Certain information within this clinical study report has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Statistical Analysis Plan

Study Title: A Phase 1, Open-label, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Pharmacodynamics of TAK-385 Alone in Hormone Treatment-naive Japanese Patients With Non-metastatic Prostate Cancer

Study Number: TAK-385/TB-AK160108

Sponsor: Takeda Pharmaceutical Company Limited

[redacted]

[redacted]

[redacted]

Version 2.0: July 20, 2017

Table of Contents

Glossary

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after the start of study drug
- Descriptive statistics: number of subjects, mean, standard deviation (SD), maximum (max), minimum (min), and quartiles
- CV: coefficient of variation
- Randomized set: All subjects who were randomized. The first maintenance dose prescribed will be used as the treatment group when conducting analyses.
- Treatment group: For part A, the assigned cohort will be the treatment group. For part B, the first maintenance dose prescribed will be the treatment group.
- PK: pharmacokinetic
- MAV: markedly abnormal value
- ATC: anatomical therapeutic chemical
- LDH: lactic dehydrogenase
- GGT: gamma-glutamyl transpeptidase
- CK (CPK): creatine phosphokinase/kinase
- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. If the date of the observation is on the same date or after the day of the first dose, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1. Follow-up Day will be calculated relative to Day 1.

Definition of Visit Window

When calculating Study Day relative to a reference date (i.e., date of first dose of study drug [Day 1]), if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0. When calculating Study Time relative to a reference time (i.e., time of each dose of study drug), it will be calculated as: time of observation - reference time.

When calculating Follow-up Day relative to a reference date (i.e., date of last dose of study drug [Follow-up Day 0]), it will be calculated as: date of observation - reference date. Hence, reference day is always Follow-up Day 0.

All evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day/Study Time to the scheduled Study Day/Study Time will be used. If there are two observations equidistant to the scheduled Study Day/Study Time, the later observation will be used. This does not apply to the end of study visit. For the end of study visit, the last observation obtained in the corresponding time interval will be used.

<Part A>

PSA

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Baseline (Week 0)	Study Day: 1	-28 - 1
D28	Study Day: 28	2 - 35

Pharmacokinetic Assessments

Visit	Scheduled Study Time (hours)	Time Interval	
		Study Day (days)	Study Time (hours)
D1	-1	1	-3.00 - 0.00
D1	0.5	1	0.33 - 0.67
D1	1	1	0.75 - 1.24
D1	1.5	1	1.25 - 1.74
D1	2	1	1.75 - 2.33
D1	4	1	3.67 - 4.33
D1	6	1	5.50 - 6.50
D1	8	1	7.50 - 8.50
D1	12	1	11.00 - 13.00
D2	-1	2	-2.00 - 0.00
D3	-1	3	-2.00 - 0.00
D3	2	3	1.67 - 2.33
D7	-1	7	-2.00 - 0.00
D7	2	7	1.67 - 2.33
D12	-1	12	-2.00 - 0.00
D13	-1	13	-2.00 - 0.00
D14	-1	14	-2.00 - 0.00
D14	0.5	14	0.33 - 0.67

Visit	Scheduled Study Time (hours)	Time Interval	
		Study Day (days)	Study Time (hours)
D14	1	14	0.75 - 1.24
D14	1.5	14	1.25 - 1.74
D14	2	14	1.75 - 2.33
D14	4	14	3.67 - 4.33
D14	6	14	5.50 - 6.50
D14	8	14	7.50 - 8.50
D14	12	14	11.00 - 13.00
D15	Study Day: 15	15	16.00 - 34.00 (from last dose)
D21	Study Day: 21	18 - 24	16.00 - 34.00 (from last dose)
D28	-1	28	-2.00 - 0.00
D28	1	28	0.75 - 1.24
D28	2	28	1.67 - 2.33
D28	4	28	3.67 - 4.33
D28	8	28	7.50 - 8.50
D28	12	28	11.00 - 13.00
D29	24 (from D28)	29	23.00 - 25.00 (from D28)
D30	48 (from D28)	30	44.00 - 52.00 (from D28)
D31	72 (from D28)	31	68.00 - 76.00 (from D28)
D35	168 (from D28)	35	164.00 - 172.00 (from D28)

Pharmacodynamic Assessments

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Baseline (Week 0)	Study Day: 1	-28 - 1
D2	Study Day: 2	2
D3	Study Day: 3	3 - 4
D7	Study Day: 7	5 - 10
D14	Study Day: 14	11 - 17
D21	Study Day: 21	18 - 24
D28	Study Day: 28	25 - 29
D31	Study Day: 31	30 - 34
D35	Study Day: 35	35

Laboratory Tests (Hematology, Biochemistry, Urinalysis)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	- 1	
D7	Study Day: 7	2 - 10	< 15
D14	Study Day: 14	11 - 17	< 15
D21	Study Day: 21	18 - 24	< 15
D28	Study Day: 28	25 - 42	< 15
SFU	Follow-up Day: 40		15 - 40

Laboratory Tests (Lipid and Glycated Hemoglobin in Blood)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	- 1	
D28	Study Day: 28	2 - 42	< 15

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
SFU	Follow-up Day: 40		15 - 40

Vital Signs, Weight

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-28 - 1	
D7	Study Day: 7	2 - 10	< 15
D14	Study Day: 14	11 - 17	< 15
D21	Study Day: 21	18 - 24	< 15
D28	Study Day: 28	25 - 42	< 15
SFU	Follow-up Day: 40		15 - 40

12-Lead Electrocardiogram

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-28 - 1	
D14	Study Day: 14	2 - 20	< 15
D28	Study Day: 28	21 - 42	< 15
SFU	Follow-up Day: 40		15 - 40

ECOG Performance Status

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-28 - 1	

<Part B>

PSA

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Baseline (Week 0)	Study Day: 1	-28 - 1
WK5D1	Study Day: 29	2 - 42
WK9D1	Study Day: 57	43 - 70
WK13D1	Study Day: 85	71 - 98
WK17D1	Study Day: 113	99 - 126
WK21D1	Study Day: 141	127 - 154
WK25D1	Study Day: 169	155 - 210
WK37D1	Study Day: 253	211 - 294
WK49D1	Study Day: 337	295 - 378
WK61D1	Study Day: 421	379 - 462
WK73D1	Study Day: 505	463 - 546
WK85D1	Study Day: 589	547 - 630
WK97D1	Study Day: 673	631 - 680
WK13D1 (LOCF)	Study Day: 85	2 - 98
End of Study		2 -

Pharmacokinetic Assessments

Visit	Scheduled Study Time (hours)	Time Interval	
		Study Day (days)	Study Time (hours)
WK1D1	-1	1	-3.00 - 0.00
WK1D1	2	1	1.75 - 2.33
WK1D2	-1	2	-2.00 - 0.00
WK1D4	Study Day: 4	3 - 6	16.00 - 34.00 (from last dose)

Visit	Scheduled Study Time (hours)	Time Interval	
		Study Day (days)	Study Time (hours)
WK2D1	Study Day: 8	7 - 12	16.00 - 34.00 (from last dose)
WK3D1	Study Day: 15	13 - 22	16.00 - 34.00 (from last dose)
WK5D1	Study Day: 29	23 - 43	-2.00 - 0.00
WK5D1	2	23 - 43	1.67 - 2.33
WK9D1	Study Day: 57	44 - 71	16.00 - 34.00 (from last dose)
WK13D1	Study Day: 85	72 - 99	16.00 - 34.00 (from last dose)
WK17D1	Study Day: 113	100 – 127	16.00 - 34.00 (from last dose)
WK21D1	Study Day: 141	128 - 155	16.00 - 34.00 (from last dose)
WK25D1	Study Day: 169	156 - 183	16.00 - 34.00 (from last dose)
WK37D1	Study Day: 253	233 - 274	16.00 - 34.00 (from last dose)
WK49D1	Study Day: 337	317 - 358	16.00 - 34.00 (from last dose)

Imaging Assessments

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
WK49D1	Study Day: 337	2 - 344
WK97D1	Study Day: 673	345 - 680

QOL Assessment

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-28 - 1	
WK5D1	Study Day: 29	2 - 42	< 15
WK9D1	Study Day: 57	43 - 70	< 15
WK13D1	Study Day: 85	71 - 112	< 15
WK21D1	Study Day: 141	113 - 154	< 15
WK25D1	Study Day: 169	155 - 238	< 15
WK45D1	Study Day: 309	239 - 322	< 15
WK49D1	Study Day: 337	323 - 378	< 15
WK61D1	Study Day: 421	379 - 462	< 15
WK73D1	Study Day: 505	463 - 546	< 15
WK85D1	Study Day: 589	547 - 630	< 15
WK97D1	Study Day: 673	631 - 687	< 15
SFU	Follow-up Day: 40		15 - 40

Pharmacodynamic Assessments (Excluding High-Sensitivity Serum Testosterone)

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Baseline (Week 0)	Study Day: 1	-28 - 1
WK1D2	Study Day: 2	2 - 3
WK1D4	Study Day: 4	4 - 5
WK2D1	Study Day: 8	6 - 11
WK3D1	Study Day: 15	12 - 21
WK5D1	Study Day: 29	22 - 42
WK9D1	Study Day: 57	43 - 70
WK13D1	Study Day: 85	71 - 98

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
WK17D1	Study Day: 113	99 - 126
WK21D1	Study Day: 141	127 - 154
WK25D1	Study Day: 169	155 - 210
WK37D1	Study Day: 253	211 - 294
WK49D1	Study Day: 337	295 - 378
WK61D1	Study Day: 421	379 - 462
WK73D1	Study Day: 505	463 - 546
WK85D1	Study Day: 589	547 - 630
WK97D1	Study Day: 673	631 - 680

