Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Escalating Single and Multiple Doses of TAK 831 in Healthy Asian Subjects

NCT Number: NCT03687684

Statistical analysis plan Approve Date: 27-JUN-2019

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-831-1002

A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Escalating Single and Multiple Doses of TAK 831 in Healthy Asian Subjects

PHASE 1

Version: 2nd

Date: 27 June 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 3

Protocol Date: 26 February 2019

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUEC	area under the effect-time curve
BMI	body mass index
BUN	blood urea nitrogen
CL/F	apparent clearance after extravascular administration
Cmax	maximum observed plasma concentration
CPK	creatine phosphokinase
CRF	case report form
ECG	Electrocardiogram
Emax	maximum effect
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	patient-reported outcome
QOL	quality-of-life
Rac	accumulation ratio
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
Tmax	time of first occrurrence of Cmax

TLGs	tables, listings, and graphs
T1/2z	terminal disposition phase half-life
ULN	upper limit of normal
Vz/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

To evaluate the safety and tolerability of single and multiple doses of TAK-831 in healthy adult Asian subjects.

4.2 Secondary Objectives

To evaluate the PK of single and multiple doses of TAK-831 in healthy adult Asian subjects.

4.3 Additional Objectives

To assess the effect of TAK-831 on the concentrations of D-serine and L-serine in plasma (and concentrations of D-serine and L-serine in cerebrospinal fluid as necessary) after TAK-831 administration to healthy Asian subjects.

4.4 Study Design

This is a double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, PK and PD of TAK-831 in healthy adult Asian subjects. This study will include up to 5 cohorts of healthy adult Japanese or Chinese subjects.

In Cohort 1, a single dose of TAK-831 will be administered at each dose level under a 3-sequential dose escalation design. Eight healthy adult Japanese subjects will be randomized to the sequence of administration A, B, and C at a 4:2:2 ratio. A single dose of TAK-831 or placebo will be administered on Days 1 and 9 with subjects followed for approximately 72 hours of assessments for safety, tolerability, and PK and PD before discharge.

In Cohort 2, a single dose of study drug will be administered to healthy adult Japanese subjects, followed by multiple doses. Of these subjects, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4, which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Cohorts 3 to 5 will be optional, in which a single dose of study drug will be administered followed by multiple doses, and Cohorts 3 and 4 may be studied based on emerging data from Cohorts 1 and 2.

Cohort 3 will include 8 healthy adult Chinese subjects, and Cohort 4 and 5 will include 8 healthy adult Japanese subjects. Of these subjects in the respective cohorts, 6 will be randomly assigned to the TAK-831 group and 2 to the placebo group. A single dose of TAK-831 or placebo will be administered, followed by their multiple doses. A single dose of TAK-831 or placebo will be administered on Day 1 with subjects followed for approximately 72 hours of assessments for safety, PK and PD. Treatment for multiple doses will start with a once-daily regimen on Day 4,

which will continue to Day 17 (for 14 days). Subjects will be kept in the study site for at least 48 hours after the last TAK-831/Placebo dose on Day 17 for safety, PK, and PD assessments before discharge.

Table 4.a shows the summary of cohorts, and Figure 4.a shows the schematic of the study design.

Table 4.a Summary of Cohorts

Cohort	Subject	Dose	Remarks
1	Japanese 8 subjects	Part 1: 100 mg (4×25 mg T3 tablet formulation) Fasted, single dose	Wash out period between part 1 and 2 will be 8 days.
		Part 2: 300 mg (1×300 mg T3 tablet formulation) Fasted, single dose	
2	Japanese 8 subjects	600 mg (2×300 mg T3 tablet formulation) Fasted, single dose + multiple dose (once daily)	
3	Chinese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 3 may be run if emerging data from Cohorts 1 and 2 suggest ethnic-related differences in the tolerability and/or PK profile. Dose level will be determined based on the results from Cohorts 1 and 2.
4	Japanese 8 subjects	TBD Fasted, single dose + multiple dose (once daily)	Cohort 4 may be run based on the emerging data from Cohorts 1 and 2 in Asian subjects.
5	Japanese 8 subjects	50 mg (2×25 mg T3 tablet formulation) Fasted, single dose + multiple dose (once daily)	

TBD: To be decided.

Figure 4.a Schematic of Study Design

<Cohort 1>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment				Follow-up period (b)
Screening	Hospitalization	Part 1	Washout interval		Part 2	
Day -28 to -2	Day -1	Day 1 to 4	Day 5 to 7	Day 8	Day 9 to 12	23 (±2)
	◄-------Hospitalization -------►		◄-----Hospitalization -----►			

(a) TAK-831 or placebo will be administered on Days 1 and 9.
(b) The Follow-up Visit will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In these cases, subjects may then be brought back to the study site for re-evaluation per investigator's discretion.

<Cohorts 2 to 5>

Screening period		Treatment period (a) Safety, Pharmacokinetic and Pharmacodynamic assessment		Follow-up period (b)
Screening (c)	Hospitalization (c)	Single dose part	Multiple dose part	
Day -28 to -2	Day -1	Day 1 to 3	Day 4 to 19	31 (±2)
	◄----------Hospitalization ----------►			

(a) TAK-831 or placebo will be administered on Day 1 in the single dose part and on Days 4 to 17 in the multiple dose part.
(b) The Follow-up Visit will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In these cases, subjects may then be brought back to the study site for re-evaluation per investigator's discretion.
(c) After Cohort 3, Screening will be on Days -28 to -3, hospitalization will be on Day -2 and an examination at hospitalization will be on Day -1.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

- Safety: Adverse events (AEs), laboratory tests, vital signs, weight, 12-lead electrocardiogram (ECG)

5.1.2 Secondary Endpoints

PK: The following parameters will be calculated.

- Cmax (Cohort 1, Day 1 of Cohorts 2 to 5).
- Cmax,ss (Day 17 of Cohorts 2 to 5).
- tmax (Cohort 1, Days 1 and 17 of Cohorts 2 to 5).
- AUClast (Cohort 1, Day 1 of Cohorts 2 to 5).
- AUCinf (Cohort 1, Day 1 of Cohorts 2 to 5).
- AUCtau (Days 1 and 17 of Cohorts 2 to 5).

5.1.3 Additional Endpoints

- PK: Rac (Cmax) and Rac(AUC) on Days 1 and 17 (Cohorts 2 to 5), t1/2z, CL/F, Vz/F
- Concentration of TAK-831 cerebrospinal fluid (if collected cerebrospinal fluid samples for PD)
- PD: Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine in plasma, AUEC24, Emax and time to Emax
- Concentrations of D-serine, L-serine and the ratio of D-serine to total serine in cerebrospinal fluid (Days -1 and 18) (may be assessed in Cohort 2 or thereafter based on PD in plasma).

6.0 DETERMINATION OF SAMPLE SIZE

Each cohort will include 8 subjects (6 for TAK-831, 2 for placebo) which is the sample size required to assess the safety, tolerability, and PK of each cohort. This is not based on any statistical rationale.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose onset occurs on or after the start of study drug.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug.
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Dose:
  - Cohort 1: Placebo (sequence B part 2 and sequence C part 1 combined), TAK-831 100 mg (sequence A part 1 and sequence B part 1 combined), TAK-831 300 mg (sequence A part 2 and sequence C part 2 combined).
  - Cohort 2~5: Placebo (cohort 2, 4 and 5 combined), TAK-831 300 mg (Cohort 2), TAK-831 600 mg (Cohort 4), TAK-831 50 mg (Cohort 5).
- Group:
  - Cohort 1: A (TAK-831 100 mg => TAK-831 300 mg), B (TAK-831 100 mg => Placebo), C (Placebo => TAK-831 300 mg).
  - Cohort 2~5: TAK-831, Placebo.
- Visit/Time Point: Scheduled time point at which the assessment was made.
- Coefficient of variation (CV) (%): Standard deviation / mean * 100.
- Geometric CV (%): (exp(Log-transformed Standard deviation)^2 – 1) * 100.
- Pharmacokinetic parameters normalized by dose: Pharmacokinetic parameters / dose (rounded to 3 significant digits).
- Total serine: D-serine + L-serine.
- QTcF interval (msec): QT interval (msec) / (RR interval (sec))0.33 (rounded to the nearest whole number).
- Change from time-matched baseline: For SRD part, values of Day -1 subtracted from values of Day 1 (and Day 9 in cohort 1) in the matching column in the table below for each subject. For MRD part, values of Day -1 subtracted from values of Day 17 in the matching column in the table below for each subject.

