be performed at 5% level. If the p-value is >0.05, then the test will be stopped.

Sensitivity analysis using PPS will be performed. In addition, evaluation of the impact of missing data on the primary analysis will be performed as described in Section 7.1.7.

The above MMRM analysis will also be performed for other MWT parameters.

The above MMRM analysis will also be performed using data from Part B subjects in the following groups defined in Section 7.1.1 if each of the subgroups contains at least 20% of the total subjects in Part B. FAS will be used. The treatment groups will be compared within each subgroup. [redacted]

[redacted]

7.9.1.2 [redacted]

7.9.1.2.1 [redacted]

[redacted]

7.9.1.2.2 [redacted]

7.9.1.2.3 [redacted]

7.9.2 Epworth Sleepiness Scale (ESS)

ESS will be measured at baseline and Days 1 (post dose), 14 (Week 2), [redacted], 42 (Week 6) and 56 (Week 8), and the total scores will be derived and summarized for each visit. Change from baseline in the ESS total scores to each post dose visit will be derived for each subject and summarized. ESS data will be presented in the listing. Summary statistics by treatment will be provided for observed ESS total score at baseline and post dose days, as well as for the change and percent change from baseline. In addition, number and percent of subjects with total ESS score <10 will be summarized at each visit by treatment groups. Shift tables will be presented. FAS will be used.

7.9.2.1 The Analysis of the Key Secondary Endpoint – Change from Baseline in Total ESS Score to Week 8

Similar to the analysis of the primary efficacy endpoint, linear mixed effect model for repeated measures (MMRM) will also be used to evaluate the effect of TAK-994 on the change from baseline in the total ESS score. Baseline total ESS score will be included as the covariate in the

model. Visit, treatment, and treatment-by-visit interaction will be included as fixed effect. Baseline CSF orexin levels may be evaluated as a covariate in a sensitivity analysis if there is sufficient data. The least squares means of change from baseline in total ESS score for each treatment and the associated SE and 95% CI will be calculated for each visit, along with all pairwise differences from placebo and associated SEs, 95% CIs, and p-values.

FAS will be used as the primary analysis. Following fixed hierarchical testing order using the p-values from above MMRM model will be used to control the overall type 1 error rate of 0.05 if the p-value for Step 2 in Section 7.9.1.1 is ≤0.05:

> Step 3: A test for significant difference between TAK-994 high dose vs. placebo will be performed at 5% level. If the p-value is ≤0.05, then proceed to Step 4. Otherwise, the test will be stopped.
>
> Step 4: A test for significant difference between TAK-994 middle dose vs. placebo will be performed at 5% level. If the p-value is >0.05, then the test will be stopped.

Sensitivity analysis using PPS will be performed. In addition, evaluation of the impact of missing data will be performed as described in Section 7.1.7.

Above MMRM analysis will also be performed using data from Part B subjects in the following groups defined in Section 7.1.1 if each of the subgroups contains at least 20% of the total subjects in Part B. FAS will be used. The treatment groups will be compared within each subgroup. [redacted]

[redacted]

7.9.2.2 [redacted]

7.9.2.2.1 [redacted]

[redacted]

[redacted]

7.9.2.2.2 [redacted]

[redacted]

7.9.3 Weekly Cataplexy Rate (WCR) [redacted]

Subjects with narcolepsy will complete a daily ePRO diary to record narcolepsy symptoms. Subjects will record partial or complete episodes of cataplexy, including the time of occurrence, severity (including body location), and other aspects, in the diary. [redacted] Information on nocturnal awakenings, total sleep time, and naps during the day will also be recorded. All above information will be provided in the listings.

Weekly cataplexy rate (WCR) at baseline will be derived as the average number of cataplexy episodes over the last 2 weeks prior to the first dose of the study drug over non-missing diary days. with a minimum 11 out of 14 compliant days in completion of the self-reported electronic diary for cataplexy episodes are required. Otherwise, the baseline WCR will be considered missing.

WCR for post dose visit will be calculated for [redacted] ([redacted] Week 8), and will be calculated as below:

[redacted]

If a diary for a given day reports ≥0 cataplexy, the day will be counted as a non-missing diary day. If a diary for a given day does not report any cataplexy count (including 0), the day will be counted as a missing diary day for the cataplexy. A minimum of 10 out of 14 non-missing diary days are required for the calculation of the WCR. Otherwise, the WCR will be considered missing for that week.

WCR will be summarized by treatment at baseline and post dose weeks ([redacted] Week 8). In addition to the means, geometric means for the observed WCR will be presented. The change and % change in the WCR from baseline to post dose weeks will also be summarized. FAS will be used.

For the inferential analyses in the following Section 7.9.3.1 to Section 7.9.3.4, post dose WCR at [redacted] Week 8 will be calculated using Study Days [redacted] and Study Days 29 to 56, respectively:

$$WCR = \left(\frac{Total\ number\ of\ cataplexy\ over\ a\ number\ of\ non-missing\ diary\ days\ for\ a\ given\ duration}{number\ of\ non-missing\ diary\ days\ in\ that\ duration}\right) * 7$$

A minimum of 70% non-missing diary days are required for the calculation of the WCR at [redacted] Week 8. Otherwise, the WCR will be considered missing for that week.

7.9.3.1 Analysis of the Key Secondary Endpoints – Weekly Cataplexy Rate at Week 8

A generalized linear-mixed model for repeated measures featuring Poisson regression will be used to evaluate the drug effect on the WCR. The response variable will be the total number of cataplexy for Weeks 4 and 8. The model will include treatment, weeks and treatment by weeks interaction as fixed factors, and adjusted for baseline WCR, and exposure time (as in weeks) as offset variables. In case of overdispersion (the estimated scale parameter >2), a negative binomial regression will be used. An unstructured variance-covariance structure will be used initially in these models. Other variance-covariance structures will be evaluated if there are convergence issues with the model. If lack-of-convergence still exist, the analysis will be done for Week 4 and Week 8 separately. The estimated incident rate ratio (IRR) of weekly cataplexy comparing treatment groups to placebo for each week, and the associated SEs, 95% CIs, and p-values will be estimated from the model. If lack-of-convergence still exists, then non-parametric analysis described in Section 7.9.3.2 will be performed.

