STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-994-1504

A 3-Period Extension Study with Dose-Blind Period, Double-blind, Placebo-Controlled, Randomized Withdrawal Period and Open-Label Extension Period to Evaluate the Safety and Explore the Pharmacokinetics and Pharmacodynamics of TAK-994 in Subjects With Narcolepsy With Cataplexy (Narcolepsy Type 1)

PHASE 2

Version: Original

Date: 25 May 2021

Prepared by:

[redacted], Ph.D

[redacted], Statistics and Quantitative Sciences

Based on:

Protocol Version: Original

Protocol Date: 03 FEB 2021

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

CPK	creatine phosphokinase
GGT	γ-glutamyl transferase
LLN	lower limit of normal
[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bpm	beats per minute
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
ePRO	electronic patient-reported outcome
[redacted]	[redacted]
ESS	Epworth Sleepiness Scale
FAS	full analysis set
HR	heart rate
IRT	interactive response technology
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MWT	maintenance of wakefulness test
[redacted]	[redacted]
[redacted]	[redacted]
NT1	narcolepsy type 1
[redacted]	[redacted]
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
[redacted]	[redacted]
PT	preferred term
[redacted]	[redacted]

QTc	corrected QT
QTcF	QT interval with Fridericia correction method
REM	rapid eye movement
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
[redacted]	[redacted]
WCR	weekly cataplexy rate

4.0 OBJECTIVES

4.1 Period I and Period III

4.1.1 Primary Objective

- To evaluate the safety and tolerability of TAK-994.

4.1.2 Exploratory Objectives

[redacted]

[redacted]

4.2 Period II

4.2.1 Primary Objectives

- To evaluate the safety and tolerability of TAK-994 versus placebo.
- To assess the effect of TAK-994 on excessive day-time sleepiness, as measured by the ESS, for subjects who meet the responder criteria at Baseline II*.
- To assess the effect of TAK-994 on cataplexy for subjects who meet the responder criteria* at Baseline II.

4.2.2 Secondary Objective

- To assess the effect of TAK-994 on excessive day-time sleepiness, as assessed by the change in mean sleep latency from MWT for subjects who meet the responder criteria at Baseline II*.

4.2.3 Exploratory Objectives

[redacted]

[redacted]

** Response will be defined as a Baseline II ESS score <10, or a change from Baseline I in ESS score ≥6, or a WCR≤3.*

4.3 Study Design

This is a phase 2, multicenter, 3-period extension study of TAK-994-1501. Up to 112 male and female subjects with narcolepsy type 1 (NT1) who have completed Part B of TAK-994-1501 will be invited to participate. An interactive response technology system will be used for the randomization of subjects to treatment.

The study will consist of an 8-week dose-blind active drug extension period (Period I), followed by a 4-week double-blind randomized withdrawal period (Period II), and an 8-week open-label extension period (Period III).

Baselines for each of the treatment periods are defined as follows:

- Data from the final assessments in TAK-994-1501 Part B, performed on Days 55 to 57 of that study, will serve as baseline for Period 1 of TAK-994-1504 (ie, Baseline I). Note: for assessments performed multiple times during Days 55 to 57 of TAK-994-1501 Part B, the final assessment will serve as baseline, ie, the electrocardiogram (ECG) performed on Day 57.
- Data from the final assessments in Period I, performed prior to the first dose in Period II, will serve as baseline for Period II (ie, Baseline II).
- Data from the final assessments in Period II, performed before the first dose in Period III, will serve as baseline for Period 3 (ie, Baseline III).

During Period I, all subjects will be randomized to TAK-994 30, 90, or 180 mg twice daily (BID) (used in TAK-994-1501 Part B) stratified by region. For blinding purposes the randomization ratio will not be disclosed. The first intake in the current study will take place on Day 57 in TAK-994-1501 Part B, immediately after all final TAK-994-1501 assessments have been completed. The last dose in TAK-994-1501 Part B is planned on Day 56. No dosing gap is expected. Note: for subject safety and comfort, site staff may opt to [redacted] assessment of TAK-994-1501 and the pre-dose samples for the current study. Sites may also choose to administer the pregnancy test for female subjects of child-bearing potential first thing in the morning on Day 57 of TAK-994-1501 Part B (ie, Day 1 of the current study).

Upon completion of Period I, subjects will continue into Period II and will be randomized in a 1:1 ratio stratified by Epworth Sleepiness Scale (ESS) total score (<10, ≥10) and total number of cataplexy episodes in the last 7 days (≤3, >3) prior to Baseline II (defined above) to TAK-994 or placebo with the same dose (taken during Period 1).