Figure 7.a Change from Time-Matched Baseline

Day	Time postdose (hour)			
Day -1	-20	-16	-12	0*
Day 1** or Day 17	4	8	12	24

* : Just prior to dosing, ** : Day 9 in cohort 1.

- Percent change from time-matched baseline: For SRD part, (values of Day -1 divided from values of Day 1 (and Day 9 in cohort 1) in the matching column in the table below -1) * 100 for each subject. For MRD part, (values of Day -1 divided from values of Day 17 in the matching column in the table below -1) * 100 for each subject.

Figure 7.b Percent Change from Time-Matched Baseline

Day	Time postdose (hour)			
Day -1	-20	-16	-12	0*
Day 1** or Day 17	4	8	12	24

* : Just prior to dosing, ** : Day 9 in cohort 1.

7.1.2 Definition of Study Visit Windows

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

7.1.3 Conventions for Missing Adverse Event Dates

Not applicable.

7.1.4 Conventions for Missing Concomitant Medication Dates

Not applicable.

7.2 Analysis Sets

- Safety analysis set:
  All subjects who received at least one dose of double-blind study drug.
- Pharmacokinetic analysis set:
  All subjects who received at least one dose of double-blind study drug, and who were appropriately evaluable for at least 1 PK parameter. All subjects with at least 1 measurable concentration for TAK-831 will be included in the summaries and analyses for that concentration.
- Pharmacodynamic analysis set:
  All subjects who received at least one dose of double-blind study drug, and who were appropriately evaluable for at least 1 PD parameter. All subjects with at least 1 post dose measurament of D-serine or L-serine concentration will be included in the summaries and analyses for that concentration.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Date First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

SAS Version Used for Creating the Datasets

Analytical Method(s):

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variable(s):

Age (years)

Gender [Male, Female]

Race [White, Asian]

Analytical Method(s):

(1) Screen Failures

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

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Eligibility Status

[Eligible for Randomization, Not Eligible for Randomization]

Primary Reason for Subject Not Being Eligible

[Death, Pretreatment Event/Adverse Event, Screen Failure, Significant Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal, Study Termination, Pregnancy, Sample Size Sufficient, Other]

Analytical Method(s):

(1) Eligibility for Randomization

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Disposition of Subjects

7.3.4.1 Cohort 1

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Study Completion Status

[Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]

Reason for Discontinuation of Study Visits

[Death, Adverse Event, Significant Protocol Deviation, Lost to Follow-up, Pregnancy, Voluntary Withdrawal, Study Termination, Other]

Analytical Method(s):

(1) Disposition of Subjects

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

7.3.4.2 Cohort 2

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.4.1 will be performed for the Cohort 2.

7.3.4.3 Cohort 3

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.4.1 will be performed for the Cohort 3 only when Cohort 3 will have been conducted. The same applies following analysis for the Cohort 3.

7.3.4.4 Cohort 4

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.4.1 will be performed for the Cohort 4 only when Cohort 4 will have been conducted. The same applies following analysis for the Cohort 4.

7.3.4.5 Cohort 5

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.4.1 will be performed for the Cohort 5.

7.3.4.6 Cohort 2, 4, 5

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.4.1 will be performed for the Cohort 2, 4, 5.

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Cohort 1

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s):

(1) Protocol Deviations

Frequency distribution will be provided by group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

Cohort 2

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

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

Cohort 3

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

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

Cohort 4

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.5.1 "Cohort 1" will be performed for the Cohort 4.

Cohort 5

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.5.1 "Cohort 1" will be performed for the Cohort 5.

7.3.5.2 Analysis Sets

Cohort 1

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Handling of Subjects

[No appropriate evaluable PK parameters, No appropriate evaluable PD parameters, Other Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Safety Analysis Set	[Included]
Pharmacokinetic Analysis Set	[Included]
Pharmacodynamic Analysis Set	[Included]

Analytical Method(s):

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided by group. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

Cohort 2, 4, 5

Analysis Set:

All Subjects Who Entered the Treatment Period

Analytical Method(s):

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided for each group by cohort for (1), and by dose and overall for (2). For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once. For (2), the placebo in the Cohort 2, 4 and 5 will be pooled. The same applies following analysis for the Cohort 2, 4, and 5.

Cohort 3

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.5.2 "Cohort 1" will be performed for the Cohort 3.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Age (years)

Gender [Male, Female]

Height (cm)

Weight (kg)

BMI (kg/m^2)

Smoking Classification

[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]

Alcohol Classification

[Everyday, 2 to 3 Days a Week, 2 to 3 Days a Month, Never]

Caffeine Classification [Yes, No]

Analytical Method(s):

(1) Summary of Demographics and Baseline Characteristics

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

7.4.2 Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Analysis Method(s):

The same analysis as section 7.4.1 will be performed for the Cohort 2, 4, and 5.

7.4.3 Cohort 3

Analysis Set:

Safety Analysis Set

Analysis Method(s):

The same analysis as section 7.4.1 will be performed for the Cohort 3.

7.5 Medical History and Concurrent Medical Conditions

Not applicable.

7.6 Medication History and Concomitant Medications

Not applicable.

7.7 Study Drug Exposure and Compliance

7.7.1 Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Number of Times the Study Drug was Taken [1, 2]

Analytical Method(s):

(1) Study Drug Exposure

Frequency distributions will be provided by group.

7.7.2 Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Number of Times the Study Drug was Taken [1, 2<= - <=14, 15]

Analytical Method(s):

(1) Study Drug Exposure

Frequency distributions and descriptive statistics will be provided by dose.

7.7.3 Cohort 3

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Number of Times the Study Drug was Taken [1, 2<= - <=14, 15]

Analytical Method(s):

The same analysis as section 7.7.2 will be performed for the Cohort 3.

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

See the section 7.9.2.

7.8.4.2 Handling of Dropouts or Missing Data

Missing data will not be included in the summary statistics, which means the N for the mean, SD etc. does not include the subject with missings.

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

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

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

Not applicable.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma/CSF Concentrations

<u>*Cohort 1*</u>

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Plasma Concentrations of TAK-831

Visit/Time Point:

Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Plasma Concentrations by Visit/Time Point

Descriptive statistics, and CV will be provided by visit.

(2) Case Plot of Plasma Concentrations

Plots over time for each subject will be presented by dose level. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. Visit/Time Point will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations

Mean will be plotted. Visit/Time Point will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

Cohort 2, 4, 5 (SRD Part)

Analysis Set:

Pharmacokinetic Analysis Set

Visit/Time Point:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

Analytical Method(s):

The same analysis as section 7.9.1.1 "Cohort 1" will be performed for the Cohort 2, 4, and 5 (SRD Part).

Cohort 2, 4, 5 (MRD Part)

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Plasma Concentrations of TAK-831

CSF Concentrations of TAK-831

Visit/Time Point:

Plasma Concentrations of TAK-831: Predose at Day 4, Predose at Day 11, Predose at Day 14, Predose at Day 17, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16 and 24 Hours Postdose at Day 17

CSF Concentrations of TAK-831: Day -1, 24 Hours Postdose at Day 17

Analytical Method(s):

For plasma concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) ~ (4) will be performed for the Cohort 2, 4, and 5 (MRD Part).

For CSF concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) will be performed for the Cohort 2, 4, and 5 (MRD Part).