The FAS will be used for this analysis. Following fixed hierarchical testing order using the p-values from the convergent model will be used to control the overall type 1 error rate of 0.05 if the p-value for Step 4 in Section 7.9.2.1 is ≤0.05:

> Step 5: A test for significant difference between TAK-994 high dose vs. placebo will be performed at 5% level. If the p-value is ≤0.05, then proceed to Step 6. Otherwise, the test will be stopped.
>
> Step 6: A test for significant difference between TAK-994 middle dose vs. placebo will be performed at 5% level. If the p-value is >0.05, then the test will be stopped.

Sensitivity analysis using PPS will be performed. In addition, evaluation of the impact of missing data will be performed as described in Section 7.1.7.

The above analysis will also be performed using data from Part B subjects in the following groups defined in Section 7.1.1 if each of the subgroups contains at least 20% of the total subjects in Part B. FAS will be used. The treatment groups will be compared within each subgroup. [redacted]

7.9.3.2 Non-Parametric Analysis

In addition to the Poisson model, %change in weekly cataplexy frequency from baseline to each Week 4 and Week 8 will be compared with treatment group and placebo using a non-parametric the Kruskal–Wallis One-way ANOVA test by ranks. Chi-square statistics with associated degree of freedom and p-values will be reported from the test. FAS will be used for this analysis.

7.9.3.3 Linear-Mixed Effect for Repeated Measures on the Natural Log Scale

The third type of analysis to evaluate the effect of TAK-994 on WCR is Week 4 and Week 8 to baseline WCR ratios, respectively. For each subject, the ratio of WCR at Weeks 4 and 8 to that of baseline will be naturally log-transformed. MMRM will be used to analyze the log-transformed ratios. A natural-log-transformed baseline WCR will be included in the model as a covariate, each post dose visit, treatment, and treatment-by-visit interaction will be the fixed effect. Visit will be the repeated factor. An unstructured variance-covariance structure will be used. In the case that if WCR is 0 for one subject at a visit, 0.0001 will be added to all values for the calculation of log transformation.

MMRM will include calculation of least-squares means (LSM) as well as the difference between each of TAK-994 dose group and placebo in the LSM. Central value ratios will be calculated using the exponentiation of the difference between treatment LSM. These ratios will be expressed as a percentage relative to the placebo. 95% confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSMs resulting from the MMRM on the ln-transformed WCR ratio's. The CIs will be expressed as a percentage relative to placebo. FAS will be used for this analysis.

7.9.3.4 [redacted]

7.9.3.4.1 [redacted]

[redacted]

7.9.3.4.2 [redacted]

[redacted]

7.9.4 Efficacy Evaluation at the Low Dose

If the p-value in Step 6 (Section 7.9.3.4.1) is ≤0.05, following hypothesis testing will be performed to evaluate the drug effect at low dose:

Step 7: A test for significant difference in the change from baseline in mean sleep latency between TAK-994 low dose vs. placebo will be performed at 5% level using the MMRM model described in Section 7.9.1.1. If the p-value is ≤0.05, then proceed to Step 8. Otherwise, the test will stop.

Step 8: A test for significant difference in the change from baseline in the total ESS score between TAK-994 low dose vs. placebo will be performed at 5% level using the MMRM model described in Section 7.9.2.1. If the p-value is ≤0.05, then proceed to Step 9. Otherwise, the test will stop.

Step 9: A test for significant difference in the weekly incidence rate of cataplexy between TAK-994 low dose vs. placebo will be performed at 5% level using the Poisson model described in Section 7.9.3.1. If the p-value is ≤0.05, then statistical significance at the low dose for WCR will be considered achieved.

7.10 Pharmacokinetic Analysis

For Part A and D, the PK parameters of TAK-994 will be determined for Study Days 1, 14 and 28 from serial samples collected on Study Days 1-2, 14, and 28-29 using noncompartmental analysis methods as data permit.

[redacted]

All PK summaries and analyses will be based on the PK set by dose levels within each part or each group.

Individual plasma concentrations of TAK-994 in subjects with NT1 or NT2 will be presented in a data listing, and summarized using descriptive statistics (N, arithmetic mean, SD, coefficient of variation, median, minimum, maximum) by each scheduled time point and dose level.

Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following PK parameters will be calculated from plasma concentrations of TAK-994, as data permit:

Table 7.e Plasma PK Parameters Definition

Symbol/Term	Definition
AUC_{τ}	AUC during a dosing interval, where τ is the length of the dosing interval
AUC_{last}	AUC from time 0 to time of the last quantifiable concentration
$C_{av,ss}$	Average plasma concentration during a dosing interval, at steady state, calculated as AUC_{τ}/τ
C_{max}	Maximum observed concentration
$C_{max,ss}$	Maximum observed concentration during a dosing interval, at steady state
C_{trough}	Trough plasma concentration at steady state (observed concentration at the end of a dosing interval measured directly before the next study drug administration)
t_{max}	Time to reach C_{max}

Additional PK parameters may be calculated as appropriate. Details will be documented in the CPAP.

Individual PK parameters will be presented in a data listing for each subject. The listings will include study parts and cohorts. Summary statistics for PK parameters (N, arithmetic mean,

standard deviation, geometric mean, coefficient of variation, median, minimum, maximum) will be provided by day and dose level.