Upon completion of Period II, subjects will continue into Period III during which all subjects will initially be dosed with TAK-994 at 90 mg BID. All subjects will remain on 90 mg BID dose

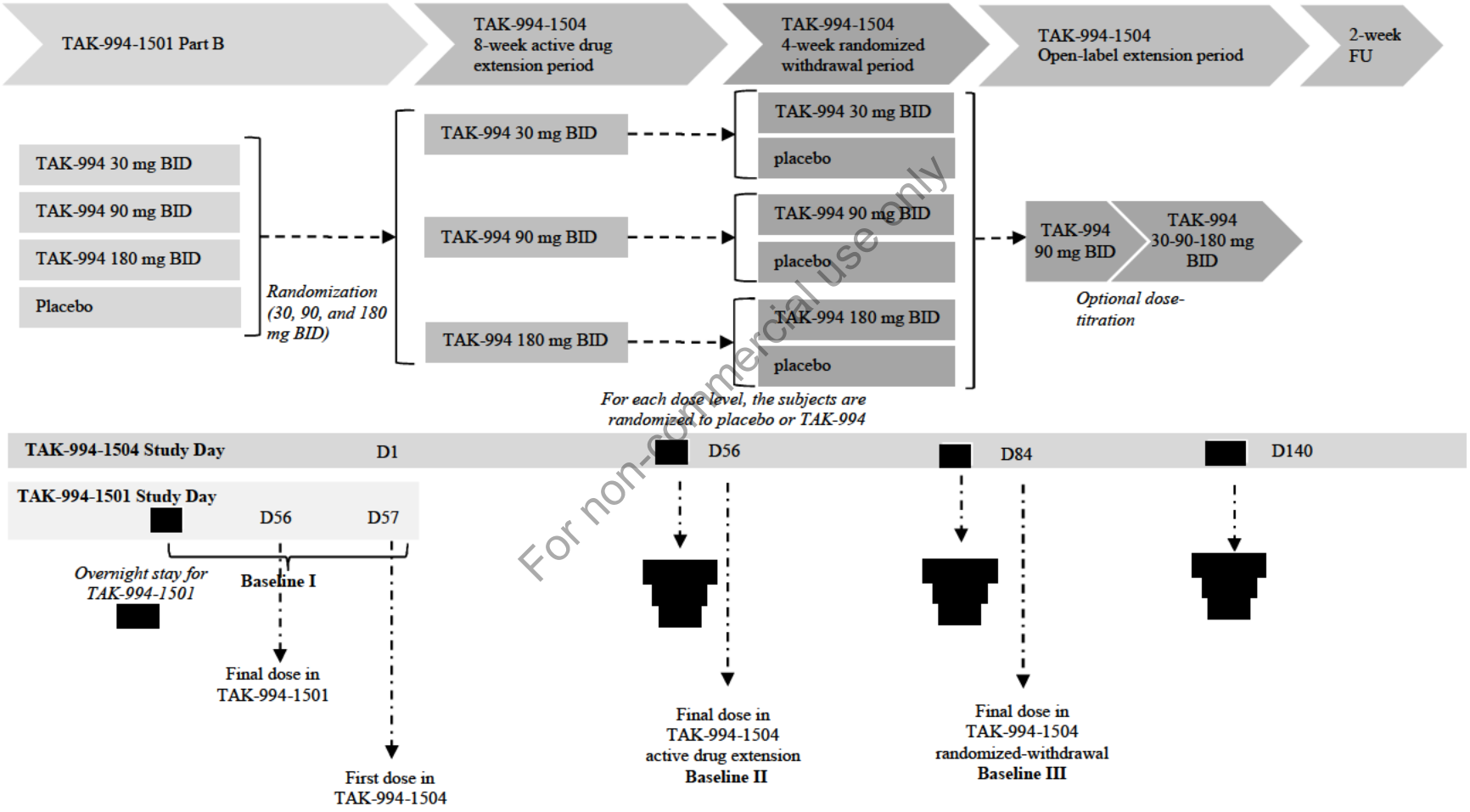
for the first 2 weeks of Period III. After these first 2 weeks, in order to optimize therapy, the dose can be increased to 180 mg BID at the discretion of the investigator in case there is a clinically significant increase in weekly cataplexy rate (WCR) or ESS score compared to Baseline III (defined above). (Note that the dose should never exceed 180 mg BID.) The dose can be decreased to 30 mg BID for safety reasons. From Week 4 onwards, dosing adjustments will only be allowed for safety reasons. Detailed dosing guidelines will be provided in a separate document.

During Period I, in-clinic assessments are planned at Weeks 2, 4, 6, and 8. During Period II, in-clinic assessments are planned at Weeks 10 and 12. During Period III, in-clinic assessments are at Weeks 16, 18, and 20. In between certain visits, sites will contact the subject for well-being calls. Subjects will continue to complete the daily electronic patient reported outcome (ePRO) diary to record self-reported narcolepsy symptoms (eg, WCR) started in TAK-994-1501 Part B; [redacted]. Subjects will stay overnight at the clinic on Days 55 (end of Period I), Day 83 (end of Period II), and Day 139 (end of Period III). Subjects will be discharged on Days 56, 84, and 140, respectively. [redacted] No other visits will require overnight stays. (Note that subjects are also staying overnight at Day -2 and -1 [part of TAK-994-1501 Part B].) [redacted] The second scenario may require additional stays at the clinic.

Following completion of Period III, subjects will have the option to roll over into an additional open-label extension study (TAK-994-3003).