ECOG Performance Status

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-28 - 1	

Pharmacodynamic Assessments (High-Sensitivity Serum Testosterone)

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Baseline (Week 0)	Study Day: 1	-28 - 1
WK2D1	Study Day: 8	2 - 11
WK3D1	Study Day: 15	12 - 21
WK5D1	Study Day: 29	22 - 42
WK9D1	Study Day: 57	43 - 70
WK13D1	Study Day: 85	71 - 98
WK17D1	Study Day: 113	99 - 126
WK21D1	Study Day: 141	127 - 154

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
WK25D1	Study Day: 169	155 - 210
WK37D1	Study Day: 253	211 - 294
WK49D1	Study Day: 337	295 - 344

Laboratory Tests (Hematology)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	- 1	
WK5D1	Study Day: 29	2 - 42	< 15
WK9D1	Study Day: 57	43 - 70	< 15
WK13D1	Study Day: 85	71 - 126	< 15
WK25D1	Study Day: 169	127 - 210	< 15
WK37D1	Study Day: 253	211 - 294	< 15
WK49D1	Study Day: 337	295 - 378	< 15
WK61D1	Study Day: 421	379 - 462	< 15
WK73D1	Study Day: 505	463 - 546	< 15
WK85D1	Study Day: 589	547 - 630	< 15
WK97D1	Study Day: 673	631 - 687	< 15
SFU	Follow-up Day: 40		15 - 40

Laboratory Tests (Biochemistry)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	- 1	
WK5D1	Study Day: 29	2 - 42	< 15
WK9D1	Study Day: 57	43 - 70	< 15
WK13D1	Study Day: 85	71 - 98	< 15
WK17D1	Study Day: 113	99 - 126	< 15
WK21D1	Study Day: 141	127 - 154	< 15
WK25D1	Study Day: 169	155 - 182	< 15
WK29D1	Study Day: 197	183 - 210	< 15
WK33D1	Study Day: 225	211 - 238	< 15

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
WK37D1	Study Day: 253	239 - 266	< 15
WK41D1	Study Day: 281	267 - 294	< 15
WK45D1	Study Day: 309	295 - 322	< 15
WK49D1	Study Day: 337	323 - 378	< 15
WK61D1	Study Day: 421	379 - 462	< 15
WK73D1	Study Day: 505	463 - 546	< 15
WK85D1	Study Day: 589	547 - 630	< 15
WK97D1	Study Day: 673	631 - 687	< 15
SFU	Follow-up Day: 40		15 - 40

Laboratory Tests (Lipid and Glycated Hemoglobin in Blood, Urinalysis)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	- 1	
WK5D1	Study Day: 29	2 - 42	< 15
WK9D1	Study Day: 57	43 - 70	< 15
WK13D1	Study Day: 85	71 - 126	< 15
WK25D1	Study Day: 169	127 - 252	< 15
WK49D1	Study Day: 337	253 - 378	< 15
WK61D1	Study Day: 421	379 - 462	< 15
WK73D1	Study Day: 505	463 - 546	< 15
WK85D1	Study Day: 589	547 - 630	< 15
WK97D1	Study Day: 673	631 - 687	< 15
SFU	Follow-up Day: 40		15 - 40

12-Lead Electrocardiogram

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-28 - 1	
WK3D1	Study Day: 15	2 - 21	< 15
WK5D1	Study Day: 29	22 - 98	< 15
WK25D1	Study Day: 169	99 – 252	< 15
WK49D1	Study Day: 337	253 – 420	< 15
WK73D1	Study Day: 505	421 – 588	< 15
WK97D1	Study Day: 673	589 - 687	< 15
SFU	Follow-up Day: 40		15 - 40

Vital Signs, Weight

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-28 - 1	
WK2D1	Study Day: 8	2 - 11	< 15
WK3D1	Study Day: 15	12 - 21	< 15
WK5D1	Study Day: 29	22 - 42	< 15
WK9D1	Study Day: 57	43 - 70	< 15
WK13D1	Study Day: 85	71 - 126	< 15
WK25D1	Study Day: 169	127 - 252	< 15
WK49D1	Study Day: 337	253 - 378	< 15
WK61D1	Study Day: 421	379 - 462	< 15
WK73D1	Study Day: 505	463 - 546	< 15
WK85D1	Study Day: 589	547 - 630	< 15
WK97D1	Study Day: 673	631 - 687	< 15
SFU	Follow-up Day: 40		15 - 40

Bone Mineral Density (DXA)

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Baseline (Week 0)	Study Day: 1	-28 - 1
WK25D1	Study Day: 169	2 - 252
WK49D1	Study Day: 337	253 - 420
WK73D1	Study Day: 505	421 - 588
WK97D1	Study Day: 673	589 - 713

Others

- Duration of exposure to study drug (days) : date of last dose of study drug - date of first dose of study drug + 1
- Dose intensity (mg/day): total amount of doses taken / duration of exposure to study drug (rounded to 1 decimal place)
- Relative dose intensity (%): (total amount of doses taken / total dose expected per initial dose) * 100 (rounded to 1 decimal place)
- Dosing compliance: (total amount of doses taken / total dose expected) * 100 (rounded to 1 decimal place)
- Disease duration (days): date subject signed Informed Consent Form - date of diagnosis + 1
  - For the date subject signed Informed Consent Form, the year, the month, and the day will be used for the calculation.
  - If the year is unknown, then the date of diagnosis will be treated as missing. If the month is unknown, then the month will be treated as January and the day will be treated as the 1st day of the month. If only the day is unknown, then the day will be treated as the 1st day of the month for the calculation.
- PK parameters:
  - AUC_{last} --Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
  - $AUC_{last, ss}$ --Area under the concentration-time curve from time 0 to time of the last quantifiable concentration, at steady state.
  - AUC_{τ} --Area under the concentration-time curve during a dosing interval (= 24 hours).
  - $AUC_{\tau, ss}$ --Area under the concentration-time curve during a dosing interval (= 24 hours), at steady state.
  - $AUC_{\tau, ss}/D$ --Dose-normalized AUC_{τ}, at steady state.
  - CL/F_{ss} --Apparent clearance after extravascular administration, at steady state, calculated using AUC_{τ}.
  - C_{max} --Maximum observed concentration.
  - $C_{max, ss}$ --Maximum observed concentration, at steady state.
  - $C_{max, ss}/D$ --Dose-normalized C_{max}, at steady state.
  - $C_{min, ss}$ --Minimum observed concentration during a dosing interval, at steady state.
  - λ_z --Terminal disposition phase rate constant.
  - t_{max} --Time of first occurrence of C_{max}.
  - $t_{max, ss}$ --Time of first occurrence of C_{max}, at steady state.
  - $t_{1/2z}$ --Terminal disposition phase half-life.
  - V_z/F_{ss} --Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using AUC_{τ}.

1 Study Subjects, Demographics, and Other Baseline Characteristics (Part A)

1.1 Disposition of Subjects

1.1.1 Study Information (Part A and Part B)

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
WHO Drug 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.

1.1.2 Screen Failures

Analysis Set: All Subjects Who Did Not Enter the Treatment Period

Analysis Variable(s) :

Age (years)	[Min<= - <=64, 65<= - <=74, 75<= - <=Max]
Gender	[Male, Female]

Analytical Method(s) : (1) Screen Failures
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

1.1.3 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s) :	Eligibility Status	[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]
	Primary Reason for Subject Not Being Eligible	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Did Not Meet Entrance Criteria, Other]

Analytical Method(s) : (1) Eligibility for Entrance into the Treatment Period

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.

1.1.4 Number of Subjects Who Entered the Treatment Period by Site and Treatment Group

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Status of Entrance into the Treatment Period	[Entered]
Stratum:	Site	[Site numbers will be used as categories]

Analytical Method(s) : (1) Number of Subjects Who Entered the Treatment Period by Site and Treatment Group

Frequency distribution will be provided for each stratum by treatment group and overall.

1.1.5 Disposition of Subjects

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Study Drug Administration Status	[Eligible but Not Treated]
Reason for Not Being Treated	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Other]
Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
Reason for Discontinuation of Study Drug	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Other]
Completion Status of the Safety Follow-up	[Completed Safety Follow-up, Prematurely Discontinued Safety Follow-up]
Reason for Discontinuation of the Safety Follow-up	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Other]

Analytical Method(s):

(1) Disposition of Subjects

Frequency distributions will be provided for each treatment group and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of study drug, the total number of subjects who prematurely discontinued the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of the safety follow-up, the total number of subjects who prematurely discontinued the safety follow-up will be used as the denominator.

1.1.6 Protocol Deviations and Analysis Sets

1.1.6.1 Protocol Deviations

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s): Protocol Deviation [Major GCP Violations, Deviations of Protocol Entry Criteria, Deviations of Discontinuation Criteria, Deviations Related to Treatment Procedure or Dose, Deviations Concerning Excluded Medication or Therapy, Deviations to Avoid Emergency Risk]

Analytical Method(s): (1) Protocol Deviations

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

1.1.6.2 Analysis Sets

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s): Handling of Subjects and Subject Data [Categories are based on the specifications in Handling Rules for Analysis Data]

Analysis Sets

Full Analysis Set	[Included]
Safety Analysis Set	[Included]
DLT Analysis Set	[Included]
Pharmacokinetic Analysis Set	[Included]

Analytical Method(s): (1) Subjects Excluded from Analysis Sets

(2) Subject Data Excluded from Analysis Sets

(3) Analysis Sets

Frequency distributions will be provided by treatment group for (1) and (2) and by treatment group and overall for (3). For (1) and (2), 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.