Additionally, all individual TAK-994 plasma concentration-time data collected in this study will be combined with other clinical study data to develop a population PK model of TAK-994 in subjects with NT1 or NT2. The objectives and details of this modeling approach will be described in a separate analysis plan, and the results of this analysis will be reported separately.

For every Part, the intrinsic CYP3A4/5 activity will be evaluated by the ratio of 4β-hydroxycholesterol vs cholesterol concentrations. The ratios of 4β-hydroxycholesterol over cholesterol, and the ratios of the postdose values to that of baseline will be summarized by each treatment group (dose) and day in each Part.

7.11 [redacted]

[redacted]

7.11.1 [redacted]

[redacted]

7.11.1.1 [redacted]

[redacted]

[redacted]

7.11.1.2 [redacted]

[redacted]

7.11.1.3 [redacted]

[redacted]

[redacted]

7.11.2 [redacted]

[redacted]

7.11.3 [redacted]

[redacted]

[redacted]

7.11.4 [redacted]

[redacted]

7.11.5 [redacted]

[redacted]

7.11.6 [redacted]

[redacted]

[redacted]

7.11.7 [redacted]

[redacted]

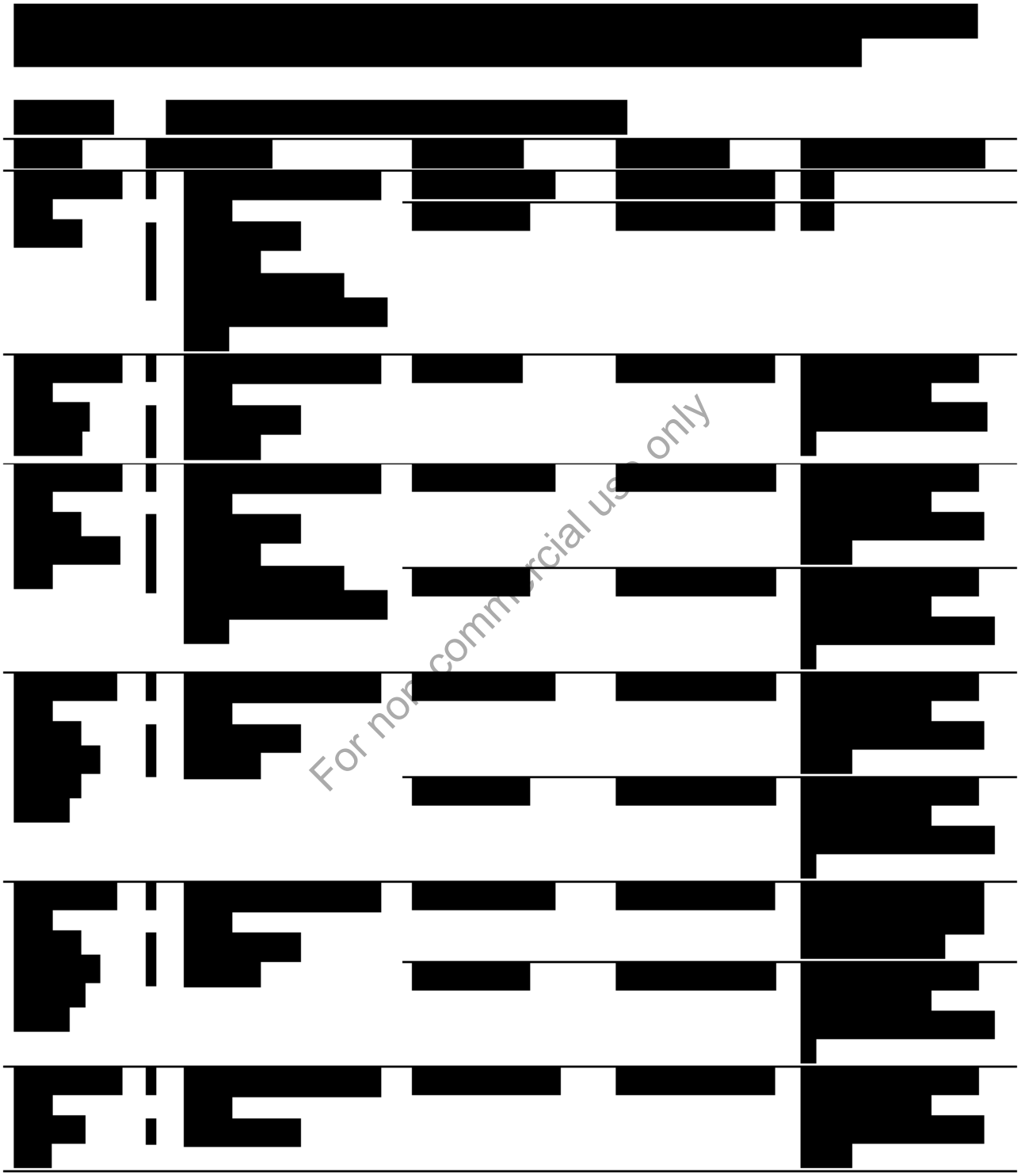
[redacted]