A schematic of the study design is included as Figure 4.a. A Schedule of Study Procedures is provided in Appendix A in the protocol.

Figure 4.a Schematic of Study Design



D: day; [redacted].
[a]Not required for subjects rolling over into TAK-994-3003

During confinement, study drug will be administered TAK-994/placebo orally in the morning (at approximately 0800) and in the afternoon (approximately 1300) per the Schedule of Study Procedures (Appendix A in the protocol) and Section 8.1.3 in the protocol. Study assessments will be obtained per the Schedule of Study Procedures (Appendix A in the protocol) in accordance with the priority specified in Section 9.1.1 in the protocol. Subjects will remain as inpatient from check-in at Days 55, 83, and 139 and will be discharged after completion of all planned assessments on Days 56, 84, and 140 respectively.

While at home, subjects will take TAK-994/placebo 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 ePRO diary.

Subjects will return to the clinic for safety, [redacted], and/or PD assessments on in-clinic visit days. Subjects will return home on the discharge day after each in-clinic period.

A follow-up will be planned approximately 2 weeks after the final study drug intake for subjects not participating in TAK-994-3003.

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 Study Procedures (Appendix A in the protocol), 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 Study Procedures (Appendix A in the protocol). Alternative approaches to study procedures and data collection for the current study are described in Section 9.1.2 in the protocol.

5.0 ANALYSIS ENDPOINTS

5.1 Period I and Period III

5.1.1 Primary Endpoints

- Subjects with at least 1 treatment-emergent adverse event (TEAE).
- Subjects with at least 1 markedly abnormal value (MAV) for postdose laboratory values.
- Subjects with at least 1 MAV for postdose vital signs.
- Subjects with at least 1 MAV for postdose ECG parameters.

5.1.2 Exploratory Endpoints

[redacted]

[redacted]

5.2 Period III

5.2.1 Primary Endpoints

- Subjects with at least 1 TEAE.
- Subjects with at least 1 MAV for postdose laboratory values.
- Subjects with at least 1 MAV for postdose vital signs.
- Subjects with at least 1 MAV for postdose ECG parameters.
- Change in subjective daytime sleepiness evaluated to Week 4 of Period III using the ESS total score for subjects who meet the responder criteria at Baseline II *.
- Weekly cataplexy rate based on patient-reported diaries at Week 4 of Period III for subjects who meet the responder criteria at Baseline II *.

5.2.2 Secondary Endpoint

- Change in sleep latency using the MWT for subjects who meet the responder criteria at Baseline II*.

5.2.3 Exploratory Endpoints

[redacted]

** Response will be defined as a Baseline II ESS score <10, or a change from Baseline I in ESS score ≥6, or a WCR≤3.*

6.0 DETERMINATION OF SAMPLE SIZE

Assuming that 60 subjects from TAK-994-1501 Part B will complete Period II (4-week double-blind randomized withdrawal period) (ie, 20 subjects in each of the 3 dose groups split 1:1 between TAK-994 and Placebo), the study will provide at least 85% power to detect for each dose group a 10-point difference between placebo and TAK-994 in the change in mean ESS total score from Baseline II to the completion of Period II. This assumes a common SD of 7 for the change in ESS total score from Baseline II and a two-sided significance level of 5% using a t-test. The study will also provide 85% power to detect for each dose group a WCR ratio of 2 between placebo and TAK-994 at the completion of Period II, under a Poisson model and using

the Variance Stabilized Maximum Likelihood Estimation test statistic, assuming a WCR of 3 for subjects randomized to TAK-994 at Week 4, and a WCR ratio of 1 under the null hypothesis. Hypothesis tests will be conducted in a hierarchical manner to adjust for multiplicity.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Subjects are considered enrolled if they were on placebo in TAK-994-1501 Part B and receive a randomization number or if they are on active drug in TAK-994-1501 Part B and receive a dose of study drug in the TAK-994-1504 study. All subjects who are enrolled in TAK-994-1504 will have an enrollment number which is different from the subject ID or the randomization numbers.

Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, 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.

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

7.1.1 Study Definitions

7.1.1.1 Baseline Definition

Baseline I is defined as the last measurement before the first dose in the first active drug extension period of this study. Baseline I results from assessments of part B of TAK-994-1501 for some endpoints.

Baseline II is defined as the last measurement before the first dose in the randomized withdrawal period of this study.

Baseline III is defined as the last measurement before the first dose of the second active drug extension period of this study.

[redacted]

7.1.2 Definition of Study Days

Day 1 for Period 1 (dose blind active drug extension period) is defined as the day on which a subject is administered their first dose of the medication in TAK-994-1504. Days prior to the first dose of study drug in Period 1 will be calculated as: {date of assessment/event – date of first dose of study drug of the subject}. Days on or after the first dose of study drug in Period 1 until first dose in the randomized withdrawal period will be calculated as: {date of assessment/event – date of first dose of study drug of the subject + 1}.

Day 1 for Period 2 (randomized withdrawal period) is defined as the day on which a subject is administered their first dose of the medication in TAK-994-1504 randomized withdrawal period.