1.2 Demographics and Other Baseline Characteristics

1.2.1 Summary of Demographics and Other Baseline Characteristics

Analysis Set:	Safety Analysis Set	
Analysis		
Variable(s) :	Age (years)	[Min<= - <=64, 65<= - <=74, 75<= - <=Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg) (Week 0)	
	BMI (kg/m^2) (Week 0)	
	Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
	ECOG Performance Status (Week 0)	[0, 1, 2, 3, 4]
	Diagnostic Method	[Histological Diagnosis, Cytological Diagnosis, Other]
	Disease Duration (days)	
	Gleason Grading System (Gleason Score)	[2, 3, 4, 5, 6, 7, 8, 9, 10]
	Histologic Type	[Adenocarcinoma, Other]
	Degree of Differentiation	[Well Differentiated Adenocarcinoma, Moderately Differentiated Adenocarcinoma, Poorly Differentiated Adenocarcinoma, Unclassified Adenocarcinoma]
	TNM Classification T	[T0, T1, T2, T3, T4, TX]
	TNM Classification N	[N0, N1, NX]
	TNM Classification M	[M0, M1, MX]
	Prostatectomy	[Yes, No]
	Radical Prostatectomy	[Yes, No]
	High-Intensity Focused Ultrasound	[Yes, No]
	Radiation Therapy	[Yes, No]
	Other Treatment	[Yes, No]
	PSA (ng/mL) (Week 0)	
	Testosterone (ng/mL) (Week 0)	

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

1.2.2 Medical History and Concurrent Medical Conditions

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : Medical History
Concurrent Medical Conditions
Analytical
Method(s) : (1) Medical History by System Organ Class and Preferred Term
(2) Concurrent Medical Conditions by System Organ Class and Preferred Term
Frequency distributions will be provided for each treatment group and overall. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.
A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

1.2.3 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : Medication History
Concomitant Medications
Analytical
Method(s) : (1) Medication History by Preferred Medication Name
(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by ATC Pharmacological Subgroup and Preferred Medication Name
Frequency distributions will be provided for each treatment group and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names for (1) and using both ATC pharmacological subgroup and preferred medication names for (2). ATC

pharmacological subgroup will be sorted alphabetically and preferred medication names will be sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

1.3 Treatment Compliance

1.3.1 Study Drug Exposure and Compliance

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Duration of Exposure to Study Drug (days)	[1<= - <=7, 8<= - <=14, 15<= - <=21, 22<= - <=Max]
	Total Amount of Doses Taken (mg)	
	Dose Intensity (mg/day)	
	Relative Dose Intensity (%)	
	Subjects with Any Dose Held	[Yes, No]
	Reason for Dose Being Held	
	Adverse Event	[Yes]
	Other	[Yes]
	Dosing Compliance (%)	[Min<= - <=79.9, 80.0<= - <=89.9, 90.0<= - <=Max]
Analytical Method(s) :	(1) Study Drug Exposure and Compliance Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.	

2 Study Subjects, Demographics, and Other Baseline Characteristics (Part B)

2.1 Disposition of Subjects

2.1.1 Screen Failures

Analysis Set: All Subjects Who Were Not Randomized

Analysis Variable(s) :	Age (years)	[Min<= - <=64, 65<= - <=74, 75<= - <=Max]
	Gender	[Male, Female]

Analytical Method(s) : (1) Screen Failures

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

2.1.2 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	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Did Not Meet Entrance Criteria, 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.

2.1.3 Number of Subjects Randomized by Site and Treatment Group

Analysis Set: Randomized Set

Analysis Variable(s) :	Randomization Status	[Randomized]
Stratum:	Site	[Site numbers will be used as categories]

Analytical Method(s) : (1) Number of Subjects Randomized by Site and Treatment Group

Frequency distribution will be provided for each stratum by treatment group and overall.

2.1.4 Disposition of Subjects

Analysis Set:	Randomized Set Subjects from the Randomized Set Who Completed Study Drug (48 Weeks)	
Analysis Variable(s) :	Study Drug Administration Status	[Randomized but Not Treated]
	Reason for Not Being Treated	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Other]
	Study Drug Completion Status (48 Weeks)	[Completed Study Drug (48 Weeks), Prematurely Discontinued Study Drug (48 Weeks)]
	Reason for Discontinuation of Study Drug	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Other]
	Entrance into the Extension Treatment Period	[Entered the Extension Treatment Period, Did Not Enter the Extension Treatment Period]
	Reason for Not Entering the Extension Treatment Period	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Start of Other Treatment, Other]
	Study Drug Completion Status (96 Weeks)	[Completed Study Drug (96 Weeks), Prematurely Discontinued Study Drug (96 Weeks)]
	Reason for Discontinuation of Study Drug	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Completed 48 Weeks of Treatment but Did Not Enter Extension, Other]

	Completion Status of the Safety Follow-up	[Completed Safety Follow-up, Prematurely Discontinued Safety Follow-up]
	Reason for Discontinuation of the Safety Follow-up	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Other]

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

Randomized set will be used to perform the following analysis, with the exception of the summary for entrance into the extension treatment period and the reasons for not entering which will use subjects from the randomized set who completed study drug (48 weeks). Frequency distributions will be provided for each treatment group and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation at 48 weeks and 96 weeks, the total number of subjects who prematurely discontinued the study drug before 48 weeks and 96 weeks (including subjects who completed 48 weeks of study drug treatment but did not enter the extension treatment period), respectively, will be used as the denominator. When calculating percentages for the reasons for not entering the extension treatment period, the total number of subjects who completed 48 weeks of study drug treatment but did not enter the extension treatment period will be used as the denominator.

2.1.5 Study Drug Completion Status

Analysis Set: Randomized Set

Analysis Variable(s) :	Study Drug Completion Status (96 Weeks)	[Completed Study Drug (96 Weeks), Prematurely Discontinued Study Drug (96 Weeks)]
	Reason for Discontinuation of Study Drug	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Lack of Efficacy, Completed 48 Weeks of Treatment but Did Not Enter Extension, Other]

Categories:	Duration of Exposure to Study Drug (days)	[0<= - <=90, 91<= - <=180, 181<= - <=270, 271<= - <=360, 361<= - <=450, 451<= - <=540, 541<= - <=630, 631<= - <=Max]
Analytical Method(s) :	(1) Study Drug Completion Status Frequency distribution will be provided for each category of duration of exposure to study drug by treatment group and overall.	

2.1.6 Protocol Deviations and Analysis Sets

2.1.6.1 Protocol Deviations

Analysis Set:	Randomized Set	
Analysis Variable(s) :	Protocol Deviation	[Major GCP Violations, Deviations of Protocol Entry Criteria, Deviations of Discontinuation Criteria, Deviations Related to Treatment Procedure or Dose, Deviations Concerning Excluded Medication or Therapy, Deviations to Avoid Emergency Risk]
Analytical Method(s) :	(1) Protocol Deviations Frequency distribution will be provided by treatment group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.	

2.1.6.2 Analysis Sets

Analysis Set:	Randomized Set	
Analysis Variable(s) :	Handling of Subjects and Subject Data	[Categories are based on the specifications in Handling Rules for Analysis Data]
	Analysis Sets	
	Full Analysis Set	[Included]
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]

Analytical Method(s) :

(1) Subjects Excluded from Analysis Sets

(2) Subject Data Excluded from Analysis Sets

(3) Analysis Sets

Frequency distributions will be provided by treatment group for (1) and (2) and by treatment group and overall for (3). For (1) and (2), 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.

2.2 Demographics and Other Baseline Characteristics

2.2.1 Summary of Demographics and Other Baseline Characteristics

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Age (years)	[Min<= - <=64, 65<= - <=74, 75<= - <=Max]
Gender	[Male, Female]
Height (cm)	
Weight (kg) (Week 0)	
BMI (kg/m^2) (Week 0)	
Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
ECOG Performance Status (Week 0)	[0, 1, 2, 3, 4]
Diagnostic Method	[Histological Diagnosis, Cytological Diagnosis, Other]
Disease Duration (days)	
Gleason Grading System (Gleason Score)	[2, 3, 4, 5, 6, 7, 8, 9, 10]
Histologic Type	[Adenocarcinoma, Other]
Degree of Differentiation	[Well Differentiated Adenocarcinoma, Moderately Differentiated Adenocarcinoma, Poorly Differentiated Adenocarcinoma, Unclassified Adenocarcinoma]
TNM Classification T	[T0, T1, T2, T3, T4, TX]

TNM Classification N	[N0, N1, NX]
TNM Classification M	[M0, M1, MX]
Prostatectomy	[Yes, No]
Radical Prostatectomy	[Yes, No]
High-Intensity Focused Ultrasound	[Yes, No]
Radiation Therapy	[Yes, No]
Other Treatment	[Yes, No]
PSA (ng/mL) (Week 0)	
Testosterone (ng/mL) (Week 0)	

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

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

2.2.2 Medical History and Concurrent Medical Conditions

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medical History

Concurrent Medical Conditions

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

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

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

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

2.2.3 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medication History

Concomitant Medications

Analytical Method(s) :

(1) Medication History by Preferred Medication Name

(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by ATC Pharmacological Subgroup and Preferred Medication Name

Frequency distributions will be provided for each treatment group and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names for (1) and using both ATC pharmacological subgroup and preferred medication names for (2). ATC pharmacological subgroup will be sorted alphabetically and preferred medication names will be sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

2.3 Treatment Compliance

2.3.1 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Duration of Exposure to Study Drug (days)	[1<= - <=90, 91<= - <=180, 181<= - <=270, 271<= - <=360, 361<= - <=450, 451<= - <=540, 541<= - <=630, 631<= - <=Max]
Total Amount of Doses Taken (mg)	
Dose Intensity (mg/day)	
Relative Dose Intensity (%)	
Subjects with Any Dose Held	[Yes, No]
Reason for Dose Being Held	
Adverse Event	[Yes]
Other	[Yes]
Subjects with Any Dose Reduction	[Yes, No]
Reason for Dose Being Reduced	
Adverse Event	[Yes]
Other	[Yes]
Dosing Compliance (%)	[Min<= - <=79.9, 80.0<= - <=89.9, 90.0<= - <=Max]

Analytical

Method(s) : (1) Study Drug Exposure and Compliance

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

2.3.2 Dosing Pattern Details

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Dosing Pattern	[80 mg, 120 mg, 80 / 120 mg, 80 / 120 / 80 mg, 80 / 40 mg, 120 / 160 mg, 120 / 160 / 120 mg, 120 / 80 mg, etc.] *These categories are merely an example and may change in accordance with the actual data.
	Last Dose	[40 mg, 80 mg, 120 mg, 160 mg]

Analytical Method(s) : (1) Dosing Pattern Details

Frequency distributions will be provided by treatment group and overall.