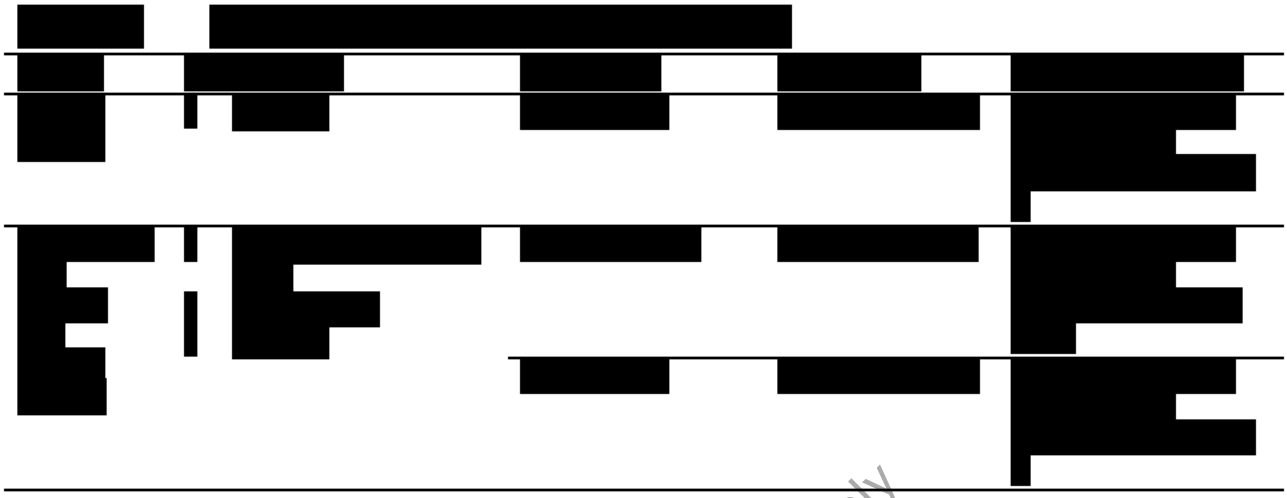
7.11.8 [redacted]

[redacted]

7.11.9 [redacted]

[redacted]





7.12 Safety Analysis

Safety measures include TEAEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters. The Safety Analysis Set will be used for all summaries for safety data.

The safety summaries will be presented by treatment group for each part. Data from subjects receiving placebo will be pooled across cohorts in Parts A and D. Details about analysis by parts will be described in Section 7.12.1 to 7.12.6. Group analysis for selected safety endpoints will be performed. Subjects receiving the same treatment across different parts will be pooled together in these analyses. Details about group analyses will be described in Section 7.12.7.

7.12.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA.

The Treatment-Emergent Adverse Events (TEAE) summary tables will include numbers and percentages of subjects experiencing at least one TEAE by SOC and PT and will be tabulated by treatment. The TEAEs will also be summarized for all subjects in the overview assessment. The following is a list of TEAE summary tables to be generated:

- Overview of Treatment-Emergent Adverse Events. Overall will be presented in this table only.
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Treatment-Emergent Adverse Events by Preferred Term.
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Most Frequent (≥2 subjects or ≥5% based on total number of safety set subjects in any treatment group, whichever larger) Treatment-Emergent Adverse Events by Preferred Term.

- Most Frequent (≥2 subjects or ≥5% based on total number of safety set subjects in any treatment group, whichever larger) Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by Preferred Term.
- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Treatment-Emergent Adverse Events by alcohol consumption status (Yes or No) and treatment group (for Part B, C and D only)

In addition, the details of urinary TEAEs symptom will be listed (the listing will include all the item in the urinary symptoms form as well as the corresponding TEAE onset time, duration, and treatment group). The number of subjects with at least one urinary symptom, the number of subjects with >=1 increased urinary frequency reported, and descriptive statistics (N, mean, SD, median, minimum and maximum) for each symptom in the form of urinary event caused by TEAE will be provided for each treatment group.

Data listings will be provided for all AEs including: TEAEs, AEs leading to death, AEs leading to study drug or study visit discontinuation, SAEs and death.

7.12.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis. A list of all the clinical laboratory evaluations can be found in Protocol Section 9.2.1.1.

Descriptive statistics (N, mean, SD, median, minimum and maximum) of clinical laboratory variables will be summarized for baseline and post-dose values, as well as change from baseline to post dose values by study visits and treatment. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for clinical laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal values (MAV) criteria (Appendix A) using the result and criteria in SI units. All subjects with at least 1 post-dose laboratory result that meets the MAV criteria will be presented in a data listing.

The number and percentage of subjects with at least 1 post-dose markedly abnormal laboratory test result will also be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying laboratory result. All post-dose clinical lab MAV results, including scheduled and unscheduled measurements, will be included in the MAV summaries.

Listings of all clinical safety laboratory data will be provided in the listings and will be presented in both SI and conventional units (and CV units, if available). Laboratory data outside of the normal reference range will be indicated in the listings.

7.12.3 Vital Signs

Vital sign measurements include blood pressure (SBP and DBP), pulse, respiratory rate, and body temperature.

SBP, DBP and pulse will be summarized (N, mean, SD, median, minimum and maximum) for baseline, postdose, and change from baseline (or change from time-matched baseline to postdose, if appropriate) by treatment. Only the scheduled measurements will be included in the summary.

Summary statistics (N, mean, SD, median, minimum and maximum) of vital sign measurements will be provided for those scheduled pre dose measurements.

Respiratory rate, weight and temperature will be summarized for baseline, postdose, and change from baseline at each time point by treatment.

All individual vital signs that meet Takeda's predefined criteria for MAVs (Appendix B) will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal vital sign measurement will be summarized by treatment. Time-matched baselines should be used when they are available for blood pressure and pulse. Subjects who meet the MAV criteria will be mapped to their respective qualifying vital sign result. All post-dose MAV vital signs, including both scheduled and unscheduled measurements, will be included in the MAV summaries. Listings of all vital signs data will be provided in the listings, and vital sign MAVs will be flagged.

In addition, the drug effect on clinic BP and pulse at pre and post treatment time points will be analyzed by post dose visit using a linear mixed effects model for repeated measures (MMRM). In this model, change from time-matched baseline to the post dose visit will be the response; baseline will be the covariate, treatment, time points, and treatment by time point interaction will be the fixed effects. The estimated change from baseline in SBP, DBP and pulse for each treatment and the associated SE and 95% CI will be extracted from the model at each time, along with all pairwise differences from placebo and associated SEs, 95% CIs, and p-values. Unstructured variance-covariance structure will be used initially in these models. Other variance-covariance structures will be evaluated if there are convergence issues with the model.