Days prior to the first dose of study drug in Period 2 will be calculated as: {date of assessment/event – date of first dose of study drug of the subject}. Days on or after the first dose of study drug until first dose in the open label active drug extension period will be calculated as: {date of assessment/event – date of first dose of study drug of the subject + 1}.

Day 1 for Period 3 (open label active drug extension period) is defined as the day on which a subject is administered their first dose of the medication in TAK-994-1504 open-label active drug extension period. Days prior to the first dose of study drug in Period 3 will be calculated as: {date of assessment/event – date of first dose of study drug of the subject}. 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}.

For the entire study, Study Day 1 is defined as the day on which a subject is administered their first dose of the medication in TAK-994-1504. 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 will be defined in order establish a time interval around which data for that visit will be considered. 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 the analyses for by-visit summaries is the value within the specified window that is 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 for the active drug extension period are presented in Table 7.a, for the randomized withdrawal period are presented in Table 7.b and for the open label active drug extension period are presented in Table 7.c. Cut-off days for inclusion in the window (number of days following the date of the last dose of study drug) are provided. Days are presented as days within the period, not overall study day.

Table 7.a Visit Windows (Days) for Scheduled Visits During the First Active Drug Extension Period

Visit	Scheduled Day	Lab, VS, ECG
Baseline I[a]	-1	≤1
Day 1	1	1
Week 1	7	4 – 10
Week 2	14	11 – 21
Week 4	28	22 – 35
Week 6	42	36 – 49
Week 8/ET	56/ET	(Last Dose +- 7)

a: last non-missing value prior to the first dose of study drug in 1504 is defined as Baseline I.

Table 7.b Visit Windows (Days) for Scheduled Visits During the Randomized Withdrawal Period

Visit	Scheduled Day	MWT	ESS	Lab, VS, ECG
Baseline II[a]	-1	<1	<1	≤1
Week 1	7	NA	4 – 10	NA
Week 2	14	NA	11 - 17	1-21
Week 3	21	NA	18 - 24	NA
Week 4/ET	28/ET	(Last Dose -3)-(Last Dose)	(Last Dose)	(Last Dose Day -3) to (Last Dose Day +7)

a: last non-missing value prior to the first dose in the randomized withdrawal period is defined as Baseline II.

Table 7.c Visit Windows (Days) for Scheduled Visits During the Open Label Period

Visit	Scheduled Day	Lab, VS, ECG
Baseline III[a]	1	<1
Week 4	112	14-42
Week 6	126	NA
Week 8/ET	140/ET	(Last Dose +- 7)

a: last non-missing value prior to the first dose in the open label active drug extension period is defined as Baseline III.

For other efficacy and safety data, data that are obtained more than 7 days after the last dose of study medication (date of procedure – last dose date >7) 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 >30) will be listed but excluded from the summaries and analyses.

[redacted]

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.
  - Use the date of first dose.

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.

To determine TEAE, AE onset date and time will be used to compare with the first dosing day and time. If the AE onset time on Day 1 is missing, the AE will be considered as TEAE. If the AE onset time on other study days is missing, the AE onset date will be used to compare with the first dosing date.

To determine AE duration, both AE onset and end date and time should be used. if the onset or end time is missing, the dates will be used. For ongoing AEs at the end of study, duration will not be calculated.

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 Dosing Date and Time

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. This rule applies to the Day 1 for each period as well.

If the date of last double-blind study drug dose for a period collected in the eCRF 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 for the period (recorded in the eCRF), last double-blind study drug return date for the period, and the for the dose blind active drug extension period the earlier date between the last double-blind study drug dispense date (following the last drug return date) + 14 and the first dosing date of the randomized withdrawal period -1, for the randomized withdrawal period, the earlier date between after the last double-blind drug dispense date (following the last drug return date) +7 days and the first dosing date of the open label active drug extension period -1, or if it is the open label active drug extension period, the last drug dispense date (following the last drug return date) +14 days. These rules are laid out in Table 7.d

Table 7.d Inference last dosing day

Period	Take the Earliest of:
Dose Blind Active Drug Extension Period	Date of Death
	Date of last visit for this period
	Last study drug return date for this period
	First dose in randomized withdrawal period –1 day
	Last drug dispense date +14 days
Randomized Withdrawal Period	Date of Death
	Date of last visit for this period
	Last study drug return date for this period
	First dose in open label active drug extension period –1 day
	Last drug dispense date +7days
Open Label Active Drug Extension Period	Date of Death
	Date of last visit for this period
	Last study drug return date for this period
	Last drug dispense date +14 days

7.1.7 Group Level Definitions

These treatment group categories are shown below. For the dose blind active drug extension period use Table 7.e, for the randomized withdrawal period use Table 7.f and for the open label active drug extension period use Table 7.g. For summary statistics referencing Table 7.e, in addition to summarizing for each of these groups, summaries should be provided for the categories in the last column of table.

For the first Active Drug Extension Period data presentation, subjects will be disaggregated based on whether or not they were on placebo in TAK-994-1501 Part B for each dose level, as well as total by dose.