3 Efficacy, Pharmacokinetic, and Pharmacodynamic Analysis (Part A)

3.1 Efficacy Analysis

3.1.1 Antitumor Effects

Analysis Set: Full Analysis Set

Analysis Variable(s): PSA (ng/mL)

Visit: Baseline, D28

Analytical Method(s): The following analysis will be performed using the full analysis set.
For the observed values, descriptive statistics and two-sided 95% confidence intervals of the mean will be provided for each visit by treatment group. The same analysis will be performed for the percent change from baseline.

3.2 Pharmacokinetic Analysis

3.2.1 Plasma Concentrations

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Plasma concentrations of TAK-385 (ng/mL)

Visit: D1 and D14: Before dosing, 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours after dosing
D28: Before dosing, 1, 2, 4, 8, 12, 24, 48 and 72 hours after dosing
D3 and D7: Before dosing and 2 hours after dosing
D2, D12, D13, D15, D21 and D35: Before dosing

Analytical Method(s): Number of subjects, mean, SD, min, median, max, geometric mean, and CV will be used to summarize plasma concentrations at each visit for each treatment group.
Linear plots of plasma concentration-time profiles will be provided for each treatment group using individual and mean (SD) concentrations in separate plots. Mean (SD) plots will include the plasma concentration plot for all visits, separate plots for each of Day 1, Day 14, Day 28, and a plot for the plasma trough concentrations.

3.2.2 Pharmacokinetic Parameters

Listing

Analysis Set: Full Analysis Set

Analysis Variable(s): D1: AUC_{τ}, C_{max} and t_{max}

D14: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, $C_{max, ss}$, $C_{max, ss}/D$, $C_{min, ss}$, $t_{max, ss}$

D28: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, CL/F_{ss}, $C_{max, ss}$, $C_{max, ss}/D$, $t_{max, ss}$, $t_{1/2z}$, V_z/F_{ss}, λ_z, number of data points with first and last data points used in the terminal disposition phase regression analysis and adjusted R^2 (coefficient of determination) for the terminal disposition phase regression analysis

Analytical Method(s) : PK parameters will be calculated by using individual plasma concentrations with actual sampling times. Plasma concentrations from D1 to D2, D14 to D15 and D28 to D35 will be used for the calculation of PK parameters on D1, D14 and D28 respectively. Plasma concentrations deviated from the visit window will be also used for the calculation. A standard non-compartmental analysis will be performed using the linear trapezoidal rule. If subject received prohibited concomitant medications, therapies or foods, then the plasma concentrations measured on and after this day will be used to estimate the PK parameters for the listing but the results will be treated as reference values.

Individual PK parameters will be listed. The listings will include the treatment group, subject ID and evaluation day (D1, D14, and D28) in addition to the PK parameters.

Descriptive Statistics

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s) :
D1: AUC_{τ}, C_{max} and t_{max}
D14: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, $C_{max, ss}$, $C_{max, ss}/D$, $C_{min, ss}$, $t_{max, ss}$
D28: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, CL/F_{ss}, $C_{max, ss}$, $C_{max, ss}/D$, $t_{max, ss}$, $t_{1/2z}$, V_z/F_{ss}, λ_z

Analytical Method(s) : For the pharmacokinetic parameters, the number of subjects, mean, SD, min, median, max, geometric mean, and CV will be provided for each treatment group. PK parameters which are treated as reference values will be excluded from the summary statistics.

Graphical assessment of dose-proportionality on $C_{max, ss}$ and $AUC_{\tau, ss}$ will be conducted on D14 and D28 by plotting individual dose-normalized exposure parameters, i.e., $C_{max, ss}/D$ or $AUC_{\tau, ss}/D$ versus dose.

3.3 Pharmacodynamic Analysis

3.3.1 Serum Testosterone Concentrations

Analysis Set: Full Analysis Set

Analysis Variable(s): Serum Testosterone Concentrations (ng/mL)

Visit: Baseline, D2, D3, D7, D14, D21, D28, D31, D35

Analytical Method(s): The following analysis will be performed using the full analysis set.
For observed values and percent change from baseline, descriptive statistics and two-sided 95% confidence intervals of the mean will be provided for each visit by treatment group. Case plots as well as the mean and standard deviation plots of changes over time will be provided for observed values for each treatment group. A reference line will be drawn where the serum testosterone concentration is 0.5 ng/mL.

3.3.2 Serum Concentrations of LH, FSH, DHT, and SHBG

Analysis Set: Full Analysis Set

Analysis Variable(s): (1) Serum Concentrations of LH (mIU/mL)
(2) Serum Concentrations of FSH (mIU/mL)
(3) Serum Concentrations of DHT (ng/mL)
(4) Serum Concentrations of SHBG (nmol/L)

Visit: Baseline, D2, D3, D7, D14, D21, D28, D31, D35

Analytical Method(s): The following analysis will be performed using the full analysis set.
For the analysis variables (1) to (4), descriptive statistics of the observed values and the two-sided 95% confidence intervals of the mean will be provided for each visit by treatment group. The same analysis will be performed for the percent change from baseline. Case plots as well as the mean and standard deviation plots of changes over time will be provided for observed values for each treatment group.

3.4 Statistical/Analytical Issues

3.4.1 Adjustments for Covariates

Not applicable in this study.

3.4.2 Handling of Dropouts or Missing Data

Missing test results and data determined to be non-evaluable according to the Handling Rules for Analysis Data will not be used for hypothesis testing and estimations.

Values less than or equal to the lower limit of quantification will be treated as the value of the lower limit of quantification for PSA, serum testosterone, LH, FSH, DHT, and SHBG, and all others will be treated as zero when calculating the descriptive statistics.

Values less than the lower limit of quantification will be treated as zero except for the calculation of geometric mean for plasma concentration of TAK-385. For the geometric mean, values less than the lower limit of quantification will be treated as missing.

3.4.3 Interim Analyses and Data Monitoring

No interim analysis is planned in this study.

3.4.4 Multicenter Studies

Although this study is a multicenter study, treatment-by-center interaction will not be explored since the number of subjects for each center is not sufficient for such exploration.

3.4.5 Multiple Comparison/Multiplicity

Not applicable in this study.

3.4.6 Use of an "Efficacy Subset" of Subjects

Not applicable in this study.

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

Not applicable in this study.

3.4.8 Examination of Subgroups

Not applicable in this study.

4 Efficacy, Pharmacokinetic, and Pharmacodynamic Analysis (Part B)

4.1 Efficacy Analysis

4.1.1 Antitumor Effects

Analysis Set: Full Analysis Set

Analysis Variable(s) :
(1) PSA (ng/mL)
(2) Rate of Progression Based on PSA (%)
(3) Rate of Progression Based on Imaging Assessments (%)

Visit :
(1) Baseline, WK5D1, WK9D1, WK13D1, WK17D1, WK21D1, WK25D1, WK37D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1, WK13D1 (LOCF), End of Study
(3) WK49D1, WK97D1

Analytical Method(s) :
The following analysis will be performed using the full analysis set.

(1) For the observed values, descriptive statistics and two-sided 95% confidence intervals of the mean will be provided for each visit by treatment group. Case plots as well as the mean and standard deviation plots of changes over time will be provided for each treatment group. The same analysis will be performed for the percent change from baseline.

The percent change from baseline at WK13D1 (LOCF) as well as the percent change from baseline when the PSA value is at its minimum since the start of the study drug administration will be shown using waterfall plots for each treatment group.

(2) Rate of progression based on PSA will be defined as the proportion of subjects who have a 25% or greater increase as well as an absolute increase of 2 ng/mL or more in the value of PSA at least 4 weeks from the nadir. If the value of PSA never decreased from baseline, the above conditions will be fit to the value obtained after WK13D1. A missing value will be assigned if neither of the following conditions is met: "there are at least two observations after study drug administration" or "there is at least one observation on or after WK13D1 and the baseline is not missing". If the same minimum PSA value occurs at several visits, then the PSA value with the earliest date will be used as the nadir. Frequency distributions will be provided for each treatment group.

(3) Rate of progression based on imaging assessments will be defined as the proportion of subjects who have developed new lesions. Frequency distributions will be provided for each visit by treatment group.

4.1.2 QOL Assessment

Analysis Set: Full Analysis Set

Analysis Variable(s) :
(1) AMS
(2) EORTC-QLQ-C30
(3) EPIC

Visit : Baseline, WK5D1, WK9D1, WK13D1, WK21D1, WK25D1, WK45D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1, SFU

Analytical Method(s) : The following analysis will be performed using the full analysis set. The scoring procedures are described in detail in the Appendix.

(1) Descriptive statistics for the actual values and the percent change from baseline of AMS subscale scores and total scores will be provided for each visit by treatment group.

(2) Descriptive statistics for the actual values and the change from baseline of Global health status/QoL score and each Functional scales score (physical, role, emotional, cognitive, social) will be provided for each visit by treatment group.

(3) Descriptive statistics for the actual values and the change from baseline of each HRQOL Domain Summary Score (urinary, bowel, sexual, hormonal) will be provided for each visit by treatment group.