The post dose visit with matched timepoint is summarized in Table 7.h.

Table 7.h Summary of VS Post Dose Visit and Matched Timepoint

Visit	Post Dose Timepoints	Baseline Time-matched Timepoints
Day 1	Predose, hour 1, 3, 5, 7, 9, 12, 14 and 24	Study Day -1 measures at 1, 3, 5, 7, 9, 12, 14 hour will be used to match timepoints of 1, 3, 5, 7, 9, 12, 14 h post Study Day 1 AM dose; Study Day 1 pre-dose measure will be used to match Study Day 1 24 post dose
Week 2 (Part A and D only)	Predose, hour 1, 3, 5, 7, 9 and 12	Study Day -1 measures at 1, 3, 5, 7, 9, 12, 14 hour will be used to match timepoints of 1, 3, 5, 7, 9, 12, 14 h post Study Day 14 AM dose; Study Day 1 pre-dose measure will be used to match Study Day 14 24 post dose
Week 4/ET	Predose, hour 1, 3, 5, 7, 9, 12, 14 and 24	Study Day -1 measures at 1, 3, 5, 7, 9, 12, 14 hour will be used to match timepoints of 1, 3, 5, 7, 9, 12, 14 h post Study Day 28 AM dose; Study Day 1 pre-dose measure will be used to match Study Day 28 24 post dose
Week 8/ET (Part B and C only)	Predose, hour 1, 3, 5, 7, 9, 12, 14 and 24	Study Day -1 measures at 1, 3, 5, 7, 9, 12, 14 hour will be used to match timepoints of 1, 3, 5, 7, 9, 12, 14 h post Study Day 56 AM dose; Study Day 1 pre-dose measure will be used to match Study Day 56 24 post dose

7.12.4 Analysis for ABPM

7.12.4.1 Derivation of ABPM Parameters

The analysis of ambulatory BP will be based on the following variables that are obtained by summarizing the individual ambulatory BP measurements (SBP, DBP and HR), namely: hourly mean ABPM (baseline and post dose), 0- to 24-hour post dose mean ambulatory BP, 0- to 12-hour post dose mean ambulatory BP, daytime mean ambulatory BP, and nighttime mean ambulatory BP. The derived parameters will be:

- The hourly mean ABPM values will be calculated by taking the average of all observations in each hour post dose.
- The baseline 0- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the first ABPM observation and including all observations recorded over the subsequent 24 hours (any observations that are recorded ≥24 hours after the first observation will be excluded).
- The Day 5 0- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the Day 5 study medication dose and including all observations recorded over the 24-hour period following that dose.

- The Day 19 0- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the Day 19 study medication dose and including all observations recorded over the 24-hour period following that dose.
- The baseline 0- to 12-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the first ABPM observation and including all observations recorded over the subsequent 12 hours.
- The Day 5 0- to 12-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the Day 5 study medication dose and including all observations recorded over the 12-hour period following that dose.
- The Day 19 0- to 12-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the Day 19 study medication dose and including all observations recorded over the 12-hour period following that dose.
- The baseline 12- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning at 12-hour first ABPM observation and over the subsequent 12 hours.
- The Day 5 12- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the 12-hr post the Day 5 study medication dose and up to the 24-hr post the Day 6 dosing.
- The Day 19 12- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the 12-hr post the Day 19 study medication dose and up to the 24-hr post the Day 19 dosing.
- The Day 54 0- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the Day 54 study medication dose and over the 24-hour period following that dose. (for Part B and C only)
- The Day 54 0- to 12-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the Day 54 study medication dose and over the 12-hour period following that dose. (for Part B and C only)
- The Day 54 12- to 24-hour mean ambulatory BP will consist of the average (arithmetic mean) of ABPM measurements over the time period beginning with the 12-hr post the Day 54 study medication dose and up to the 24-hr post the Day 54 dosing. (for Part B and C only)
- The daytime mean ambulatory BP will consist of the average of those ABPM measurements that were included in the respective 24-hour mean ambulatory BP calculations and were also recorded between the hours of 6 AM (inclusive) and 10 PM (exclusive).
- The nighttime mean ambulatory BP will consist of the average of those ABPM measurements that were included in the respective 24-hour mean ambulatory BP calculations and were also recorded between the hours of 12 AM (inclusive) and 6 AM (exclusive).

Those parameters are summarized in the Table 7.i below:

Table 7.i Summary of ABPM Derived Parameters

ABPM Parameters (apply for SBP, DBP and HR)	Applied Parts
Hour mean of ambulatory BP	Part A, B, C and D
The baseline 0- to 24-hour mean ambulatory BP	Part A, B, C and D
The Day 5 0- to 24-hour mean ambulatory BP	Part A, B, C and D
The Day 19 0- to 24-hour mean ambulatory BP	Part A, B, C and D
The baseline 0- to 12-hour mean ambulatory BP	Part A, B, C and D
The Day 5 0- to 12-hour mean ambulatory BP	Part A, B, C and D
The Day 19 0- to 12-hour mean ambulatory BP	Part A, B, C and D
The baseline 12- to 24-hour mean ambulatory BP	Part A, B, C and D
The Day 5 12- to 24-hour mean ambulatory BP	Part A, B, C and D
The Day 19 12- to 24-hour mean ambulatory BP	Part A, B, C and D
The Day 54 0- to 24-hour mean ambulatory BP	Part B and C
The Day 54 0- to 12-hour mean ambulatory BP	Part B and C
The Day 54 12- to 24-hour mean ambulatory BP	Part B and C
The daytime mean ambulatory BP	Part A, B, C and D
The nighttime mean ambulatory BP	Part A, B, C and D

7.12.4.2 Summary Statistics of ABPM Parameters

The ABPM parameters listed above will be presented in summary tables by descriptive statistics (including mean, SD, median, minimum, and maximum). Change from Baseline for the ABPM variables will also be summarized in this fashion.