Cohort 3 (SRD Part)

Analysis Set:

Pharmacokinetic Analysis Set

Visit/Time Point:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

Analytical Method(s):

The same analysis as section 7.9.1.1 "Cohort 1" will be performed for the Cohort 3 (SRD Part).

Cohort 3 (MRD Part)

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Plasma Concentrations of TAK-831

CSF Concentrations of TAK-831

Visit/Time Point:

Plasma Concentrations of TAK-831: Predose at Day 4, Predose at Day 11, Predose at Day 14, Predose at Day 17, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16 and 24 Hours Postdose at Day 17

CSF Concentrations of TAK-831: Day -1, 24 Hours Postdose at Day 17

Analytical Method(s):

For plasma concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) ~ (4) will be performed for the Cohort 3 (MRD Part).

For CSF concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) will be performed for the Cohort 3 (MRD Part).

7.9.1.2 Pharmacokinetic Parameters

Cohort 1

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax, Tmax, AUClast, AUCinf, AUC24, T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax, AUClast, AUCinf and AUC24, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of pharmacokinetic Parameters Normalized by Dose

For Cmax, AUClast, and AUCinf, normalized by dose, descriptive statistics, geometric mean, CV, and geometric CV will be provided.

Cohort 2, 4, 5 (SRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax, Tmax, AUClast, AUCinf, AUCtau, T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax, AUClast, AUCinf and AUCtau, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of pharmacokinetic Parameters Normalized by Dose

For Cmax, AUClast, and AUCinf, normalized by dose, descriptive statistics, geometric mean, CV, and geometric CV will be provided.

Cohort 2, 4, 5 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, Tmax, AUClast, AUCtau, Rac(Cmax), Rac(AUC), T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax,ss, AUClast, and AUCtau, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of pharmacokinetic Parameters Normalized by Dose

For Cmax,ss, and AUClast, normalized by dose, descriptive statistics, geometric mean, CV, and geometric CV will be provided.

Cohort 3 (SRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax, Tmax, AUClast, AUCinf, AUCtau, T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 2, 4, 5 (SRD Part)" will be performed for the Cohort 3 (SRD Part).

Cohort 3 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, Tmax, AUClast, AUCtau, Rac(Cmax), Rac(AUC), T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 2, 4, 5 (MRD Part)" will be performed for the Cohort 3 (MRD Part).

7.9.1.3 Assessment of Dose Proportionality in Pharmacokinetic Parameters

Cohort 2, 4, 5 (SRD Part)

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax, AUClast, AUCinf

Analytical Method(s):

The following summaries will be provided. Subjects administered placebo will be excluded from the analysis.

(1) Plot of Pharmacokinetic Parameters

Pharmacokinetic Parameters and Pharmacokinetic parameters normalized by dose will be plotted by dose. Dose will be plotted on the horizontal axis and each of the

analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

Cohort 2, 4, 5 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, AUClast, AUCtau

Analytical Method(s):

The same analysis as section 7.9.1.3 "Cohort 2, 4, 5 (SRD Part)" will be performed for the Cohort 2, 4, 5 (MRD Part).

7.9.2 Pharmacodynamic Analysis

7.9.2.1 Plasma/CSF Concentrations

Cohort 1

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Plasma Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine

Visit/Time Point:

-20, -16, and -12 Hours Predose, Predose, 1, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Plasma Concentrations by Visit/Time Point

Descriptive statistics, and CV for observed values will be provided by visit.

(2) Summary of Change from time-matched baseline by Visit

Descriptive statistics, and CV for change from time-matched baseline will be provided by visit.

(3) Summary of Percent change from time-matched baseline by Visit

Descriptive statistics, and CV for percent change from time-matched baseline will be provided by visit.

(4) Case Plot of Plasma Concentrations

Plots over time for each subject will be presented by dose level. The vertical axis will be a normal scale and a common logarithmic scale.

(5) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. Visit/Time Point will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

Cohort 2, 4, 5 (SRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Visit/Time Point:

-20, -16, and -12 Hours Predose, Predose, 1, 4, 8, 12, and 24 Hours Postdose

Analytical Method(s):

The same analysis as section 7.9.2.1 "Cohort 1" will be performed for the Cohort 2, 4, and 5 (SRD Part).

Cohort 2, 4, 5 (MRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Plasma Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine

CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine

Visit/Time Point:

Plasma Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine: Predose at Day 11, Predose at Day 14, Predose at Day 17, 1, 4, 8, 12, and 24 Hours Postdose at Day 17

CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine: Day -1, 24 Hours Postdose at Day 17

Analytical Method(s):

For plasma concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the same analysis as section 7.9.2.1 "Cohort 1" will be performed for the Cohort 2, 4, and 5 (MRD Part).

For CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the following summaries will be provided, only when CSF samples will have been collected.

(1) Summary of CSF Concentrations by Visit/Time Point

Descriptive statistics, and CV for observed values change from baseline (24 hours Postdose at Day 17 – Day -1) and percent change from baseline (100 * (24 hours Postdose at Day 17 – Day -1) / Day -1) will be provided for each visit by dose level.

(2) Histogram of Mean and Standard Deviation of Percent Change from baseline of CSF Concentrations by Dose Level

Histogram of Mean will be plotted with error bar of standard deviation. Dose level will be plotted on the horizontal axis and percent change from baseline of CSF concentration will be plotted on the vertical axis. The vertical axis will be a normal scale.

(3) ANCOVA model

The analysis variables will be analyzed using an ANCOVA model with the change from baseline (24 Hours Postdose at Day 17 – Day -1) as response, dose level as factors and value at Day -1 as covariate. LS means and the two-sided 95% confidence intervals will be provided for each dose level. The differences in the LS means between each TAK-831 dose and the placebo (each TAK-831 dose – the placebo) and the two-sided 95% confidence intervals will be provided. The same analysis will be conducted for the natural log-transformed ratio (log (24 Hours Postdose at Day 17 / Day -1)) as response, log-transformed value at Day -1 as covariate. The results will be provided original scale.

Cohort 3 (SRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Visit/Time Point:

-20, -16, and -12 Hours Predose, Predose, 1, 4, 8, 12, and 24 Hours Postdose

Analytical Method(s):

The same analysis as section 7.9.2.1 “Cohort 1” will be performed for the Cohort 3 (SRD Part).

Cohort 3 (MRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Plasma Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine

CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine

Visit/Time Point:

Plasma Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine: Predose at Day 11, Predose at Day 14, Predose at Day 17, 1, 4, 8, 12, and 24 Hours Postdose at Day 17

CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine: Day -1, 24 Hours Postdose at Day 17

Analytical Method(s):

For plasma concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the same analysis as section 7.9.2.1 "Cohort 1" will be performed for the Cohort 3 (MRD Part).

For CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the following summaries will be provided, only when CSF samples will have been collected.

(1) Summary of CSF Concentrations by Visit/Time Point

Descriptive statistics, and CV for observed values change from baseline (24 hours Postdose at Day 17 – Day -1) and percent change from baseline (100 * (24 hours Postdose at Day 17 – Day -1) / Day -1) will be provided for each visit by dose level.

7.9.2.2 Pharmacodynamic Parameters

Cohort 1

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine

AUEC24, Emax, Time to Emax

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 and Day 9 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 1 and Day 9 will be used as the Postdose visit)

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Pharmacodynamic parameters by Visit/Time Point

For AUEC24, and Emax, Descriptive statistics, and CV for observed values, changes from baseline (each postdose visit - Predose) and percent changes from baseline (100 * (each postdose visit – Predose) / Predose) will be provided by visit. For Time to Emax, Descriptive statistics for observed values will be provided by visit.

Cohort 2, 4, 5 (SRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine

AUEC24, Emax, Time to Emax

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 1 will be used as the Postdose visit)

Analytical Method(s):

For AUEC24 and Emax, following summaries (1) ~ (3) will be provided. For (1) and (2) will be provided by dose.