4.2 Pharmacokinetic Analysis

4.2.1 Plasma Concentrations

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s) : Plasma concentrations of TAK-385 (ng/mL)

Visit : WK1D1 and WK5D1: Before dosing and 2 hours after dosing.
WK1D2, WK1D4, WK2D1, WK3D1, WK9D1, WK13D1, WK17D1, WK21D1, WK25D1, WK37D1 and WK49D1: Before dosing

Analytical Method(s) : Descriptive statistics, geometric mean, and CV will be used to summarize plasma concentrations at each visit for each treatment group.

Case plots as well as the mean and standard deviation plots of changes over time will be provided for plasma concentrations for each treatment group.

4.3 Pharmacodynamic Analysis

4.3.1 Serum Testosterone Concentrations

Analysis Set: Full Analysis Set

Analysis Variable(s) :
(1) Serum Testosterone Concentrations (ng/mL)
(2) High-sensitivity Serum Testosterone Concentrations (ng/dL)
(3) Castration Rate (%)

Visit :
(1) Baseline, WK1D2, WK1D4, WK2D1, WK3D1, WK5D1, WK9D1, WK13D1, WK17D1, WK21D1, WK25D1, WK37D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1
(2) Baseline, WK2D1, WK3D1, WK5D1, WK9D1, WK13D1, WK17D1, WK21D1, WK25D1, WK37D1, WK49D1

Analytical Method(s) :
The following analysis will be performed using the full analysis set.
For the analysis variables (1) and (2), descriptive statistics and two-sided 95% confidence intervals of the mean will be provided for the observed values and the percent change from baseline for each visit by treatment group. Case plots as well as the mean and standard deviation plots of changes over time will be provided for observed values for each treatment group. For (1), a reference line will be drawn where the serum testosterone concentration is 0.5 ng/mL.
(3) Castration rate will be defined as the proportion of subjects who have serum testosterone concentrations of less than 0.5 ng/mL at all visits through WK5D1 to WK25D1. Subjects who have no testosterone measurements between WK5D1 and WK25D1 will be excluded from this analysis. Frequency distributions will be provided for each treatment group. The two-sided 95% confidence interval will also be provided.

4.3.2 Serum Concentrations of LH, FSH, DHT, and SHBG

Analysis Set: Full Analysis Set

Analysis Variable(s) :
(1) Serum Concentrations of LH (mIU/mL)
(2) Serum Concentrations of FSH (mIU/mL)
(3) Serum Concentrations of DHT (ng/mL)
(4) Serum Concentrations of SHBG (nmol/L)

Visit :
Baseline, WK1D2, WK1D4, WK2D1, WK3D1, WK5D1, WK9D1, WK13D1, WK17D1, WK21D1, WK25D1, WK37D1, WK49D1, WK61D1,

WK73D1, WK85D1, WK97D1

Analytical Method(s) : The following analysis will be performed using the full analysis set.
For the analysis variables (1) to (4), descriptive statistics of the observed values and the two-sided 95% confidence intervals of the mean will be provided for each visit by treatment group. The same analysis will be performed for the percent change from baseline. Case plots as well as the mean and standard deviation plots of changes over time will be provided for observed values for each treatment group.

4.4 Statistical/Analytical Issues

4.4.1 Adjustments for Covariates

Not applicable in this study.

4.4.2 Handling of Dropouts or Missing Data

Missing test results and data determined to be non-evaluable according to the Handling Rules for Analysis Data will not be used for hypothesis testing and estimations.

Values less than or equal to the lower limit of quantification will be treated as the value of the lower limit of quantification for PSA, serum testosterone, high-sensitivity serum testosterone, LH, FSH, DHT, and SHBG, and all others will be treated as zero when calculating the descriptive statistics.

Values less than the lower limit of quantification will be treated as zero for the calculation of descriptive statistics except for geometric mean for plasma concentration of TAK-385. For the geometric mean, values less than the lower limit of quantification will be treated as missing.

4.4.3 Interim Analyses and Data Monitoring

No interim analysis is planned in this study.

4.4.4 Multicenter Studies

Although this study is a multicenter study, treatment-by-center interaction will not be explored since the number of subjects for each center is not sufficient for such exploration.

4.4.5 Multiple Comparison/Multiplicity

Not applicable in this study.

4.4.6 Use of an "Efficacy Subset" of Subjects

Not applicable in this study.

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

Not applicable in this study.

4.4.8 Examination of Subgroups

Not applicable in this study.

5 Safety Analysis (Part A)

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

5.1 Treatment-Emergent Adverse Events

Analysis will be performed on TEAEs that occurred in Part A.

5.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE

Categories: Relationship to Study Drug [Related, Not Related]

Intensity [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

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

TEAEs will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

(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.

<u>Number of subjects</u>

- 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.

5.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]
	Time of Onset (day)	[1<= - <=7, 8<= - <=14, 15<= - <=21, 22<= - <=Max]

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

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

TEAEs will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

(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) Drug-Related Treatment-Emergent Adverse Events by Preferred Term

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

(7) Intensity of Drug-Related Treatment-Emergent Adverse Events by

System Organ Class and Preferred Term

(8) Treatment-Emergent Adverse Events with Intensity of Grade 3 or Higher by System Organ Class and Preferred Term

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

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

(11) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(12) Special Interest Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

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

Number of subjects

- Summary tables other than (6), (7), (8), and (11)

  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. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (6), (7), and (8)

  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. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (11)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.

  When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

5.1.3 Displays of Dose-Limiting Toxicities

Analysis Set: DLT Analysis Set

Analysis Variable(s): TEAE

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

TEAEs considered as dose-limiting toxicities 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) Treatment-Emergent Adverse Events Considered as Dose-Limiting Toxicities 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 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. Percentages will be based on the number of subjects in the DLT analysis set.

5.2 Pretreatment Events

5.2.1 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

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.

5.3 Laboratory and Other Safety Data

5.3.1 Laboratory Test Results

5.3.1.1 Hematology, Biochemistry, and Lipid and Glycated Hemoglobin in Blood

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Hematology

Red Blood Cell	White Blood Cell	Hemoglobin
Hematocrit	Platelets	

Differential WBC (Neutrophils, Neutrophil Count, Basophils, Eosinophils, Lymphocytes, Monocytes)

Biochemistry

Protein Total	Albumin	Glucose
Creatinine	Blood Urea Nitrogen	Uric Acid
Bilirubin Total	ALT (GPT)	AST (GOT)
LDH	GGT	Alkaline Phosphatase
CK (CPK)	Sodium	Potassium
Chloride	Calcium	Corrected Calcium
Phosphorus	PT-INR	

Lipid and Glycated Hemoglobin in Blood

Triglycerides	Total Cholesterol	HDL Cholesterol
LDL Cholesterol	TSH	HbA1c

Categories: Intensity [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit: (1) and (2):

Hematology, Biochemistry: Baseline, D7, D14, D21, D28, SFU

Lipid and Glycated Hemoglobin in Blood: Baseline, D28, SFU

Analytical Method(s) : For each variable, summaries (1) and (2) will be provided by treatment group. For applicable variables, summaries (3), (4), and (5) will be provided by treatment group. Takeda Preferred SI Units will be used for all summaries.

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

Descriptive statistics for observed values and changes from baseline will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Elevated Liver Enzyme

Laboratory Parameters

Overall frequency distributions of elevated hepatic parameters will be provided. Further details are given in the Appendix.

(4) Number and Percentage of Subjects with Laboratory Test Abnormalities by Grade

Frequency distributions for each laboratory test abnormality will be provided by grade. Evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained after baseline will be used. A subject with multiple occurrences of laboratory test abnormality will be counted once for the abnormality with the maximum intensity.

(5) Maximum Grade Shift From Baseline of Laboratory Parameters

The maximum post-baseline grade will be determined for each subject. Shift tables showing the number of subjects in each grade category at baseline and post-baseline visit will be provided using evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data).

5.3.1.2 Urinalysis

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	pH	
	Specific Gravity	
	Protein	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Glucose	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Occult blood	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Ketones	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Urobilinogen	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Bilirubin	[-, +-, 1+, 2+, 3+, 4+, 5+]
Categories:	Intensity	[Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]
Visit:	(1), (2), and (3): Baseline, D7, D14, D21, D28, SFU	
Analytical Method(s) :	For pH and specific gravity, summaries (1) and (2) will be provided by treatment group. For each variable other than pH and specific gravity, summary (3) will be provided by treatment group. For protein, summaries (4) and (5) will also be provided by treatment group.	

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

Descriptive statistics for observed values and changes from baseline will be provided for each visit.

(2) Case Plots

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 baseline and each post-baseline visit will be provided.

(4) Number and Percentage of Subjects with Urine Laboratory Test Abnormalities by Grade

Frequency distributions for each urine laboratory test abnormality will be provided by grade. Evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained after baseline will be used. A subject with multiple occurrences of laboratory test abnormality will be counted once for the abnormality with the maximum intensity.

(5) Maximum Grade Shift From Baseline of Urine Laboratory Parameters

The maximum post-baseline grade will be determined for each subject. Shift tables showing the number of subjects in each grade category at baseline and post-baseline visit will be provided using evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data).

5.3.2 Vital Signs, Physical Findings, and Other Observations Related to Safety

5.3.2.1 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis Variable(s): Body Temperature (C)
Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
Pulse (bpm)
Weight (kg)

Visit: (1) and (2): Baseline, D7, D14, D21, D28, SFU

Analytical Method(s): For each variable, summaries (1) and (2) will be provided by treatment group. For applicable variables, summary (3) will be provided by treatment group.