Only observed data will be used for the summary and analyses of ABPM parameters. No imputation will be performed for missing data. ABPM parameters and ABPM related data collected on the eCRF will be included in the data listings. Raw 24-hour ABPM recordings will not be presented in a listing.

Following figures will be prepared:

- Average baseline ambulatory BP values by hour for the 0- to 24-hour interval, final ABPM values by hour for the 0- to 24-hour interval and change from baseline in ABPM values by hour for the 0- to 24-hour interval.
- Average baseline ambulatory BP values by hour for day-time interval, final ABPM values by hour for the daytime interval, and change from baseline in ABPM values by hour for the daytime interval.

- Average baseline ambulatory BP values by hour for the night time interval, final ABPM values by hour for the night time interval, and change from baseline in ABPM values by hour for the night-time interval.

7.12.4.3 Bayesian Analysis of ABPM Parameters

A generalized linear Bayesian model will be used on change from baseline in 24-hour mean SBP by ABPM to estimate the posterior probability of the true TAK-994 effect on the difference in systolic blood pressure between treatment and placebo to be <2, < 5, and <10 mmHg at each visit. The model includes effects of baseline, treatment, visit (Day 5, Day 19 and Day 54 (Part B and C only)), and treatment-by-visit interaction. The posterior mean, SD, and the 95% credible interval for the change from baseline in SBP for each treatment, along with those for the differences between TAK-994 and placebo, will be estimated using the model. The posterior probabilities of the true effect on the SBP being <2 mmHg, < 5 mmHg and < 10 mmHg will be calculated for each of the TAK-994 doses given the difference from placebo at each visit. A non-informative prior will be used for TAK-994 and placebo. This analysis will also be performed for change from baseline in 24-hour mean ABPM DBP.

7.12.4.4 MMRM Analysis of ABPM Parameters

Linear mixed effect model for repeated measures (MMRM) will be performed on change from baseline in 24-hour mean SBP by ABPM. In this model, change from baseline will be the response, baseline will be a covariate, treatment, post dose visit, and treatment by post dose visit interaction will be the fixed effects. The LS means of change from baseline in 24-hour mean ABPM SBP for each treatment and the associated SE and 95% CI will be extracted from the model at each time, along with all pairwise differences from placebo and associated SEs, 95% CIs, and p-values. This analysis will also be performed for change from baseline in 24-hour mean ABPM DBP and 24-hour mean HR. Similar analyses will be performed for the following ABPM parameters: Mean daytime (6 AM to 10 PM) SBP, Mean daytime DBP and Mean daytime HR.

7.12.4.5 Dipper Analysis

The following blood pressure dipping categories [3] will be defined using the ratio of mean daytime and night-time ABPM SBP (daytime defined as (0900 to 2100h) and nighttime defined as (0100 to 0600h):

- Non-dipping or riser: Night-time/Day-time ≥1.0.
- Mild dipper: 0.9 <Night-time/Day-time 1.0<1.0.
- Dipper: 0.8< Night-time/Day-time ≤0.9.
- Extreme Dipping: Night-time/Day-time ≤0.8.

The dipper ratio will be summarized by treatment for each visit.

Number and percent of subjects in each dipping category at baseline and each post dose visits will be summarized by treatment. Shift tables will be presented.

Above summaries will also be presented for ABPM DBPs. Additional analyses might be performed if deemed appropriate.

7.12.5 12-Lead ECGs

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The following parameters will be calculated automatically by the ECG machine: heart rate, PR interval, QT interval, QRS interval, and QT interval with Fridericia correction method (QTcF).

Descriptive statistics of the continuous ECG parameters will be summarized for baseline, post-dose, and change from baseline at each post-dose time point by treatment and time. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed ECG parameters.

All individual ECGs that meet Takeda's predefined criteria for MAVs (Appendix C) will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal ECG measurement will be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying ECG result. All post-dose MAV ECG parameters, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

Individual subject ECGs will be presented in a data listing.

7.12.6 Other Observations

C-SSRS data results and Physical examination findings, will be presented in the data listings.

Alcohol consumption status and amount data will be presented in the data listings.

[redacted]

7.12.7 Group Analyses for Selected Safety Endpoints

Selected safety endpoints will be evaluated using the data from the groups defined in Section 7.1.1. Summary statistics described in each of these safety endpoint sections (Section 7.12.1-7.12.6) will be conducted for each of these groups. Inferential statistical analysis

will be performed for clinic BP and pulse as well as ABPM parameters only. Safety Sets will be used for the summaries and analysis. Details are provided in Table 7.j.