For Time to Emax, following summaries (1) and (2) will be provided by dose.

(1) Summary of Pharmacodynamic parameters by Visit/Time Point

For AUEC24, and Emax, Descriptive statistics, and CV for observed values, changes from baseline (each postdose visit - Predose) and percent changes from baseline (100 * (each postdose visit – Predose) / Predose) will be provided by visit. For Time to Emax, Descriptive statistics for observed values will be provided by visit.

(2) Histogram of Mean and Standard Deviation of Pharmacodynamic parameters by Dose Level by Race

For percent change from baseline of AUEC, and Emax, histogram of Mean will be plotted with error bar of standard deviation, including the data of Cohort 3. Dose level and race will be plotted on the horizontal axis and each of analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(3) ANCOVA model

The analysis variables will be analyzed using an ANCOVA model with the change from baseline (Postdose - Predose) as response, dose level as factors and Predose as covariate. LS means and the two-sided 95% confidence intervals will be provided for each dose level. The differences in the LS means between each TAK-831 dose and the placebo (each TAK-831 dose – the placebo) and the two-sided 95% confidence intervals will be provided. The same analysis will be conducted for the natural log-transformed ratio (log (Postdose / Predose)) as response, natural log-transformed Predose as covariate. The results will be provided original scale.

Cohort 2, 4, 5 (MRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine

AUEC24, Emax, Time to Emax

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 at SRD part will be used as the Predose visit. Data from Day 17 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 17 will be used as the Postdose visit)

Analytical Method(s):

For AUEC24 and Emax, following summaries (1) ~ (3) will be provided. For (1) and (2) will be provided by dose.

For Time to Emax, following summaries (1) and (2) will be provided by dose.

(1) Summary of Pharmacodynamic parameters by Visit/Time Point

For AUEC24, and Emax, Descriptive statistics, and CV for observed values, changes from baseline (each postdose visit - Predose) and percent changes from baseline (100 * (each postdose visit – Predose) / Predose) will be provided by visit. For Time to Emax, Descriptive statistics for observed values will be provided by visit.

(2) Histogram of Mean and Standard Deviation of Pharmacodynamic parameters by Dose Level by Race

For percent change from baseline of AUEC, and Emax, histogram of Mean will be plotted with error bar of standard deviation, including the data of Cohort 3. Dose level and race will be plotted on the horizontal axis and each of analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(3) ANCOVA model

The analysis variables will be analyzed using an ANCOVA model with the change from baseline (Postdose - Predose) as response, dose level as factors and Predose as covariate. LS means and the two-sided 95% confidence intervals will be provided for each dose level. The differences in the LS means between each TAK-831 dose and the placebo (each TAK-831 dose – the placebo) and the two-sided 95% confidence intervals will be provided. The same analysis will be conducted for the natural log-transformed ratio (log (Postdose / Predose)) as response, natural log-transformed Predose as covariate. The results will be provided original scale.

Cohort 3 (SRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 1 will be used as the Postdose visit)

Analytical Method(s):

The same analysis as section 7.9.2.2 “Cohort 1” will be performed for the Cohort 3 (SRD Part).

Cohort 3 (MRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 at SRD part will be used as the Predose visit. Data from Day 17 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 17 will be used as the Postdose visit)

Analytical Method(s):

The same analysis as section 7.9.2.2 "Cohort 1" will be performed for the Cohort 3 (MRD Part).

7.10 Other Outcomes

7.10.1 Assessment of the potential relationship between TAK-831 exposure and biomarker response

7.10.1.1 Cohort 1, and 2, 3, 4, 5 (SRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine: Changes from baseline and Percent changes from baseline of AUEC, Emax

Pharmacokinetic parameters of TAK-831: AUClast

Analytical Method(s):

The following summaries will be provided. Pharmacokinetic parameters of subjects administered placebo will be treated as 0.

(1) Scatter Plot for Pharmacodynamic Parameters and Pharmacokinetic Parameters

Scatter plot for each Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine and each Pharmacokinetic parameters of TAK-831 will be provided.

7.10.1.2 Cohort 2, 3, 4, 5 (MRD Part)

Analysis Set:

Pharmacodynamic Analysis Set

Analysis Variable(s):

Pharmacodynamic parameters, and CSF Concentration of D-serine, L-serine, and the ratio of D-serine to total serine: Changes from baseline and Percent changes from baseline of AUEC, CSF Concentration of D-serine, L-serine, and the ratio of D-serine to total serine

Pharmacokinetic parameters of TAK-831: AUCtau

Analytical Method(s):

The same analysis as section 7.10.1.1 will be performed for the Cohort 2, 3, 4, and 5 (MRD Part).

7.11 Safety Analysis

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

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

TEAE

Categories:

Relationship to Study Drug	[Related, Not Related]
Intensity	[Mild, Moderate, Severe]

Analytical Method(s):

The following summaries will be provided by dose.

(1) Overview of Treatment-Emergent Adverse Events

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

7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)

8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below. Percentages will be based on the number of subjects in the safety analysis set.

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

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

Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Analytical Method(s):

The same analysis as section 7.11.1.1 "Cohort 1" will be performed for the Cohort 2, 4, and 5.

Cohort 3

Analysis Set:

Safety Analysis Set

Analytical Method(s):

The same analysis as section 7.11.1.1 "Cohort 1" will be performed for the Cohort 3.

7.11.1.2 Displays of Treatment-Emergent Adverse events

Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

TEAE

Categories:

Intensity [Mild, Moderate, Severe]

Analytical Method(s):

The following summaries will be provided using frequency distribution by dose.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below. Percentages will be based on the number of subjects in the safety analysis set.

Number of subjects

- Summary tables other than (5) and (6)

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

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity.

Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Analytical Method(s):

The same analysis as section 7.11.1.2 "Cohort 1" will be performed for the Cohort 2, 4, and 5.

Cohort 3

Analysis Set:

Safety Analysis Set

Analytical Method(s):

The same analysis as section 7.11.1.2 "Cohort 1" will be performed for the Cohort 3.

7.11.1.3 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

PTE

Analytical Method(s):

The following summaries will be provided using frequency distribution.

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

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

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

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

Number of subjects

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

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Hematology

Erythrocytes (RBC), Hemoglobin, Hematocrit, Platelets, Leukocytes (WBC)

WBC Differentials (Neutrophils/Leukocytes, Eosinophils/Leukocytes, Basophils/Leukocytes, Lymphocytes/Leukocytes, Monocytes/Leukocytes), PT, APTT

Serum Chemistry

Total Protein, Albumin, Blood Urea Nitrogen, Creatinine, Direct Bilirubin, Total Bilirubin, Sodium, Potassium, Chloride, Calcium, Alkaline Phosphatase, Creatine Kinase (CPK), AST, ALT, Gamma Glutamyl Transferase (GGT), Glucose

Visit/Time Point:

Predose, 72 Hours Postdose

(Data from Day -1 and Day 8 will be used as the Predose visit)

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit/Time Point

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Laboratory Test Results

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.

For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Analytical Method(s):

The same analysis as section 7.11.2.1 "Cohort 1" will be performed for the Cohort 2, 4, and 5.

Cohort 3

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Analytical Method(s):

The same analysis as section 7.11.2.1 "Cohort 1" will be performed for the Cohort 3.

7.11.2.2 Urinalysis

Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Specific Gravity

pH	[5.0 <= - <= 8.0, 8.5 <= - <= 9.0]
Protein	[-, +-, +, 2+, 3+, 4+]
Glucose	[-, +-, +, 2+, 3+, 4+]
Occult blood	[-, +-, +, 2+, 3+]
Nitrite	[-, +, 2+]

Visit/Time Point:

Predose, 72 Hours Postdose

(Data from Day -1 and Day 8 will be used as the Predose visit)

Analytical Method(s):

For specific gravity, summaries (1), (2) and (4) will be provided by dose.

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

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit/Time Point

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Urine Laboratory Test Results

Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.