(1) Summary of Vital Signs and Weight Parameters and Change from

Baseline by Visit

Descriptive statistics for observed values and changes from baseline will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters

Overall frequency distributions of MAV will be provided. If a vital sign parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

5.3.2.2 12-lead ECG

Analysis Set:	Safety Analysis Set	
Analysis		
Variable(s) :	Heart Rate (bpm)	
	RR Interval (msec)	
	PR Interval (msec)	
	QRS Interval (msec)	
	QT Interval (msec)	
	QTcF Interval (msec)	observed value: [Min<= - <=449, 450<= - <=479, 480<= - <=499, 500<= - <=Max]
		change from baseline : [Min<= - <=29, 30<= - <=59, 60<= - <=Max]
	QTcB Interval (msec)	observed value: [Min<= - <=449, 450<= - <=479, 480<= - <=499, 500<= - <=Max]
		change from baseline : [Min<= - <=29, 30<= - <=59, 60<= - <=Max]
	12-Lead ECG Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit:	(1), (2), and (4): Baseline, D14, D28, SFU	
Analytical Method(s) :	For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by treatment group. For applicable variables, summary (3) will be provided by treatment group. For 12-lead ECG interpretation, summary (4) will be provided by treatment	

group.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline will be provided for each visit. Frequency distributions for the categorical variables will be provided for each visit.

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

(3) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
Overall frequency distributions of MAV will be provided. If an ECG parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(4) Summary of Shifts of ECG Parameters
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

5.4 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis Set: Safety Analysis Set
DLT Analysis Set

Analysis Variable(s) : TEAE

Analytical Method(s) : The following TEAEs will be summarized in the same way as in section 5.1.2 and section 5.1.3. All SOC and PT will be presented in Japanese.

(1) Treatment-Emergent Adverse Events by Preferred Term
(2) Drug-Related Treatment-Emergent Adverse Events by Preferred Term
(3) Treatment-Emergent Adverse Events with Intensity of Grade 3 or Higher by System Organ Class and Preferred Term
(4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
(5) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(6) Treatment-Emergent Adverse Events Considered as Dose-Limiting Toxicities by System Organ Class and Preferred Term

6 Safety Analysis (Part B)

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

6.1 Treatment-Emergent Adverse Events

Analysis will be performed on TEAEs that occurred in Part B.

6.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE

Categories: Relationship to Study Drug [Related, Not Related]

Intensity [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

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

TEAEs will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

(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.

<u>Number of subjects</u>

- 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.

6.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]
	Time of Onset (day)	[1<= - <=90, 91<= - <=180, 181<= - <=270, 271<= - <=360, 361<= - <=450, 451<= - <=540, 541<= - <=630, 631<= - <=Max]

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

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

TEAEs will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

(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) Drug-Related Treatment-Emergent Adverse Events by Preferred Term

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

(7) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(8) Treatment-Emergent Adverse Events with Intensity of Grade 3 or Higher by System Organ Class and Preferred Term
(9) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
(10) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(11) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time
(12) Special Interest Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

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

Number of subjects

- Summary tables other than (6), (7), (8), and (11)

  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. Percentages will be based on the number of subjects in the safety analysis set.
- Summary tables for (6), (7), and (8)

  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. Percentages will be based on the number of subjects in the safety analysis set.
- Summary table for (11)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.

  When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

6.2 Pretreatment Events

6.2.1 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

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.

6.3 Laboratory and Other Safety Data

6.3.1 Laboratory Test Results

6.3.1.1 Hematology, Biochemistry, and Lipid and Glycated Hemoglobin in Blood

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Hematology

Red Blood Cell	White Blood Cell	Hemoglobin
Hematocrit	Platelets	

Differential WBC (Neutrophils, Neutrophil Count, Basophils, Eosinophils, Lymphocytes, Monocytes)

Biochemistry

Protein Total	Albumin	Glucose
Creatinine	Blood Urea Nitrogen	Uric Acid
Bilirubin Total	ALT (GPT)	AST (GOT)
LDH	GGT	Alkaline Phosphatase
CK (CPK)	Sodium	Potassium
Chloride	Calcium	Corrected Calcium
Phosphorus	PT-INR	

Lipid and Glycated Hemoglobin in Blood

Triglycerides	Total Cholesterol	HDL Cholesterol
LDL Cholesterol	TSH	HbA1c

Categories: Intensity [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit: (1) and (2):

Hematology: Baseline, WK5D1, WK9D1, WK13D1, WK25D1, WK37D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1, SFU

Biochemistry: Baseline, WK5D1, WK9D1, WK13D1, WK17D1, WK21D1, WK25D1, WK29D1, WK33D1, WK37D1, WK41D1, WK45D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1, SFU

Lipid and Glycated Hemoglobin in Blood: Baseline, WK5D1, WK9D1, WK13D1, WK25D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1, SFU

Analytical Method(s) : For each variable, summaries (1) and (2) will be provided by treatment group. For applicable variables, summaries (3), (4), and (5) will be provided by treatment group. Takeda Preferred SI Units will be used for all summaries.

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

Descriptive statistics for observed values and changes from baseline will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Elevated Liver Enzyme Laboratory Parameters

Overall frequency distributions of elevated hepatic parameters will be provided. Further details are given in Appendix.

(4) Number and Percentage of Subjects with Laboratory Test Abnormalities by Grade

Frequency distributions for each laboratory test abnormality will be provided by grade. Evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained after baseline will be used. A subject with multiple occurrences of laboratory test abnormality will be counted once for the abnormality with the maximum intensity.

(5) Maximum Grade Shift From Baseline of Laboratory Parameters

The maximum post-baseline grade will be determined for each subject. Shift tables showing the number of subjects in each grade category at baseline and post-baseline visit will be provided using evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data).

6.3.1.2 Urinalysis

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	pH	
	Specific Gravity	
	Protein	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Glucose	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Occult blood	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Ketones	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Urobilinogen	[-, +-, 1+, 2+, 3+, 4+, 5+]
	Bilirubin	[-, +-, 1+, 2+, 3+, 4+, 5+]
Categories:	Intensity	[Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit: (1), (2), and (3):
Baseline, WK5D1, WK9D1, WK13D1, WK25D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1, SFU

Analytical Method(s) : For pH and specific gravity, summaries (1) and (2) will be provided by treatment group.
For each variable other than pH and specific gravity, summary (3) will be provided by treatment group.
For protein, summaries (4) and (5) will also be provided by treatment group.

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

(2) Case Plots
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 baseline and each post-baseline visit will be provided.

(4) Number and Percentage of Subjects with Urine Laboratory Test Abnormalities by Grade
Frequency distributions for each urine laboratory test abnormality will be provided by grade. Evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained after baseline will be used. A subject with multiple occurrences of laboratory test abnormality will be counted once for the abnormality with the maximum intensity.

(5) Maximum Grade Shift From Baseline of Urine Laboratory Parameters
The maximum post-baseline grade will be determined for each subject. Shift tables showing the number of subjects in each grade category at baseline and post-baseline visit will be provided using evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data).

6.3.2 Vital Signs, Physical Findings, and Other Observations Related to Safety

6.3.2.1 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis

Variable(s) : Body Temperature (C)
Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
Pulse (bpm)
Weight (kg)

Visit: (1) and (2):
Baseline, WK2D1, WK3D1, WK5D1, WK9D1, WK13D1, WK25D1, WK49D1, WK61D1, WK73D1, WK85D1, WK97D1, SFU

Analytical

Method(s) : For each variable, summaries (1) and (2) will be provided by treatment group. For applicable variables, summary (3) will be provided by treatment group.

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

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

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters
Overall frequency distributions of MAV will be provided. If a vital sign parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

6.3.2.2 12-lead ECG

Analysis Set: Safety Analysis Set

Analysis

Variable(s) : Heart Rate (bpm)
RR Interval (msec)
PR Interval (msec)
QRS Interval (msec)
QT Interval (msec)
QTcF Interval (msec) observed value: [Min<= - <=449, 450<= - <=479, 480<= - <=499, 500<= - <=Max]

		change from baseline : [Min<= - <=29, 30<= - <=59, 60<= - <=Max]
	QTcB Interval (msec)	observed value: [Min<= - <=449, 450<= - <=479, 480<= - <=499, 500<= - <=Max]
		change from baseline : [Min<= - <=29, 30<= - <=59, 60<= - <=Max]
	12-Lead ECG Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit: (1), (2), and (4):
Baseline, WK3D1, WK5D1, WK25D1, WK49D1, WK73D1, WK97D1, SFU

Analytical Method(s) : For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by treatment group.
For applicable variables, summary (3) will be provided by treatment group.
For 12-lead ECG interpretation, summary (4) will be provided by treatment group.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline will be provided for each visit. Frequency distributions for the categorical variables will be provided for each visit.

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

(3) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
Overall frequency distributions of MAV will be provided. If an ECG parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(4) Summary of Shifts of ECG Parameters
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

6.3.2.3 Bone Mineral Density

Analysis Set: Safety Analysis Set

Analysis Variable(s) : (1) Bone Mineral Density (L_{2-4})
(2) Bone Mineral Density (Femoral Neck)
(3) Bone Mineral Density (Total Hip)

Visit: Baseline, WK25D1, WK49D1, WK73D1, WK97D1

Analytical Method(s) : The following analysis will be performed using the safety analysis set. For (1) to (3), the descriptive statistics of the observed values and the two-sided 95% confidence intervals of the mean will be provided for each visit by treatment group. The same analysis will be performed for the percent change from baseline.

6.4 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis Set: Safety Analysis Set

Analysis Variable(s) : TEAE

Analytical Method(s) : The following TEAEs will be summarized in the same way as in section 6.1.2. All SOC and PT will be presented in Japanese.