Table 7.j Group Analysis for Selected Safety Endpoints

Groups	Safety Endpoints	Data Source	Inferential Statistics and Data Time Frame
Group 1: All NT1 subjects	• TEAEs • MAVs for safety labs, vital signs and 12-lead ECGs • Time-matched clinic BP and pulse • ABPM parameters	Parts A, B and C	Only for time-matched clinical BP and pulse with Data up to Week 4
		Parts B and C	Only for time-matched clinical BP and pulse and ABPM parameters with data up to Week 8
Group 2: All NT1 Japanese subjects	• TEAEs • MAVs for safety labs, vital signs and 12-lead ECGs • Time-matched clinic BP and pulse • ABPM parameters	Part A and B	Only for time-matched clinic BP and pulse and if N>20% of the total number of subjects in Parts A and B with data up to Week 4
Group 3: All NT1 subjects from sites in Asia	• TEAEs • MAVs for safety labs, vital signs and 12-lead ECGs • Time-matched clinic BP and pulse • ABPM parameters	Parts A, B and C	Only for time-matched clinical BP and pulse and if N>20% of the total number of subjects in Parts A, B and C; with data up to Week 4
		Parts B and C	Only for time-matched clinical BP and pulse and ABPM parameters and if N>20% of the total number of subjects in Parts B and C; with data up to Week 8
Group 4 All NT1 subjects with HLA positive results	• TEAEs • MAVs for safety labs, vital signs and 12-lead ECGs • Time-matched clinic BP and pulse • ABPM parameters	Parts A, B and C	Only for time-matched clinical BP and pulse and if N>20% of the total number of subjects in Parts A, B and C; with data up to Week 4
		Parts B and C	Only for time-matched clinical BP and pulse and ABPM parameters and if N>20% of the total number of subjects in Parts B and C; with data up to Week 8
Group 5 All NT1 subjects with HLA negative results	• TEAEs • MAVs for safety labs, vital signs and 12-lead ECGs • Time-matched clinic BP and pulse • ABPM parameters	Parts A, B and C	Only for time-matched clinical BP and pulse and if N>20% of the total number of subjects in Parts A, B and C; with data up to Week 4
		Parts B and C	Only for time-matched clinical BP and pulse and ABPM parameters and if N>20% of the total number of subjects in Parts B and C; with data up to Week 8

Table 7.j Group Analysis for Selected Safety Endpoints

Groups	Safety Endpoints	Data Source	Inferential Statistics and Data Time Frame
Group 6: All NT1 Subjects with baseline WCR≤8	• TEAEs • MAVs for safety labs, vital signs and 12-lead ECGs • Time-matched clinic BP and pulse • ABPM parameters	Parts A, B and C	Only for time-matched clinical BP and pulse and if N>20% of the total number of subjects in Parts A, B and C; with data up to Week 4
		Parts B and C	Only for time-matched clinical BP and pulse and ABPM parameters and if N>20% of the total number of subjects in Parts B and C; with data up to Week 8
Group 7: All NT1 Subjects with baseline WCR>8	• TEAEs • MAVs for safety labs, vital signs and 12-lead ECGs • Time-matched clinic BP and pulse • ABPM parameters	Parts A, B and C	Only for time-matched clinical BP and pulse and if N>20% of the total number of subjects in Parts A, B and C; with data up to Week 4
		Parts B and C	Only for time-matched clinical BP and pulse and ABPM parameters and if N>20% of the total number of subjects in Parts B and C; with data up to Week 8

7.13 [redacted]

[redacted]

7.14 Unblinded Data Reviews and Interim Analysis

7.14.1 Unblinded Data Reviews

Part A and Part D are the study parts with a MRD design. In each part, in order to select the dose for the next (sub-)cohort, unblinded data reviews will be performed by an internal review

committee (IRC) after each sentinel dose cohort or cohort. All available safety, [redacted] data will be used for dose selection. Details will be described in the IRC charter.

7.14.2 Interim Analysis

At the end of Part A Cohort A1, an IA will be performed. The purpose of this IA is to have an early look of TAK-994 efficacy and safety. The selected analyses defined in the SAP will be used for the IA and will be specified in IRC charter.

The four parts in this study are independent of each other. They are included in one protocol for administrative purposes. With this in mind, data cleaning and database lock will be performed for each of these 4 parts. Unblinded analyses described below may be performed thereafter.

- End-of-Part A: At the end of Part A, a final unblinded analyses will be performed to evaluate the safety and efficacy of TAK-994 for Part A only.
- End-of-Part B: Final unblinded analyses will be performed after Part B completes to evaluate the safety, PK and efficacy of TAK-994 for NT1 subjects in Part B only, [redacted].
- End-of-Part D: The final unblinded analyses for NT2 may be performed to evaluate the safety, PK, and efficacy at the end of Part D using Part D subjects only.
- End-of-Part C: the final unblinded analysis for sites in China may be performed at the end of Part C using subjects in Part C only.

Unblinded data and interim analyses result reviews will be performed by TAKEDA Internal Review Committee (IRC). The IRC consists of members that will not be involved with study level activities. Details will be presented in the IRC Charter.

8.0 APPENDIX

8.1 Changes From the Previous Version of the SAP

Changes made from the original version of SAP (Approved on June 15 2020) that have a **material impact to the planned statistical analysis methods** are described below. In addition, there were textual changes purely to improve the flow, organization and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

SAP Section (Previous SAP)	Impacted Text (Previous SAP)	Change (Current SAP)	Rationale for Change
7.1 General Principles	All summaries and analyses described in this document will be performed for: Cohorts 1 to 3 together (Group 1), and Cohorts 5 and 6 together (Group 5). In addition, some of the summaries and analyses might be performed for other subgroups in NT1 subjects (such as China alone, Japan alone, and/or China and Japan combined [Groups 2, 3, and/or 4, if applicable]) if deemed appropriate.	A section to define different subgroups is added as Section 7.1.1. In addition to the previously defined subgroups, subgroups based on HLA results and based on the baseline WCR are added.	Group analyses description and definition has been changed due to PA3.
7.1.3 Definition of Study Visit Windows	Table 7.a visit windows for scheduled visits during treatment period for MWT, ESS, lab, VS, ECG and PK. Table 7.b visit windows for scheduled visits during treatment period for ABPM.	Visit windows are redefined and new visit windows are added in Section 7.1.3, including Visit windows for re-designed Part B and new procedures. Table 7.a. defines the visit windows for Part A and D for MWT, ESS, lab, VS, ECG and PK. Table 7.b1. defines the visit windows for ABPM for Part A. Table 7.b2 defines the visit windows for ABPM for Part D.	Changes of the overall study design and treatment duration in PA3.