(4) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.

For each urine laboratory test, the laboratory values will be classified as “Low”, “Normal” or “High” relative to the normal reference range. The shift tables will be based on these classifications.

Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Analytical Method(s):

The same analysis as section 7.11.2.2 "Cohort 1" will be performed for the Cohort 2, 4, and 5.

Cohort 3

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Analytical Method(s):

The same analysis as section 7.11.2.2 "Cohort 1" will be performed for the Cohort 3.

7.11.3 Vital Signs and Weight

7.11.3.1 Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Temperature

Systolic Blood Pressure

Diastolic Blood Pressure

Pulse Rate

Weight

Visit/Time Point:

Variable other than weight: Predose, 1, 4, 12, 24, 36, 48, and 72 Hours Postdose

Weight: Predose, 72 Hours Postdose

(Data from Day -1 and Day 8 will be used as the Predose visit)

Analytical Method(s):

The following summaries will be provided by dose

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit/Time Point

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Vital Signs Parameters and Weight

Plots over time for each subject will be presented.

7.11.3.2 Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Variable other than weight: Predose, 1, 4, 12, 24, 36, and 48 Hours Postdose, Predose at Day 4, Predose at Day 5, Predose at Day 6, Predose at Day 7, Predose at Day 8, Predose at Day 9, Predose at Day 10, Predose at Day 11, Predose at Day 12, Predose at Day 13, Predose at Day 14, Predose at Day 15, Predose at Day 16, Predose at Day 17, 1, 4, 12, 24, and 48 Hours Postdose at Day 17

Weight: Predose, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Analytical Method(s):

The same analysis as section 7.11.3.1 will be performed for the Cohort 2, 4, and 5.

7.11.3.3 Cohort 3

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Variable other than weight: Predose, 1, 4, 12, 24, 36, and 48 Hours Postdose, Predose at Day 4, Predose at Day 5, Predose at Day 6, Predose at Day 7, Predose at Day 8, Predose at Day 9, Predose at Day 10, Predose at Day 11, Predose at Day 12, Predose at Day 13, Predose at Day 14, Predose at Day 15, Predose at Day 16, Predose at Day 17, 1, 4, 12, 24, and 48 Hours Postdose at Day 17

Weight: Predose, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Analytical Method(s):

The same analysis as section 7.11.3.1 will be performed for the Cohort 3.

7.11.4 12-Lead ECGs

7.11.4.1 Cohort 1

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Heart Rate

RR Interval

PR Interval

QRS Interval

QT Interval

QTcF Interval

Interpretation

[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit/Time Point:

Predose, 2, and 72 Hours Postdose

Analytical Method(s):

For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by dose.

For 12-lead ECG interpretation, summary (3) will be provided by dose.

(1) Summary of ECG Parameters and Change from Baseline by Visit/Time Point

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of ECG Parameters

Plots over time for each subject will be presented.

(3) Summary of Shift of 12-lead ECG Interpretation

Shift table showing the number of subjects in each category at Predose visit and each postdose visit will be provided.

7.11.4.2 Cohort 2, 4, 5

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Predose, 2 Hours Postdose, Predose at Day 4, Predose at Day 11, Predose at Day 17, 2, and 48 Hours Postdose at Day 17

Analytical Method(s):

The same analysis as section 7.11.4.1 will be performed for the Cohort 2, 4, and 5.

7.11.4.3 Cohort 3

Analysis Set:

Safety Analysis Set

Visit/Time Point:

Predose, 2 Hours Postdose, Predose at Day 4, Predose at Day 11, Predose at Day 17, 2, and 48 Hours Postdose at Day 17

Analytical Method(s):

The same analysis as section 7.11.4.1 will be performed for the Cohort 3.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

From the SAP version 1.0, the following parts were updated. Cohort 5 was added in each section. Other modified parts are as below.

Before the change

Cover

Protocol Version: Amendment 1

Protocol Date: 5 September 2018

After the change

Cover

Protocol Version: Amendment 3

Protocol Date: 26 February 2019

Reason for the change

Protocol was amended.

Before the change

Section 3.0 List of Abbreviations

ECG	electrocardiogram
LOCFlast observation carried forwardPD	pharmacodynamics
PK	pharmacokinetics
SDB	standard database

After the change

Section 3.0 List of Abbreviations

ECG	Electrocardiogram
TEAE	treatment-emergent adverse event
PD	Pharmacodynamics
PK	Pharmacokinetics

Reason for the change

To make descriptions more appropriate.

Before the change

Section 7.1.1 Study Definitions

- Dose:
  - Cohort 1: Placebo (sequence B part 2 and sequence C part 1 combined), TAK-831 100 mg, TAK-831 300 mg
  - Cohort 2~5: Placebo (cohort 2, 4 and 5 combined), TAK-831 300 mg, TAK-831 600 mg, TAK-831 50 mg

After the change

Section 7.1.1 Study Definitions

- Dose:
  - Cohort 1: Placebo (sequence B part 2 and sequence C part 1 combined), TAK-831 100 mg (sequence A part 1 and sequence B part 1 combined), TAK-831 300 mg (sequence A part 2 and sequence C part 2 combined)

- Cohort 2~5: Placebo (cohort 2, 4 and 5 combined), TAK-831 300 mg (Cohort 2), TAK-831 600 mg (Cohort 4), TAK-831 50 mg (Cohort 5)

Reason for the change

To clarify the descriptions.

Before the change

Section 7.1.1 Study Definitions

Visit/Time Point: Time point at which the assessment was made

After the change

Section 7.1.1 Study Definitions

Visit/Time Point: Scheduled time point at which the assessment was made

Reason for the change

To clarify the description.

Before the change

Section 7.1.1 Study Definitions

(New)

After the change

Section 7.1.1 Study Definitions

Geometric CV (%): (exp(Log-transformed Standard deviation)^2 – 1) * 100

Reason for the change

New analysis variables were added in the body.

Before the change

Section 7.1.1 Study Definitions

(New)

After the change

Section 7.1.1 Study Definitions

Change from time-matched baseline: For SRD part, values of Day -1 subtracted from values of Day 1 (and Day 9 in cohort 1) in the matching column in the table below for each subject. For MRD part, values of Day -1 subtracted from values of Day 17 in the matching column in the table below for each subject

Figure 7.a Change from Time-Matched Baseline

Percent change from time-matched baseline: For SRD part, (values of Day -1 divided from values of Day 1 (and Day 9 in cohort 1) in the matching column in the table below -1) * 100 for each subject. For MRD part, (values of Day -1 divided from values of Day 17 in the matching column in the table below -1) * 100 for each subject

Figure 7.b Percent Change from Time-Matched Baseline

Reason for the change

New analysis variables were added in the body.

Before the change

Section 7.2 Analysis Sets

- Pharmacokinetic analysis set:
  All subjects who received at least one dose of double-blind study drug, and who were appropriately evaluable for at least 1 PK parameter.
- Pharmacodynamic analysis set:
  All subjects who received at least one dose of double-blind study drug, and who were appropriately evaluable for at least 1 PD parameter.

After the change

Section 7.2 Analysis Sets

- Pharmacokinetic analysis set:
  All subjects who received at least one dose of double-blind study drug, and who were appropriately evaluable for at least 1 PK parameter. All subjects with at least 1 measurable concentration for TAK-831 will be included in the summaries and analyses for that concentration.
- Pharmacodynamic analysis set:
  All subjects who received at least one dose of double-blind study drug, and who were appropriately evaluable for at least 1 PD parameter. All subjects with at least 1 post dose measurament of D-serine or L-serine concentration will be included in the summaries and analyses for that concentration.

Reason for the change

Some descriptions were added to make the definitions more appropriate.

Before the change

Section 7.3.4. Disposition of Subjects

(New)

After the change

Section 7.3.4. Disposition of Subjects

7.3.4.6 Cohort 2, 4, 5

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Method(s):

The same analysis as section 7.3.4.1 will be performed for the Cohort 2, 4, 5.