(1) Treatment-Emergent Adverse Events by Preferred Term
(2) Drug-Related Treatment-Emergent Adverse Events by Preferred Term
(3) Treatment-Emergent Adverse Events with Intensity of Grade 3 or Higher by System Organ Class and Preferred Term
(4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
(5) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

7 Significance Level and Confidence Coefficient (Part A and Part B)

- Confidence coefficient: 95% (two-sided)

Amendment History

Version	Date	Author	Detailed Description of Amendments to Text
1	April 16, 2015	[redacted]	Not applicable
2	July 20, 2017	[redacted]	Refer to Appendix 1.

Appendix 1. Amendments from the Previous Version

Page	Existing Text	Revised Text	Rationale for Amendment
Cover	[redacted]	[redacted]	Updated in accordance with the current organization.
Cover	[redacted]	[redacted]	Updated in accordance with the current organization.
4	Glossary Descriptive statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles	Glossary Descriptive statistics: number of subjects, mean, standard deviation (SD), maximum (max), minimum (min), and quartiles	Added to clearly define the abbreviation.
4	Glossary (New)	Glossary CV: coefficient of variation	Added to clearly define the abbreviation.
4	Glossary (New)	Glossary PK: pharmacokinetic	Added to clearly define the abbreviation.
6	Definition of Visit Window <Part A> Pharmacokinetic Assessments Headers of the table: Visit, Scheduled Study Day	Definition of Visit Window <Part A> Pharmacokinetic Assessments Headers of the table: Visit, Scheduled Study Time	Corrected to a more appropriate expression.

Page	Existing Text	Revised Text	Rationale for Amendment
	(days), Scheduled Study Time (hours), and Time Interval (Study Day (days), Study Time (hours))	(hours), and Time Interval (Study Day (days), Study Time (hours))	
6	Definition of Visit Window <Part A> Pharmacokinetic Assessments	Definition of Visit Window <Part A> Pharmacokinetic Assessments The visit windows in the whole table were revised.	Corrected to a more appropriate expression.
11	Definition of Visit Window <Part B> Pharmacokinetic Assessments Headers of the table: Visit, Scheduled Study Day (days), Scheduled Study Time (hours), and Time Interval (Study Day (days), Study Time (hours))	Definition of Visit Window <Part B> Pharmacokinetic Assessments Headers of the table: Visit, Scheduled Study Time (hours), and Time Interval (Study Day (days), Study Time (hours))	Corrected to a more appropriate expression.
11	Definition of Visit Window <Part B> Pharmacokinetic Assessments	Definition of Visit Window <Part B> Pharmacokinetic Assessments The visit windows in the whole table were revised.	Corrected to a more appropriate expression.
20	Others PK parameters	Others The symbols and the definitions of PK parameter were revised.	Corrected according to the latest standard PK terminology
20	Others AUC(0-inf) --Area under the plasma/blood/serum concentration-time curve from time 0 to infinity, calculated as AUC(0-inf)=AUC(0-tlqc)+lqc/λz, where tlqc is the time of last quantifiable concentration and lqc is the last quantifiable concentration.	Others (deleted)	Deleted unnecessary PK parameters

Page	Existing Text	Revised Text	Rationale for Amendment
	AUMC(0-inf) -- Area under the first moment plasma/blood/serum concentration-time curve from time 0 to infinity, calculated as AUMC(0-inf)=AUMC(0-tlqc)+lqc×tlqc/λz+lqc/λz2, where tlqc is the time of last quantifiable concentration and lqc is the last quantifiable concentration.		
20	Others Cmax/D --Dose-adjusted Cmax.	Others $C_{max, ss}$/D --Dose-normalized $C_{max, ss}$.	Corrected to a more appropriate expression.
20	Others MRT -- Mean residence time, calculated as MRT=AUMC(0-inf)/AUC(0-inf).	Others (deleted)	Deleted unnecessary PK parameters
20	Others Vss/F --Apparent volume of distribution at steady state after extravascular administration, calculated as Vss/F= CL/F×MRT.	Others V_z/F_{ss} --Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using AUC_τ	Corrected to a more appropriate expression.
36	3.2.1 Plasma Concentrations Descriptive statistics, geometric mean, and coefficient of variation will be used to summarize plasma concentrations at each visit. Plasma concentration-time profiles will be provided for each treatment group using individual or mean concentrations.	3.2.1 Plasma Concentrations Number of subjects, mean, SD, min, median, max, geometric mean, and CV will be used to summarize plasma concentrations at each visit for each treatment group. Linear plots of plasma concentration-time profiles will be provided for each treatment group using individual	Corrected to clarify which descriptive statistics and linear plots will be provided.

Page	Existing Text	Revised Text	Rationale for Amendment
		and mean (SD) concentrations in separate plots. Mean (SD) plots will include the plasma concentration plot for all visits, separate plots for each of Day 1, Day 14, Day 28, and a plot for the plasma trough concentrations.	
36	(New)	Listing Analysis Set: Full Analysis Set Analysis Variable(s) : D1: AUC_{τ}, C_{max} and t_{max} D14: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, $C_{max, ss}$, $C_{max, ss}/D$, $C_{min, ss}$, $t_{max, ss}$ D28: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, CL/F_{ss}, $C_{max, ss}$, $C_{max, ss}/D$, $t_{max, ss}$, $t_{1/2z}$, V_z/F_{ss}, λ_z, number of data points with first and last data points used in the terminal disposition phase regression analysis and adjusted R^2 (coefficient of determination) for the terminal disposition phase regression analysis Analytical Method(s) : PK parameters will be calculated by using individual plasma concentrations with actual sampling times. Plasma concentrations from D1 to D2, D14 to D15 and D28 to D35 will be used for the calculation of PK	Added to separate the listing for PK parameters from the table of descriptive statistics. PK parameter calculation methods were also moved to this new section.

Page	Existing Text	Revised Text	Rationale for Amendment
		parameters on D1, D14 and D28 respectively. Plasma concentrations deviated from the visit window will be also used for the calculation. A standard non-compartmental analysis will be performed using the linear trapezoidal rule. If subject received prohibited concomitant medications, therapies or foods, then the plasma concentrations measured on and after this day will be used to estimate the PK parameters for the listing but the results will be treated as reference values. Individual PK parameters will be listed. The listings will include the treatment group, subject ID and evaluation day (D1, D14, and D28) in addition to the PK parameters.	
37	Descriptive Statistics D1: AUC(0-24), Cmax and Tmax D14: AUC(0-tlqc), AUC(0-tau), AUC(0-tau)/D, Cmax, Cmax/D, Cmin, Tmax D28: AUC(0-tlqc), AUC(0-tau), CL/F, Cmax, Tmax , T1/2, Vss/F	Descriptive Statistics D1: AUC_{τ}, C_{max} and t_{max} D14: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, $C_{max, ss}$, $C_{max, ss}/D$, $C_{min, ss}$, $t_{max, ss}$ D28: $AUC_{last, ss}$, $AUC_{\tau, ss}$, $AUC_{\tau, ss}/D$, CL/F_{ss}, $C_{max, ss}$, $C_{max, ss}/D$, $t_{max, ss}$, $t_{1/2z}$, V_z/F_{ss}, λ_z	Added the dose-normalized PK parameters ($C_{max, ss}/D$ and $AUC_{\tau, ss}/D$) and corrected PK parameter symbols according to the latest standard PK terminology.
37	Descriptive Statistics Pharmacokinetic (PK) parameters will be calculated by	Descriptive Statistics For the pharmacokinetic parameters, the number of	Corrected to specify which descriptive statistics will be provided.

Page	Existing Text	Revised Text	Rationale for Amendment
	using individual plasma concentrations with actual sampling times. Plasma concentrations from D1 to D2, D14 to D15 and D28 to D35 will be used for the calculation of PK parameters on D1, D14 and D28 respectively. Plasma concentrations deviated from the visit window will be also used for the calculation. A standard non-compartmental analysis will be performed. The listing of calculated PK parameters will be prepared for each subject. Descriptive statistics, geometric mean, and coefficient of variation will be used to summarize each pharmacokinetic parameter for each treatment group. Graphical assessment of dose-linearity on Cmax or AUC(0-tau) will be conducted on D14 and D28.	subjects, mean, SD, min, median, max, geometric mean, and CV will be provided for each treatment group. PK parameters which are treated as reference values will be excluded from the summary statistics. Graphical assessment of dose-proportionality on $C_{max, ss}$ and $AUC_{\tau, ss}$ will be conducted on D14 and D28 by plotting individual dose-normalized exposure parameters, i.e., $C_{max, ss}/D$ or $AUC_{\tau, ss}/D$ versus dose.	The rules for data handling and the method for dose-proportionality assessment were changed to what was considered more appropriate.
39	3.4.2 Handling of Dropouts or Missing Data (New)	3.4.2 Handling of Dropouts or Missing Data Values less than the lower limit of quantification will be treated as zero except for the calculation of geometric mean for plasma concentration of TAK-385. For the geometric mean, values less than the lower limit of quantification will be treated as missing.	Added to define the rules for handling values less than the lower limit of quantification.
41	4.1.2 QOL Assessment The following analysis will be performed using the full	4.1.2 QOL Assessment The following analysis will be performed using the full	Appendix containing details on the scoring procedures was added.