For the randomized withdrawal period, placebo subjects will be disaggregated based on their dose in the active period and all subjects will be disaggregated based on whether or they met the response criteria of <10 ESS, >6 change from baseline ESS or <3 cataplexies per week on average and overall.

For the open label active drug extension period subjects will be disaggregated based on their dose in the randomized withdrawal period.

Table 7.e Treatment Groups for the Dose Blind Active Drug Extension Period

Group	TAK-994-1501 Part B dose	TAK-994-1504 Dose Blind Active Drug Extension Period (Categories for the Overall Summary)
1	30mg BID	30mg BID
2	Placebo BID	
3	90mg BID	90mg BID
4	Placebo BID	
5	180mg BID	180mg BID
6	Placebo BID	

Table 7.f Treatment Groups for the Randomized Withdrawal Period

Group	Responder	TAK-994-1504 Dose Blind Active Drug Extension Period	TAK-994-1504 Randomized Withdrawal Dose
1	Yes	30mg BID	30mg BID
2	Yes & No		
3	Yes		Placebo BID
4	Yes & No		
5	Yes	90mg BID	90mg BID
6	Yes & No		
7	Yes		Placebo BID
8	Yes & No		
9	Yes	180mg BID	180mg BID
10	Yes & No		
11	Yes		Placebo BID
12	Yes & No		

Table 7.g Treatment Groups for the Open Label Active Drug Extension Period

Group	TAK-994-1504 Randomized Withdrawal Period
1	30mg BID
2	90mg BID
3	180mg BID
4	Placebo

7.2 Analysis Sets

Number of subjects in each analysis set will be summarized by treatment groups and overall for all enrolled subjects in each period.

7.2.1 Dose Blind Active Drug Extension Period (Period 1)

Safety Set

The safety set for the active drug extension period will consist of all subjects who were enrolled and received at least 1 dose of study drug during the active drug extension period. In safety summaries, subjects will be grouped based on their actual treatment received during the active drug extension period, as well as by the description in Table 7.e.

[redacted]

[redacted]

7.2.2 Randomized Withdrawal Period (Period 2)

Safety Set

The safety set for the randomized withdrawal period will consist of all subjects who took at least 1 dose of study drug in the randomized withdrawal period. In the safety summaries, the subjects will be grouped based on the actual treatment received as defined in Table 7.f.

[redacted]

Full Analysis Set

The full analysis set for the randomized withdrawal period will consist of all subjects who received at least 1 dose of study drug or placebo. In the efficacy analyses, subjects in FAS with both baseline and at least 1 evaluable PD measurement during the randomized withdrawal period will be included. Subjects will be grouped using their assigned treatments in this analysis set as defined in Table 7.f.

7.2.3 Open Label Active Drug Extension Period (Period 3)

Safety Set

The safety set for the open-label active drug extension period will consist of all subjects who were enrolled and received at least 1 dose of study drug during the active drug extension period. In the safety summaries, all subjects will be grouped together based on the actual treatment received, as well as is defined in Table 7.g.

[redacted]

7.3 Disposition of Subjects

7.3.1 Dose Blind Active Drug Extension Period (Period 1)

Disposition of all subjects who have completed Part B in TAK-994-1501 and might be eligible for TAK-994-1504 will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

- All subjects who completed TAK-994-1501 Part B.
- All subjects who were enrolled to Study 1504 blinded active drug extension period.
- All subjects who were not enrolled to Study 1504.

The primary reasons for subjects who were not enrolled to Study 1504 will be summarized.

Disposition of enrolled subjects during the active drug extension period will be tabulated as treatment groups defined in table and overall:

- All subjects who enrolled but did not receive any study drug.
- All subjects who received at least one dose of study drug during period 1.
- Subjects who completed the study drugs in the period 1.
- 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 and study period will be presented for each subject in listings.

Significant protocol deviations will be listed and summarized using the period 1 PD Set by corresponding treatment groups and overall.

7.3.2 Randomized Withdrawal Period (Period 2)

Disposition of all subjects who have completed period 1 in TAK-994-1504 will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

- All subjects who completed the period 1.
- All subjects who were randomized to period 2.
- All subjects who were not randomized to period 2.

Disposition of randomized subjects during the randomized withdrawal period will be tabulated as below by treatment groups as defined in Table 7.f and overall for each treatment received in the previous period and for all subjects. The tables will be produced separately for responders and for all subjects:

- All subjects who randomized but did not receive any study drug.
- All subjects who received at least one dose of study drug during period 2.
- Subjects who completed the study drugs in the period 2.
- 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.

Significant protocol deviations will be listed and summarized using the Full Analysis Set by corresponding treatment groups and overall.

7.3.3 Open Label Active Drug Extension Period (Period 3)

Disposition of all subjects who have completed the randomized withdrawal period will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

- All subjects who completed the randomized withdrawal period.
- All subjects who participated in Study 1504 period 3.
- All subjects who did not participate in Study 1504 period 3.

Disposition of subjects during the second active drug extension period will be tabulated as below by treatment groups in Table 7.g and overall:

- All subjects who completed period 2.
- All subjects who received at least one dose of study drug during period 3.
- Subjects who completed the study drugs in the period 3.
- 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 and study period will be presented for each subject in listings.