Reason for the change

To meet the additional request.

Before the change

Section 7.3.5.2 Analysis Sets

Cohort 2, 4

Analytical Method(s):

(2) Analysis Sets

Frequency distributions will be provided for each group by cohort for (1), and by dose and overall for (2). For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once. For (2), only when the Cohort 4 will have been conducted, the placebo in the Cohort 2 and 4 will be pooled. The same applies following analysis for the Cohort 2, 4.

After the change

Section 7.3.5.2 Analysis Sets

Cohort 2, 4, 5

Analytical Method(s):

(2) Analysis Sets

Frequency distributions will be provided for each group by cohort for (1), and by dose and overall for (2). For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once. For (2), the placebo in the Cohort 2, 4 and 5 will be pooled. The same applies following analysis for the Cohort 2, 4, and 5.

Reason for the change

Error correction.

Before the change

Section 7.4.2 Cohort 2, 4

Analysis Method(s):

The same analysis as section 7.3.5.2 "Cohort 1" will be performed for the Cohort 2, 4.

After the change

Section 7.4.2 Cohort 2, 4, 5

Analysis Method(s):

The same analysis as section 7.4.1 will be performed for the Cohort 2, 4, and 5.

Reason for the change

Error correction.

Before the change

Section 7.4.3 Cohort 3

Analysis Method(s):

The same analysis as section 7.3.5.2 "Cohort 1" will be performed for the Cohort 3.

After the change

Section 7.4.3 Cohort 3

Analysis Method(s):

The same analysis as section 7.4.1 will be performed for the Cohort 3.

Reason for the change

Error correction.

Before the change

Section 7.8.4.1 Adjustments for Covariates

Not applicable.

After the change

Section 7.8.4.1 Adjustments for Covariates

See the section 7.9.2.

Reason for the change

To make the description more appropriate.

Before the change

Section 7.8.4.2 Handling of Dropouts or Missing Data

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

After the change

Section 7.8.4.2 Handling of Dropouts or Missing Data

Missing data will not be included in the summary statistics, which means the N for the mean, SD etc. does not include the subject with missings.

Reason for the change

To make the description more appropriate.

Before the change

Section 7.9.1.1 Plasma Concentrations

Cohort 2, 4 (SRD Part)

Visit/Time Point:

Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

Analytical Method(s):

The same analysis as section 7.9.1.1 "Cohort 1" will be performed for the Cohort 2, 4 (SRD Part).

After the change

Section 7.9.1.1 Plasma/CSF Concentrations

Cohort 2, 4, 5 (SRD Part)

Visit/Time Point:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

Analytical Method(s):

The same analysis as section 7.9.1.1 "Cohort 1" will be performed for the Cohort 2, 4, and 5 (SRD Part).

Reason for the change

Another Visit/Time Point was added.

Before the change

Section 7.9.1.1 Plasma Concentrations

Cohort 2, 4 (MRD Part)

Visit/Time Point:

Predose at Day 4, Predose at Day 11, Predose at Day 14, Predose at Day 17, 0.5, 1, 1.5, 2, 4, 8, 12, 16 and 24 Hours Postdose at Day 17

Analytical Method(s):

The same analysis as section 7.9.1.1 "Cohort 1" will be performed for the Cohort 2, 4 (MRD Part)

After the change

Section 7.9.1.1 Plasma/CSF Concentrations

Cohort 2, 4, 5 (MRD Part)

Analysis Variable(s):

Plasma Concentrations of TAK-831

CSF Concentrations of TAK-831

Visit/Time Point:

Plasma Concentrations of TAK-831: Predose at Day 4, Predose at Day 11, Predose at Day 14, Predose at Day 17, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16 and 24 Hours Postdose at Day 17

CSF Concentrations of TAK-831: Day -1, 24 Hours Postdose at Day 17

Analytical Method(s):

For plasma concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) ~ (4) will be performed for the Cohort 2, 4, and 5 (MRD Part).

For CSF concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) will be performed for the Cohort 2, 4, and 5 (MRD Part).

Reason for the change

Another Visit/Time Point was added. CSF Concentrations of TAK-831 in cohort 2, 4, 5 were determined to be collected.

Before the change

Section 7.9.1.1 Plasma Concentrations

Cohort 3 (SRD Part)

Visit/Time Point:

Predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

After the change

Section 7.9.1.1 Plasma/CSF Concentrations

Cohort 3 (SRD Part)

Visit/Time Point:

Predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48 and 72 Hours Postdose

Reason for the change

Another Visit/Time Point was added.

Before the change

Section 7.9.1.1 Plasma Concentrations

Cohort 3 (MRD Part)

Analysis Set:

Pharmacokinetic Analysis Set

Visit/Time Point:

Predose at Day 4, Predose at Day 11, Predose at Day 14, Predose at Day 17, 0.5, 1, 1.5, 2, 4, 8, 12, 16 and 24 Hours Postdose at Day 17

Analytical Method(s):

The same analysis as section 7.9.1.1 "Cohort 1" will be performed for the Cohort 3 (MRD Part)

After the change

Section 7.9.1.1 Plasma/CSF Concentrations

Cohort 3 (MRD Part)

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Plasma Concentrations of TAK-831

CSF Concentrations of TAK-831

Visit/Time Point:

Plasma Concentrations of TAK-831: Predose at Day 4, Predose at Day 11, Predose at Day 14, Predose at Day 17, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 16 and 24 Hours Postdose at Day 17

CSF Concentrations of TAK-831: Day -1, 24 Hours Postdose at Day 17

Analytical Method(s):

For plasma concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) ~ (4) will be performed for the Cohort 3 (MRD Part).

For CSF concentrations of TAK-831, the same analysis as section 7.9.1.1 "Cohort 1" (1) will be performed for the Cohort 3 (MRD Part).

Reason for the change

CSF Concentrations of TAK-831 in cohort 3 was determined to be collected.

Before the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 1

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax, Tmax, AUClast, AUCinf, T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax, AUClast, and AUCinf, descriptive statistics, geometric mean, and CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of pharmacokinetic Parameters Normalized by Dose

For Cmax, AUClast, and AUCinf, normalized by dose, descriptive statistics, geometric mean, and CV will be provided.

After the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 1

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax, Tmax, AUClast, AUCinf, AUC24, T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax, AUClast, AUCinf, and AUC24, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of pharmacokinetic Parameters Normalized by Dose

For Cmax, AUClast, and AUCinf, normalized by dose descriptive statistics, geometric mean, CV, and geometric CV will be provided.

Reason for the change

Another Pharmacokinetic parameter was added.

Before the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 2, 4 (SRD Part)

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 1" will be performed for the Cohort 2, 4 (SRD Part)

After the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 2, 4, 5 (SRD Part)

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax, AUClast, AUCinf and AUCtau, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of pharmacokinetic Parameters Normalized by Dose

For Cmax, AUClast, and AUCinf, normalized by dose, descriptive statistics, geometric mean, CV, and geometric CV will be provided.

Reason for the change

Descriptions were modified considering into the difference of Pharmacokinetic parameters cohort 2, 4, 5 and cohort 1.

Before the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 2, 4 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, Tmax, AUCtau, Rac(Cmax), Rac(AUC), T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 1" will be performed for the Cohort 2, 4 (MRD Part)

After the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 2, 4, 5 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, Tmax, AUClast, AUCtau, Rac(Cmax), Rac(AUC), T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The following summaries will be provided by dose. Subjects administered placebo will be excluded from the analysis.

(1) Summary of Pharmacokinetic Parameters

For Cmax,ss, AUClast, and AUCtau, descriptive statistics, geometric mean, CV, and geometric CV will be provided. For Tmax, descriptive statistics will be provided. For all other variables, descriptive statistics and CV will be provided.

(2) Summary of pharmacokinetic Parameters Normalized by Dose

For Cmax,ss, and AUClast, normalized by dose, descriptive statistics, geometric mean, CV, and geometric CV will be provided.