Page	Existing Text	Revised Text	Rationale for Amendment
	analysis set.	analysis set. The scoring procedures are described in detail in the Appendix.	
41	4.2.1 Plasma Concentrations Descriptive statistics, geometric mean, and coefficient of variation will be used to summarize plasma concentrations at each visit. Plots of plasma concentrations at each visit will be provided for each treatment group using individual or mean concentrations.	4.2.1 Plasma Concentrations Descriptive statistics, geometric mean, and CV will be used to summarize plasma concentrations at each visit for each treatment group. Case plots as well as the mean and standard deviation plots of changes over time will be provided for plasma concentrations for each treatment group.	Corrected to a more appropriate expression.
42	4.3.1 Serum Testosterone Concentrations (2) High-sensitivity Serum Testosterone (ng/dL)	4.3.1 Serum Testosterone Concentrations (2) High-sensitivity Serum Testosterone Concentrations (ng/dL)	Added to align with other similar expressions.
42	4.3.1 Serum Testosterone Concentrations Case plots as well as the mean and standard deviation plots of changes over time will be provided for observed values for each treatment group. A reference line will be drawn where the serum testosterone concentration is 0.5 ng/mL.	4.3.1 Serum Testosterone Concentrations Case plots as well as the mean and standard deviation plots of changes over time will be provided for observed values for each treatment group. For (1), a reference line will be drawn where the serum testosterone concentration is 0.5 ng/mL.	Added to clarify which analysis will include the reference line.
44	4.4.2 Handling of Dropouts or Missing Data (New)	4.4.2 Handling of Dropouts or Missing Data Values less than the lower limit of quantification will be treated as zero for the calculation of descriptive statistics except for geometric mean for plasma	Added to define the rules for handling values less than the lower limit of quantification.

Page	Existing Text	Revised Text	Rationale for Amendment
		concentration of TAK-385. For the geometric mean, values less than the lower limit of quantification will be treated as missing.	
65	Appendix. Criteria for Markedly Abnormal Values and Elevated Liver Enzyme	Appendix 2. Criteria for Markedly Abnormal Values and Elevated Liver Enzyme	Appendix number was updated since Appendix 1 and 3 were added to the SAP.
70	(New)	Appendix 3. QOL Scoring Procedures	Added Appendix 3 to make clear of each of the QOL scoring procedures.

Appendix 2. Criteria for Markedly Abnormal Values and Elevated Liver Enzyme

(1) Criteria for Markedly Abnormal Values

1) Vital Signs, and 12-lead ECG (except Upper MAV Criteria of QTcF Interval)

For each parameter, all evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained after baseline will be classified as a MAV or not. The criteria in the table below will be used. The lower limit of the normal range and the upper limit of the normal range are abbreviated as LLN and ULN.

Vital Signs

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Systolic Blood Pressure (mmHg)	-	-	<85	>180
Diastolic Blood Pressure (mmHg)	-	-	<50	>110
Pulse (bpm)	-	-	<50	>120
Body Temperature (°C)	-	-	<35.6	>37.7

12-lead ECG

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Heart Rate (bpm)	-	-	<50	>120
QT Interval (msec)	-	-	<=50	>=460
QTcF Interval (msec)	-	-	<=50	-

Classifying Subjects for the Overall Treatment Period

For each parameter and subject, classifications will be made according to the conditions i) to iii) provided below. The lower and the upper criteria will be considered separately.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that doesn't meet the MAV criteria will be considered as a subject without MAV.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV for that parameter.

2) 12-lead ECG (Upper MAV Criteria of QTcF Interval)

All evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained after baseline will be classified as a MAV or not. The criteria in the table below will be used. Note that the observed value and the change from baseline used for classification should be measurements taken on the same day.

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
QTcF Interval (msec)	-	-	-	If either of the following conditions is met: - observed value >=500 - change from baseline >= 30 and observed value >=450

Classifying Subjects for the Overall Treatment Period

For each subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that meets any of the following will be considered as a subject without MAV.

- Observed value is less than 450 msec and not missing.
- Change from baseline is less than 30 msec and not missing, and observed value is less than 500 msec and not missing.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV.

(2) Criteria for Elevated Liver Enzyme

All evaluable data (i.e., non-missing and acceptable according to the Handling Rules for Analysis Data) obtained after baseline will be used to determine whether each criteria for elevated liver enzyme in the table below is met or not. If there is more than one parameter that need to be considered for a criteria, parameter measurements taken on the same day will be used. The following abbreviations are used: LLN for lower limit of the normal range, ULN for upper limit of the normal range, ALT for alanine aminotransferase, AST for aspartate aminotransferase, Tbili for total bilirubin, and ALP for alkaline phosphatase.

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
ALT > 3xULN	ALT is greater than 3 times the ULN	ALT is non-missing and less than or equal to 3 times the ULN
ALT > 5xULN	ALT is greater than 5 times the ULN	ALT is non-missing and less than or equal to 5 times the ULN
ALT > 8xULN	ALT is greater than 8 times the ULN	ALT is non-missing and less than or equal to 8 times the ULN
ALT > 3xULN with Tbili > 2xULN	ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
AST > 3xULN	AST is greater than 3 times the ULN	AST is non-missing and less than or equal to 3 times the ULN
AST > 5xULN	AST is greater than 5 times the ULN	AST is non-missing and less than or equal to 5 times the ULN
AST > 8xULN	AST is greater than 8 times the ULN	AST is non-missing and less than or equal to 8 times the ULN
AST > 3xULN with Tbili > 2xULN	AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
ALT or AST > 3xULN	Either ALT or AST is greater than 3 times the ULN	Both ALT and AST are non-missing and less than or equal to 3 times the ULN
ALT or AST > 5xULN	Either ALT or AST is greater than 5 times the ULN	Both ALT and AST are non-missing and less than or equal to 5 times the ULN
ALT or AST > 8xULN	Either ALT or AST is greater than 8 times	Both ALT and AST are non-missing and

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
	the ULN	less than or equal to 8 times the ULN
ALT or AST > 3xULN with Tbili > 2xULN	Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - Both ALT and AST are non-missing and less than or equal to 3 times the ULN. - Total bilirubin is non-missing and less than or equal to twice the ULN.
ALT and AST > 3xULN	Both ALT and AST are greater than 3 times the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN
ALT and AST > 5xULN	Both ALT and AST are greater than 5 times the ULN	Either ALT is non-missing and less than or equal to 5 times the ULN, or AST is non-missing and less than or equal to 5 times the ULN
ALT and AST > 8xULN	Both ALT and AST are greater than 8 times the ULN	Either ALT is non-missing and less than or equal to 8 times the ULN, or AST is non-missing and less than or equal to 8 times the ULN
ALT and AST > 3xULN with Tbili > 2xULN	Both ALT and AST are greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - ALT is non-missing and less than or equal to 3 times the ULN - AST is non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALP > 3xULN	ALP is greater than 3 times the ULN	ALP is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN with ALT > 3xULN	Both ALP and ALT are greater than 3 time the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or ALT is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN	Both ALP and AST are greater than 3	Either ALP is non-missing and less than or

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
with AST > 3xULN	times the ULN	equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

Appendix 3. QOL Scoring Procedures

(1) AMS

AMS subscale scores and total scores will be calculated as follows. If one or more of the scores required for the calculation of a subscale are missing, then that particular subscale and the total score will be treated as missing.

- Psychological subscale: sum of severity points from questions 6, 7, 8, 11, 13
- Somatic subscale: sum of severity points from questions 1, 2, 3, 4, 5, 9, 10
- Sexual subscale: sum of severity points from questions 12, 14, 15, 16, 17
- Total score: sum of severity points from all questions from 1 to 17

Reference: Moore C, Huebler D, Zimmermann T, Heinemann LA, Saad F, Thai DM. The Aging Males' Symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. Eur Urol 2004;46(1):80-7

(2) EORTC QLQ-C30

The Global health status/QoL score and each Functional scales score (physical, role, emotional, cognitive, social) will be calculated as follows. The "range" used in the calculations is the difference between the maximum possible values of the score and the minimum possible value. If more than half of the scores are missing, then the Global health status/QoL score or the Functional scales score will be treated as missing. If at least half of the scores are available, then the scores that are available will be used for the calculation.

- Global health status/QoL score: {[(average of item 29 & 30)-1]/range}*100
- Physical functioning: {1-[(average of item 1 to 5)-1]/range}*100
- Role functioning: {1-[(average of item 6 & 7)-1]/range}*100
- Emotional functioning: {1-[(average of item 21 to 24)-1]/range}*100
- Cognitive functioning: {1-[(average of item 20 & 25)-1]/range}*100
- Social functioning: {1-[(average of item 26 & 27)-1]/range}*100

Reference: Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual (3rd edition)*. Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

(3) EPIC

Each of the HRQOL Domain Summary Scores (urinary, bowel, sexual, hormonal) will be calculated according to the following steps.

1) Convert score using the conversion table below.

Conversion Table

Question No.	Answer	Converted Score
1, 2, 3, 8, 9, 14, 20, 21, 22, 23, 26, 27, 28, 29, 32	1	0
	2	25
	3	50
	4	75
	5	100
4	1	0
	2	33
	3	67
	4	100
5	0	100
	1	67
	2	33
	3	0
6A, 6B, 6C, 6D, 6E, 6F, 15A, 15B, 15C, 15D, 15E, 15F, 24A, 24B, 24C, 31A, 31B, 31C, 31D, 31E, 31F	0	100
	1	100
	2	75
	3	50
	4	25
	5	0
7, 10, 11, 12, 16, 25	1	100
	2	75
	3	50
	4	25
	5	0
13	1	100
	2	50
	3	0
17A, 17B, 17C, 19	0	0
	1	0
	2	25
	3	50
	4	75
	5	100
18	0	0
	1	0
	2	33
	3	67
	4	100
30	1	0
	2	50
	3	100
	4	50
	5	0

2) Each of the HRQOL Domain Summary Scores (urinary, bowel, sexual, hormonal) will be calculated as follows. If 20% or more of the answers are missing then the summary score will not be calculated.

- Urinary summary score: average of converted scores of question no. 1 to 7
- Bowel summary score: average of converted scores of question no. 8 to 16
- Sexual summary score: average of converted scores of question no. 17 to 25
- Hormonal summary score: average of converted scores of question no. 26 to 31

Reference: Takegami M, Suzukamo Y, iHope International. EPIC. 2002.