Significant protocol deviations will be listed and summarized using the PD Set by corresponding treatment groups and overall.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Active Drug Extension Periods

Demography and other characteristics at Baseline I and Baseline III will be summarized by treatment (as appropriate for the corresponding period) and overall for all subjects using the active drug extension Safety Set and will be listed. Descriptive statistics will be used to summarize data by assigned treatment and overall for continuous variables like age and weight (number of subjects, mean, median, SD, minimum, and maximum) and for categorical variables like sex, ethnicity, and race (number and percentage of subjects within each category). [redacted] Baseline I measurements will be based on the data in the TAK-994-1501 Part B database if applicable.

7.4.2 Randomized Withdrawal Period

For each dose group in the Period 1, demography and other characteristics at Baseline II will be summarized by randomized TAK-994 or placebo and overall using the randomized withdrawal Safety Set and will be listed. The summaries for placebo subjects will also be presented by pooling all placebo subjects together.

Descriptive statistics will be used to summarize for continuous variables like age and weight (number of subjects, mean, median, SD, minimum, and maximum) and for categorical variables like sex, ethnicity, and race (number and percentage of subjects within each category). Baseline II mean sleep latency from MWT, ESS total score and WCR will be included in the summary as well.

Above summaries will be presented for subgroups of responders and non-responders.

7.5 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.

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.

Medical history will be summarized for Period 1 only.

Concurrent medical conditions will be summarized for each period. In addition, the concurrent medical conditions will be summarized by responders and non-responders for the randomized withdraw period.

All medical history and concurrent medical condition data will be listed by subject. The listing will contain study period, 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.

7.6 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.

Medication history will be summarized for Period 1 only. Concomitant medications will be summarized for all periods

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 in Period 1, 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 in 1504, that started or continued from the informed consent and continued into the active drug extension period, or started after the first dose of the study drug in 1504. All medication history and concomitant medications data will be listed by subject.

For concomitant medications in the randomized withdrawal period (Period 2), the above summaries will be provided for the concomitant medication that started or continued from the last dose of the first active drug extension period and stopped prior to the first dose of study drug in the randomized withdrawal period, that started or continued from the last dose of the first active drug extension period and continued into the randomized withdrawal period, and started after the first dose of the study drug in the randomized withdrawal period. In addition, the above summaries will be performed for responders only. All concomitant medications data will be listed by subject.

For concomitant medications in the open label active drug extension period (Period 3), the above summaries will be provided for the concomitant medication that started or continued from the last dose of the randomized withdrawal period and stopped prior to the first dose of study drug in Period 3, that started or continued from the last dose of the randomized withdrawal period and continued into the second active drug extension period, or started after the first dose of the study drug in Period 3. All concomitant medications data will be listed by subject.

7.7 Study Drug Exposure and Compliance

All summaries in this section will be performed for each period.

The date and time of each dose for each subject will be reported in the data listing. Listings for TAK-994 plasma concentrations 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).

For inference on date of last dosing see section 7.1.6.

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

Each subject will be dispensed with 3 bottles of study drugs: one bottle with 30 mg (or 30 mg placbo) tablets and two bottles with 90 mg (or 90 mg placebo) tablets. The subject is asked to take one tablet from each bottle at each time of dosing (morning and afternoon). Percent of study drug compliance associated with the dose for each bottle (30 mg or 30 mg placebo, and for each bottle of 90 mg or 90 mg placebo) is defined as {(number of tablets dispensed – number of tablets returned)/[2*(date of last dose – date of first dose +1)]} x100%. 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, 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 compliances of 3 percentages.

For each treatment group and overall, study medication compliance will be summarized by 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: subject identifier, site number, visit number, first and last dose dates, medication identification number, date dispensed and returned, number of tablets dispensed and returned, and compliance percentage.

7.8 Efficacy Analysis

Not Applicable.

7.9 [redacted] Pharmacodynamic Analysis

7.9.1 [redacted]

[redacted]

[redacted]

7.9.2 Pharmacodynamic Analysis

PD endpoints include: MWT parameters; ESS total scores; WCR; [redacted] PVT parameters; [redacted] and subdomain scores; [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 (if applicable, ie, subjects with NT1). [redacted] All above information will be provided in the listings.

7.9.2.1 Analyses of MWT, ESS and WCR

For MWT we will take the average sleep latency of the 4 sessions on a given day. The number of microsleeps for each MWT session will be computed by the Takeda quantitative sciences team and will be averaged over the four sessions. The number of microsleeps will be summarized for each treatment group [redacted] as well as overall [redacted]. FAS or PD set (as appropriate) will be used for these summaries. For ESS all analysis will be done on the total score for the questionnaire.

[redacted] WCR at Baseline II will be derived as the average number of cataplexy episodes over the last two weeks prior to Day 1 in the randomized withdrawal period in which a minimum 8 non-missing diary days of the self-reported electronic diary out of 14 days for cataplexy episodes are completed. [redacted]

[redacted]

For the randomized withdrawal period, the WCR will be the total number of cataplexy episodes in the diary for that week period (minimum 4 out of 7 days of non-missing diary required) readjusted to 7 days via the above formula.