Reason for the change

Another Pharmacokinetic parameter was added. Descriptions were modified considering into the difference of Pharmacokinetic parameters cohort 2, 4, 5 and cohort 1.

Before the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 3 (SRD Part)

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 1" will be performed for the Cohort 3 (SRD Part)

After the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 3 (SRD Part)

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 2, 4, 5 (SRD Part)" will be performed for the Cohort 3 (SRD Part).

Reason for the change

Descriptions were modified considering into the change of the descriptions of cohort 2, 4, 5 (SRD Part).

Before the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 3 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, Tmax, AUCtau, Rac(Cmax), Rac(AUC), T1/2z, CL/F, Vz/F

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 1" will be performed for the Cohort 3 (MRD Part)

After the change

Section 7.9.1.2 Pharmacokinetic Parameters

Cohort 3 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, Tmax, AUClast, AUCtau, Rac(Cmax), Rac(AUC), T1/2z, Lambda z, CL/F, Vz/F

Analytical Method(s):

The same analysis as section 7.9.1.2 "Cohort 2, 4, 5 (MRD Part)" will be performed for the Cohort 3 (MRD Part).

Reason for the change

Another Pharmacokinetic parameters were added. Descriptions were modified considering into the change of the descriptions of cohort 2, 4, 5 (MRD Part).

Before the change

Section 7.9.1.3 Assessment of Dose Proportionality in Pharmacokinetic Parameters

Cohort 1, and 2, 4 (SRD Part)

Visit/Time Point:

Cohort 1: Day 1, Day 9

Cohort 2, 4: Day 1

Analytical Method(s):

The following summaries will be provided. Subjects administered placebo will be excluded from the analysis.

(1) Plot of Pharmacokinetic Parameters

Pharmacokinetic Parameters and Pharmacokinetic parameters normalized by dose will be plotted by dose. Dose will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(2) Regression Analysis of Pharmacokinetic Parameters on Dose

A power regression analysis will be performed for each analysis variable using the power model:

$y = a * (dose)^b * e,$

where y is the analysis variable, a and b are the regression parameters, and e is the error term of the power equation.

A linear regression will also be performed using the linear model:

$y = a + b*(dose) + e.$

Parameter estimates for a and b, and their two-sided 95% confidence intervals will be provided for each model. Because of two observations in each subject in sequence A, linear mixed model will be used.

After the change

Section 7.9.1.3 Assessment of Dose Proportionality in Pharmacokinetic Parameters

Cohort 2, 4, 5 (SRD Part)

Analytical Method(s):

The following summaries will be provided. Subjects administered placebo will be excluded from the analysis.

(1) Plot of Pharmacokinetic Parameters

Pharmacokinetic Parameters and Pharmacokinetic parameters normalized by dose will be plotted by dose. Dose will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

Cohort 2, 4, 5 (MRD Part)

Analysis Variable(s):

Pharmacokinetic parameters of TAK-831

Cmax,ss, AUClast, AUCtau

Analytical Method(s):

The same analysis as section 7.9.1.3 "Cohort 2, 4, 5 (SRD Part)" will be performed for the Cohort 2, 4, 5 (MRD Part).

Reason for the change

As the condition of PK collection in cohort 1 differs from other cohort, cohort 1 was excluded.

The formulation of Added cohort 5 differs from cohort 2 and 4, modeling analysis was deleted.

Before the change

Section 7.9.2.1 Plasma Concentrations

Cohort 1

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Plasma Concentrations by Visit/Time Point

Descriptive statistics, and CV for observed values will be provided by visit.

(2) Case Plot of Plasma Concentrations

Plots over time for each subject will be presented by dose level. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. Visit/Time Point will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

After the change

Section 7.9.2.1 Plasma/CSF Concentrations

Cohort 1

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Plasma Concentrations by Visit/Time Point

Descriptive statistics, and CV for observed values will be provided by visit.

(2) Summary of Change from time-matched baseline by Visit

Descriptive statistics, and CV for change from time-matched baseline will be provided by visit.

(3) Summary of Percent change from time-matched baseline by Visit

Descriptive statistics, and CV for percent change from time-matched baseline will be provided by visit.

(4) Case Plot of Plasma Concentrations

Plots over time for each subject will be presented by dose level. The vertical axis will be a normal scale and a common logarithmic scale.

(5) Mean and Standard Deviation Plot of Plasma Concentrations

Mean and standard deviation will be plotted. Visit/Time Point will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

Reason for the change

Error correction and other department request.

Before the change

Section 7.9.2.1 Plasma Concentrations

Cohort 2, 4 (MRD Part)

Analytical Method(s):

For plasma concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the same analysis as section 7.9.2.1 "Cohort 1" will be performed for the Cohort 2, 4 (MRD Part). For CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, descriptive statistics, and CV for observed values will be provided for each visit by dose level, only when CSF samples will have been collected.

After the change

Section 7.9.2.1 Plasma/CSF Concentrations

Cohort 2, 4, 5 (MRD Part)

Analytical Method(s):

For plasma concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the same analysis as section 7.9.2.1 "Cohort 1" will be performed for the Cohort 2, 4, and 5 (MRD Part).

For CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the following summaries will be provided, only when CSF samples will have been collected.

(1) Summary of CSF Concentrations by Visit/Time Point

Descriptive statistics, and CV for observed values change from baseline (24 hours Postdose at Day 17 – Day -1) and percent change from baseline (100 * (24 hours Postdose at Day 17 – Day -1) / Day -1) will be provided for each visit by dose level.

(2) Histogram of Mean and Standard Deviation of Percent Change from baseline of CSF Concentrations by Dose Level

Histogram of Mean will be plotted with error bar of standard deviation. Dose level will be plotted on the horizontal axis and percent change from baseline of CSF concentration will be plotted on the vertical axis. The vertical axis will be a normal scale.

(3) ANCOVA model

The analysis variables will be analyzed using an ANCOVA model with the change from baseline (24 Hours Postdose at Day 17 – Day -1) as response, dose level as factors and value at Day -1 as covariate. LS means and the two-sided 95% confidence intervals will be provided for each dose level. The differences in the LS means between each TAK-831 dose and the placebo (each TAK-831 dose – the placebo) and the two-sided 95% confidence intervals will be provided. The same analysis will be conducted for the natural log-transformed ratio (log (24 Hours Postdose at Day 17 / Day -1)) as response, log-transformed value at Day -1 as covariate. The results will be provided original scale.

Reason for the change

Another analysis was added due to other department request.

Before the change

Section 7.9.2.1 Plasma Concentrations

Cohort 3 (MRD Part)

Analytical Method(s):

For plasma concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the same analysis as section 7.9.2.1 "Cohort 1" will be performed for the Cohort 3 (MRD Part). For CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, descriptive statistics, and CV for observed values will be provided for each visit by dose level, only when CSF samples will have been collected.

After the change

Section 7.9.2.1 Plasma Concentrations

Cohort 3 (MRD Part)

Analytical Method(s):

For plasma concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the same analysis as section 7.9.2.1 "Cohort 1" will be performed for the Cohort 3 (MRD Part).

For CSF Concentrations of D-serine, L-serine, and the ratio of D-serine to total serine, the following summaries will be provided, only when CSF samples will have been collected.

(1) Summary of CSF Concentrations by Visit/Time Point

Descriptive statistics, and CV for observed values change from baseline (24 hours Postdose at Day 17 – Day -1) and percent change from baseline (100 * (24 hours Postdose at Day 17 – Day -1) / Day -1) will be provided for each visit by dose level.

Reason for the change

Another analysis was added due to other department request.

Before the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 1

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 and Day 9 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 and Day 9 will be used as the Postdose visit)

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Pharmacodynamic parameters by Visit/Time Point

For AUEC24, and Emax, Descriptive statistics for observed values, changes from baseline (each postdose visit - Predose) and percent changes from baseline (100 * (each postdose visit – Predose) / Predose) will be provided by visit. For Time to Emax, Descriptive statistics for observed values will be provided by visit.