SAP Section (Previous SAP)	Impacted Text (Previous SAP)	Change (Current SAP)	Rationale for Change
		Table 7.c. defines the visit windows for Part B and C for MWT, ESS, lab, VS, ECG and PK. Table 7.d. defines the visit windows for ABPM for Part B and C.	
7.2 Analysis Sets	No major protocol violation criteria was defined. No Full Analysis Set (FAS) and Per Protocol Set (PPS) was Defined.	Section 7.2 is changed to described the criteria for Major Protocol Violations. Section 7.3 is added to define analysis sets including Full Analysis Data Set and Per Protocol Data Set.	Due to the change in PA3, including the objectives in Part B, analyses using FAS and PPS are added accordingly.
7.7 Study Drug Exposure and Compliance	Percent of study drug compliance is defined as {(number of tablets dispensed – number of tablets returned)/[2*(date of last dose – date of first dose +1)]}x100%.	Compliance rate definition is changed to be based on the dose for each bottle	To better reflect the study drug dispense and return process in PA3.
	No section for efficacy analyses. [redacted]	Section 7.9 is changed to describe the planned efficacy analysis for Parts B and C, including primary analyses, sensitivity analyses, as well as hierarchical testing procedures applied to control the family wise type 1 error rate in Part B. [redacted]	Due to the change of the objectives of Part B in PA3.

SAP Section (Previous SAP)	Impacted Text (Previous SAP)	Change (Current SAP)	Rationale for Change
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
7.9.2.8 Sleep and Activity Parameters from Wearable Devices Analysis	Linear mixed effect models for longitudinal data was planned to be used To evaluate the effect of treatment on sleep and daily activities.	The analysis methods are updated in Section 7.11.7 Sleep and Activity Parameters from Wearable Devices Analysis. Weekly sleep and activity parameters were defined based on the daily parameters. Linear mixed effect models for repeated measures were used to evaluate the treatment effect on the change in these parameters from baseline.	Weekly mean is more clinically meaningful comparing to daily measurement. Analysis method is change accordingly.
		[redacted]	[redacted]

SAP Section (Previous SAP)	Impacted Text (Previous SAP)	Change (Current SAP)	Rationale for Change
7.10.3.1 Analysis for ABPM	For NT1 subject, an ANCOVA model is planned for ABPM parameters as those cohorts only have one post dose visit (Study Day 19) for ABPM.	In Section 7.12.4.3, a generalized linear Bayesian model is planned to estimate posterior probability of the true TAK-994 effect on the ABPM parameters comparing between treatment and placebo. In Section 7.12.4.4, a linear mixed effect model for repeated measures (MMRM) is planned to estimate TAK-994 effect on the ABPM parameters comparing to placebo for each visit. In Section 7.12.4.5, analyses for dipper categories are add.	More ABPM were added in PA3. The planned inferential analyses were changed accordingly.
7.10.5 Other Observations	Only data listings are planned for other observations.	Alcohol consumption, [redacted] are added in Section 7.12.6 Other Observations. Additional to data listing, summary statistics are added for those parameters. CYP3A4/5 activity analysis is moved to PK section (7.10).	Due to the change in PA3.
	Safety analyses for groups were not planned.	Section 7.12.7 was added to described the summaries for selected safety endpoints	Due to the change in PA3.
7.10.6 [redacted] PK/Safety Analysis	The plot of TAK-994 plasma concentration versus the post treatment SL on the MWT was planned.	The plot of PK concentration vs. SL in MWT is removed from Section 7.13 [redacted] PK/Safety Analysis	The plots will be generated and described in a separate [redacted].

SAP Section (Previous SAP)	Impacted Text (Previous SAP)	Change (Current SAP)	Rationale for Change
7.11 Interim Analysis	End-of-population analyses were planned at the end of each part.	As database lock is planned for each part in PA3, End-of-Population analyses were replaced with final analyses and described in Section 7.14.2.	In PA3, each partis considered an independent study. A formal database lock is planned at the end of each part. End-of-population analyses are replaced with formal analyses for clinical study reports after database lock.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/μL	>600 x 10^3/μL
	SI	<75 x 10^9/L	>600 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional	--	>1.5x ULN
	SI	--	>1.5x ULN
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>1.5x ULN
	SI		>1.5x ULN
Blood urea nitrogen	Conventional		>40 mg/Dl
	SI		>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>5.3 mEq/L
	SI	<3.0 mmol/L	>5.3 mmol/L
CPK	Both	--	>3x ULN
Glucose	Conventional	<50 mg/dL	>300 mg/dL
	SI	<2.8 mmol/L	>19.4 mmol/L
Calcium	Conventional	<7.7 mg/dL	>11.1 mg/dL
	SI	<1.92 mmol/L	>2.77 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<40	>115
Systolic blood pressure	mm Hg	<90	≥160
Diastolic blood pressure	mm Hg	<50	≥100
Systolic blood pressure change	mm Hg		>20, >30
Diastolic blood pressure change	mm Hg		>20, >30
Body temperature	oC		>38.5
Respiratory Rate	Breath/min		>21

Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Lower Criteria	Upper Criteria
Heart rate	<40 beats per minute	>115 beats per minute
PR	≤80 milliseconds	≥200 milliseconds
QTcF Interval	≤300 milliseconds	>500 milliseconds OR ≥30 milliseconds change from baseline and >450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds

9.0 REFERENCES

1. A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-994 in Patients with Narcolepsy with or without Cataplexy (Narcolepsy Type 1 or Narcolepsy Type 2), Takeda Development Center, Ltd., Protocol Amendment 03, TAK-994-1501, dated 15 Jan, 2021.
2. [redacted]
3. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring, Eoin O'Brien, Jun 2013, Journal of Hypertension

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	14-May-2021 20:46 UTC