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.

Active Drug Extension Periods

[redacted]

Randomized Withdrawal Period

For the randomized withdrawal period, observed sleep latency from MWT, ESS, WCR, and [redacted], and change from Baseline II (for shift tables) to postdose visits will be summarized by treatment group as defined in Table 7.f. A summary for placebo subjects will also be performed by pooling all placebo subjects in the randomized withdrawal period. FAS will be used.

For the MWT the subjects will be classified based on <8-minute decrease from Baseline II, 8 to <14-minute decrease from Baseline II, 14 to <20-minute decrease from Baseline II and ≥20-minute decrease from Baseline II in sleep latency. The number and percentage of subjects in these categories will be summarized. A shift table will be produced for number and percentage of subjects for the categories of <10 minutes, 10 to <20 minutes, 20 to <30 minutes, 30 to <40 minutes, and 40 minutes both as an average over the 4 MWT sessions as well as by time matched MWT.

A similar table will be produced for ESS where the change from Baseline II categories are <3 points increase, 3 to <7 points increase, 7 to <10 points increase and ≥10 points increase. The shift table categories for the observed total ESS scores are <10, 10 to ≤15 and >15.

Change from Baseline II to Week 4 in the randomized withdrawal period for mean sleep latency from MWT will be analyzed using ANCOVA models by the dose levels in the Active Drug Extension Period. Change from Baseline II to Week 4 will be the response; treatment (TAK-994 or placebo) will be the factor and Baseline II will be included as a covariate. This model will be performed by dose level in the active drug extension period for all subjects as well as for subjects who met the responder criteria at Baseline II.

Change from Baseline II in total ESS scores will be analyzed using linear mixed-effect models for repeated measures by the dose levels in the Active Drug Extension Period. Change from

Baseline II to post dose visits will be the response; treatment (TAK-994 or placebo) will be the factor, visit term and a visit by treatment interaction will be the fixed effects along with a visit repeated term. Baseline II total ESS scores will be used as a covariate in the model. This model will be performed by dose level in the active drug extension period for all subjects as well as for subjects who met the responder criteria at baseline II.

If data permit, a Poisson GEE model will be used to evaluate the maintenance effect of TAK-994 on WCR. WCR during the randomized withdrawal period will be the response in the model, Baseline II, week and treatment (TAK-994 or placebo) are fixed terms and a repeated term will be included for Week. A negative binomial model will be used instead of a Poisson model if the observed scale parameter is > 2 times the observed mean. Estimates of the incidence ratios of cataplexy per week for TAK-994 vs placebo and corresponding 95% C.I. at each week will be derived from the model. This model will be performed by dose level in the active drug extension period for all subjects as well as for subjects who met our responder criteria.

If neither the Poisson model or negative binomial model converge or if the observed scale parameter on the Poisson model's observed scale parameter >2 and the negative binomial model does not converge, the percent change in weekly cataplexy from baseline to Week 4 will be compared between the treatment group and placebo for each dose level using the Kruskal–Wallis One-way ANOVA test by ranks (a nonparametric test). P-values will be reported from the test. The full analysis set for the randomized withdrawal period will be used for this analysis. This analysis will be performed for both responders and overall.

The mean MWT, ESS, and WCR (if applicable) for each treatment and the associated SE and 95% CI will be estimated using the model for each post dose visit, along with all randomized withdrawal period dose-matched 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.

Tests will be performed in the following order for the analyses using responders only: 180mg versus 180mg placebo on WCR at Week 4, 180mg versus 180mg placebo on change from baseline in total ESS scores to Week 4, 90mg versus 90mg placebo on WCR at Week 4, 90mg versus 90mg placebo on change from baseline in total ESS scores to Week 4, 30mg versus 30mg placebo on WCR at Week 4, 30mg versus 30mg placebo for responders on ESS. The first test will be performed with a type 1 error of 0.05. If that test is statistically significant then the following test will be performed at the same type 1 error level; otherwise, the test will be stopped.

7.9.2.2 [redacted]

[redacted]

7.9.2.3 [redacted]

[redacted]

7.9.2.4 [redacted]

[redacted]

7.9.2.5 [redacted]

[redacted]

[redacted]

7.9.2.6 [redacted]

[redacted]

7.9.2.7 [redacted]

[redacted]

7.9.2.8 [redacted]

[redacted]

Table 7.h [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

7.9.2.9 [redacted]

[redacted]

[redacted]

7.10 Other Outcomes

A shift table will be provided for the assigned doses in the open label active drug extension period.

7.11 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 study period. Details about analysis by parts will be described in Section 7.11.1 to 7.11.6.