After the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 1

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 and Day 9 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 1 and Day 9 will be used as the Postdose visit)

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Pharmacodynamic parameters by Visit/Time Point

For AUEC24, and Emax, Descriptive statistics, and CV for observed values, changes from baseline (each postdose visit - Predose) and percent changes from baseline (100 * (each postdose visit – Predose) / Predose) will be provided by visit. For Time to Emax, Descriptive statistics for observed values will be provided by visit.

Reason for the change

Error correction.

Before the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 2, 4 (SRD Part)

Visit/Time Point:

Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 will be used as the Postdose visit)

Analytical Method(s):

The same analysis as section 7.9.2.2 "Cohort 1" will be performed for the Cohort 2, 4 (SRD Part).

After the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 2, 4, 5 (SRD Part)

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 1 will be used as the Postdose visit)

Analytical Method(s):

For AUEC24 and Emax, following summaries (1) ~ (3) will be provided. For (1) and (2) will be provided by dose.

For Time to Emax, following summaries (1) and (2) will be provided by dose.

(1) Summary of Pharmacodynamic parameters by Visit/Time Point

For AUEC24, and Emax, Descriptive statistics, and CV for observed values, changes from baseline (each postdose visit - Predose) and percent changes from baseline (100 * (each postdose visit – Predose) / Predose) will be provided by visit. For Time to Emax, Descriptive statistics for observed values will be provided by visit.

(2) Histogram of Mean and Standard Deviation of Pharmacodynamic parameters by Dose Level by Race

For percent change from baseline of AUEC, and Emax, histogram of Mean will be plotted with error bar of standard deviation, including the data of Cohort 3. Dose

level and race will be plotted on the horizontal axis and each of analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(3) ANCOVA model

The analysis variables will be analyzed using an ANCOVA model with the change from baseline (Postdose - Predose) as response, dose level as factors and Predose as covariate. LS means and the two-sided 95% confidence intervals will be provided for each dose level. The differences in the LS means between each TAK-831 dose and the placebo (each TAK-831 dose – the placebo) and the two-sided 95% confidence intervals will be provided. The same analysis will be conducted for the natural log-transformed ratio (log (Postdose / Predose)) as response, natural log-transformed Predose as covariate. The results will be provided original scale.

Reason for the change

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

Before the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 2, 4 (MRD Part)

Visit/Time Point:

Predose, Postdose

(Data from Day -1 at SRD part will be used as the Predose visit. Data from Day 17 will be used as the Postdose visit)

Analytical Method(s):

The same analysis as section 7.9.2.2 “Cohort 1” will be performed for the Cohort 2, 4 (MRD Part).

After the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 2, 4, 5 (MRD Part)

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine

AUEC24, Emax, Time to Emax

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 at SRD part will be used as the Predose visit. Data from Day 17 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 17 will be used as the Postdose visit)

Analytical Method(s):

For AUEC24 and Emax, following summaries (1) ~ (3) will be provided. For (1) and (2) will be provided by dose.

For Time to Emax, following summaries (1) and (2) will be provided by dose.

(1) Summary of Pharmacodynamic parameters by Visit/Time Point

For AUEC24, and Emax, Descriptive statistics, and CV for observed values, changes from baseline (each postdose visit - Predose) and percent changes from baseline (100 * (each postdose visit – Predose) / Predose) will be provided by visit. For Time to Emax, Descriptive statistics for observed values will be provided by visit.

(2) Histogram of Mean and Standard Deviation of Pharmacodynamic parameters by Dose Level by Race

For percent change from baseline of AUEC, and Emax, histogram of Mean will be plotted with error bar of standard deviation, including the data of Cohort 3. Dose level and race will be plotted on the horizontal axis and each of analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(3) ANCOVA model

The analysis variables will be analyzed using an ANCOVA model with the change from baseline (Postdose - Predose) as response, dose level as factors and Predose as covariate. LS means and the two-sided 95% confidence intervals will be provided for each dose level. The differences in the LS means between each TAK-831 dose and the placebo (each TAK-831 dose – the placebo) and the two-sided 95% confidence intervals will be provided. The same analysis will be conducted for the natural log-transformed ratio (log (Postdose / Predose)) as response, natural log-transformed Predose as covariate. The results will be provided original scale.

Reason for the change

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

Before the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 3 (SRD Part)

Visit/Time Point:

Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 will be used as the Postdose visit)

After the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 3 (SRD Part)

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 will be used as the Predose visit. Data from Day 1 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 1 will be used as the Postdose visit)

Reason for the change

Error correction.

Before the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 3 (MRD Part)

Visit/Time Point:

Predose, Postdose

(Data from Day -1 at SRD part will be used as the Predose visit. Data from Day 17 will be used as the Postdose visit)

After the change

Section 7.9.2.2 Pharmacodynamic Parameters

Cohort 3 (MRD Part)

Visit/Time Point:

AUEC24, Emax: Predose, Postdose

(Data from Day -1 at SRD part will be used as the Predose visit. Data from Day 17 will be used as the Postdose visit)

Time to Emax: Postdose

(Data from Day 17 will be used as the Postdose visit)

Reason for the change

Error correction.

Before the change

Section 7.10.1 Assessment of the potential relationship between TAK-831 exposure and biomarker response

Cohort 1, and 2, 4 (SRD Part)

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine: Percent changes from baseline of AUEC, Emax

Pharmacokinetic parameters of TAK-831: AUClast

After the change

Section 7.10.1 Assessment of the potential relationship between TAK-831 exposure and biomarker response

Cohort 1, and 2, 3, 4, 5 (SRD Part)

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine: Changes from baseline and Percent changes from baseline of AUEC, Emax

Pharmacokinetic parameters of TAK-831: AUClast

Reason for the change

Another analysis variables were added due to other department request.

Before the change

Section 7.10.1 Assessment of the potential relationship between TAK-831 exposure and biomarker response

Cohort 2, 4 (MRD Part)

Analysis Variable(s):

Pharmacodynamic parameters of D-serine, L-serine, and the ratio of D-serine to total serine: Percent changes from baseline of AUEC

Pharmacokinetic parameters of TAK-831: AUCtau

Analytical Method(s):

The same analysis as section 7.10.1.1 will be performed for the Cohort 2, 4 (MRD Part).

After the change

Section 7.10.1 Assessment of the potential relationship between TAK-831 exposure and biomarker response

Cohort 2, 3, 4, 5 (MRD Part)

Analysis Variable(s):

Pharmacodynamic parameters, and CSF Concentration of D-serine, L-serine, and the ratio of D-serine to total serine: Changes from baseline and Percent changes from baseline of AUEC, CSF Concentration of D-serine, L-serine, and the ratio of D-serine to total serine

Pharmacokinetic parameters of TAK-831: AUCtau

Analytical Method(s):

The same analysis as section 7.10.1.1 will be performed for the Cohort 2, 3, 4, and 5 (MRD Part).

Reason for the change

Another analysis variables were added due to other department request.

Before the change

Section 7.11.2.1 Hematology and Serum Chemistry

Cohort 2, 4

Visit/Time Point:

Predose, Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Cohort 3

Visit/Time Point:

Predose, Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

After the change

Section 7.11.2.1 Hematology and Serum Chemistry

Cohort 2, 4, 5

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Cohort 3

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Reason for the change

Error correction.

Before the change

Section 7.11.2.2 Urinalysis

Cohort 2, 4

Visit/Time Point:

Predose, Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Cohort 3

Visit/Time Point:

Predose, Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

After the change

Section 7.11.2.2 Urinalysis

Cohort 2, 4, 5

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Cohort 3

Visit/Time Point:

Predose, Predose at Day 11, 48 Hours Postdose at Day 17

(Data from Day -1 will be used as the Predose visit)

Reason for the change

Error correction.

8.0 REFERENCES

Not applicable.