7.11.1 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 and by period. 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 TEAEs. Overall will be presented in this table only.
- TEAEs by SOC and PT.
- TEAEs by PT.
- Serious TEAEs by SOC and PT.
- Most Frequent (≥2 subjects or ≥5% based on total number of safety set subjects in any treatment group, whichever larger) TEAEs by PT.
- Most Frequent (≥2 subjects or ≥5% based on total number of safety set subjects in any treatment group, whichever larger) Non-Serious TEAEs by SOC and PT.
- Relationship of TEAEs by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Drug-Related TEAEs by PT.
- Intensity of TEAEs by SOC and PT.
- Intensity of Drug-Related TEAEs by SOC and PT.

In addition, data listings will be provided for all AEs, separated by period, including: TEAEs, AEs leading to death, AEs leading to study drug or study visit discontinuation, and serious adverse events (SAEs).

7.11.2 Clinical Laboratory Evaluations

Active Drug Extension Periods

Safety clinical laboratory evaluation data will be summarized by treatment group (as described in Table 7.e and Table 7.g) and overall (number of subjects, mean, SD, median, minimum, and maximum) for baseline, postdose, and change from baseline. Observed values and change from Baseline I (or Baseline III) in these parameters will be summarized by treatment and overall.

Subjects meeting markedly abnormal criteria for safety clinical laboratory assessments will be listed and summarized by treatment group and overall. The MAV criteria is defined in Appendix A.

Randomized Withdrawal Period

Safety clinical laboratory evaluation data will be summarized by treatment group (as defined in Table 7.f) and overall (number of subjects, mean, SD, median, minimum, and maximum) for baseline, postdose, and change from baseline. Observed values and change from Baseline II in these parameters will be summarized by treatment and overall.

Subjects meeting markedly abnormal criteria for safety clinical laboratory assessments will be listed and summarized by treatment group and overall. The MAV criteria is defined in Appendix A.

7.11.3 Vital Signs

Active Drug Extension Periods

All vital signs assessments will be summarized for Baseline I or Baseline III as appropriate, postdose, and change from baseline by treatment (as defined in Table 7.e and Table 7.g) and time, if deemed appropriate.

When time-matched baseline is available, the time-matched baseline should be used in the calculation of the change from baseline. This impacts the summary and MAV tables.

Subjects meeting markedly abnormal criteria for vital signs assessments will be listed and summarized by treatment group and overall. The MAV criteria is defined in Appendix B.

Randomized Withdrawal Period

If appropriate, for the randomized withdrawal day 28/ET visit, BP and pulse measurements will be summarized by treatment group (as defined in Table 7.f) and overall (number of subjects, mean, SD, median, minimum, and maximum) for Baseline II, postdose, and change from baseline II by dose (with placebo disaggregated by dose blind active drug extension period

treatment) and time point. Linear mixed-effect models for the repeated measures will be performed to evaluate the drug effect on BP and pulse using data from inpatient monitoring. In these analyses, change from time-matched baseline to the Week 4 visit will be the response and baseline, treatment, time point, and the treatment by time point interaction will be the fixed effects.

This model will be performed by dose level in the active drug extension period for all subjects as well as for subjects who met our responder criteria.

All other vital signs assessments will be summarized for Baseline II, postdose, and change from baseline by treatment and visit, if deemed appropriate.

Subjects meeting markedly abnormal criteria for vital signs assessments will be listed and summarized by treatment group and overall. The MAV criteria is defined in Appendix B.

7.11.4 12-Lead ECGs

Active Drug Extension Periods

All ECG assessments will be summarized for Baseline I and Baseline III as appropriate, postdose, and change from baseline by treatment (as defined in Table 7.e and Table 7.g) and time, if deemed appropriate.

Subjects meeting markedly abnormal criteria for vital signs and ECG assessments will be listed and summarized by treatment group and overall. The MAV criteria is defined in Appendix C.

Randomized Withdrawal Period

All ECG assessments will be summarized for Baseline II, postdose, and change from baseline by treatment (as defined in Table 7.f) and time, if deemed appropriate.

Subjects meeting markedly abnormal criteria for ECG assessments will be listed and summarized by treatment group and overall. The MAV criteria is defined in Appendix C.

7.11.5 [redacted]

7.11.5.1 [redacted]

[redacted]

[redacted]

7.11.5.2 [redacted]

[redacted]

7.11.5.3 [redacted]

[redacted]

7.11.5.4 [redacted]

[redacted]

7.11.6 Other Observations Related to Safety

Physical examination findings and Columbia suicide severity rating scale C-SSRS data will be presented in the data listings.

We will list the patients and summarize the number of patients impacted by coronavirus disease 2019 (COVID-19) by site.

Measurements missed due to COVID-19 will be listed by subject.

7.12 Interim Analysis

Not Applicable.

7.13 Changes in the Statistical Analysis Plan

Study Title and Sections 4-6 are copied from the most current version of draft TAK-994-1504 Protocol Amendment 1. If there are discrepancies with the approved Protocol Amendment 1, then Protocol Amendment 1 should be referenced.

Pharmacodynamic (PD) set was renamed as Full Analysis Set (FAS) for the randomized withdrawal period.

[redacted] The Open Label Active Drug Extension Period and associated analyses have also been added.

8.0 REFERENCES

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	27-May-2021 15:46 UTC